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Our Science: Issue 6

This issue of Our Science opens with the Business Continuity Award won by The Unit in recognition of how we managed the political impasse in December 2016 and January 2017. This is an excellent result, owned by all our staff. The international reputation in health research gained by The Unit is outlined by its designation as a World Health Organization Collaborating Centre for New Vaccines Surveillance. The Centre, headed by Prof Martin Antonio, provides support to African countries for the surveillance of invasive bacterial diseases. This is a clear example of how scientific research can be combined with public health and capacity building. The Unit's research excellence is underlined by the MRC Foundation Award secured by the Vaccine and Immunity Theme. This award will allow for the expansion of the excellent work being done on childhood tuberculosis to other African countries; Prof Kampmann and her team are to be congratulated on this fantastic achievement. The other two research projects presented in this issue, one on malaria drug resistance and the other on nutrition interventions for adolescent girls and young women illustrate The Unit's broad research portfolio, which addresses priority health issues in sub-Saharan Africa. The Unit's capacity to carry out world-class research is supported by an excellent technical platform, which includes also the capacity of rapidly sequencing nucleic acid, namely RNA and DNA, with innovative techniques. Similarly, the Clinical Services Department, The Unit's most visible part to the general public, has undergone a number of changes to improve efficiency and also, besides providing health care, to actively contribute to the MRCG research portfolio. I am particularly pleased that The Unit's commitment to promote women in science is shown by the profiles of four women at different stages of their professional career, from a PhD student to two post-doctoral scientists and to the head of our clinical services.

- Professor Umberto D'Alessandro



MRC Unit The Gambia Wins Business Continuity Award in Resilient Workforce Category

Annual Business Continuity Awards

At a ceremony held in London marking the 19th Annual Business Continuity Awards, which celebrate achievements in business continuity, security and resilience, MRC Unit The Gambia was awarded the Business Continuity Award in the Resilient Workforce Award category.

The Business Continuity Awards is the most anticipated event in the business continuity calendar and provides unrivalled opportunities for networking, alongside a night of entertainment and celebration.

The Resilient Workforce Awarded to MRCG was received by Joan Vives Tomas (Director of Operations), Dr Jonas Lexow (Research Governance and Support Services

Manager) and Dr Davis Nwakanma (Head of Laboratory Management). The award was presented in recognition of the way The Unit managed the political impasse last December and January. This period saw MRCG's preparedness to function as a referral centre for patients while complementing the efforts and skills of the Red Cross and other healthcare providers locally.

The award recognised The Unit's most important asset, its people and showed that MRCG provided concrete evidence of business continuity practices that put people at the heart of business continuity planning.

The Unit also demonstrated the organisation's commitment to both safeguarding the workforce, and leveraging this vital asset.

Commenting on the award Joan Vives Tomas, said, "This is a well-deserved award to all our Unit workforce but also to one generation of Gambians that made history and become an example for Africa and the world."



Recipients of the award Dr Davis Nwakanma, Joan Vives Tomas and Dr Jonas Lexow

MRCG becomes a World Health Organization Collaborating Centre for New Vaccines Surveillance

In August 2017, the Medical Research Council Unit The Gambia (MRCG) was designated a World Health Organization Collaborating Centre for New Vaccines Surveillance (WHOCC NVS).

This designation was primarily in recognition of the contributions of the Molecular Microbiology Group within the Vaccines and Immunity Theme at MRCG for the control of epidemic meningitis outbreaks in West Africa. The WHOCC NVS will serve as a link between MRCG's and WHO's strategic plans to save lives and improve health across sub-Saharan Africa and beyond. All WHOCC NVS activities are jointly planned and implemented with the

WHO. The Centre's Director is Professor Martin Antonio who is also a technical advisor to the WHO on New Vaccines Surveillance and epidemic meningitis.

Since 2009, The Molecular Microbiology Group has served as the WHO Regional Reference Laboratory for Invasive Bacterial Diseases supporting more than 12 GAVI-eligible countries in Africa with 21 sentinel sites.

The WHOCC NVS provides technical orientation and support to the countries of the African Region to improve on national, regional and international surveillance of Invasive Bacterial Vaccine-Preventable Diseases (e.g. meningitis and pneumonia) in addition to contributing data to the WHO Global Invasive Bacterial Vaccine-Preventable Disease (IB-VPD) Surveillance Strategic Review thereby translating research output into practice. A key objective of the WHOCC is to promote national and regional networking and to conduct national and international training courses, workshops and seminars on vaccine preventable diseases in Africa. This is achieved through strong collaboration and capacity building with Ministries of Health in Africa.

There are 800 WHOCC worldwide; most of them based in institutions in Europe and US. In Africa, there are 25 WHOCC, 14 of which are located in South Africa. The WHOCC NVS in The Gambia is the first in The Gambia and one of six WHOCCs in West Africa. The designation as a WHO collaborating centre provides MRCG with enhanced visibility and recognition by national and international authorities, calling public attention to the global health issues on which MRCG works. It opens up improved opportunities for exchange of information and technical cooperation with other institutions in West Africa, in particular at the international level, and to mobilize additional and important resources from funding partners.



Molecular Microbiology Team of MRCG

DISEASE CONTROL AND ELIMINATION THEME

Despite the reduction in prevalence, Malaria remains one of the main infectious diseases afflicting the sub-Saharan region

There is need for continuous monitoring of the efficacy of currently used drugs as well as the genetic markers determining drug resistance

Despite the reduction in burden, malaria remains one of the main infectious diseases afflicting sub-Saharan Africa. Malaria cases are treated with antimalarial drugs. However, the malaria parasite may become resistant to them and this is why it is very important to monitor their efficacy. This is necessary for the prompt detection of emerging resistance and to review treatment policies.

In an effort to better understand drug resistance, Plasmodium falciparum parasite isolates were collected from malaria patients in The Gambia between 2012 and 2015. Each isolate was tested in the laboratory against several antimalarial drugs, especially components of the artemisinin combination treatments (ACTs). These parasites were also investigated to identify mutations in their genome that confer resistance to antimalarial drugs. During this period, we observed an increase in the concentration of lumefantrine and other quinolines needed to kill the malaria parasites. However, during the same period the concentrations of artemisinin derivatives needed to kill parasites decreased.

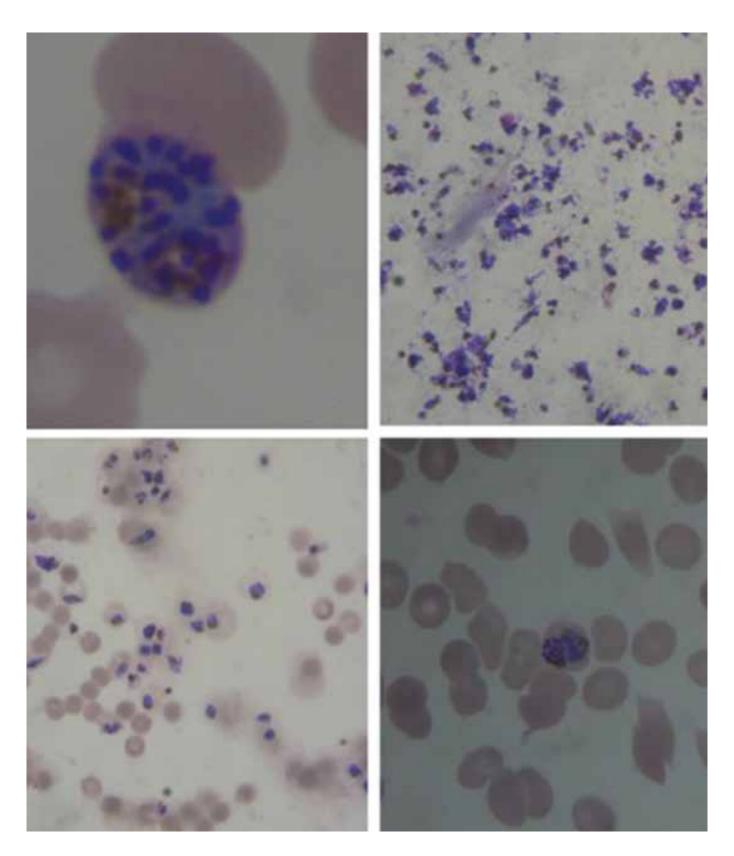
The study was led by Dr Alfred Amambua-Ngwa with the help of co-investigators Dr Joseph Okebe, Haddijatou Mbye, Fatoumatta Bojang, Sukai Ceesay, Abdullahi Ahmed, Aminata Jawara, Bakary Danso, Dr Muna Affara, Dr Davis Nwakanma and Professor Umberto D'Alessandro.

In a parallel study, we compared the genomic structure of parasite isolates collected at different time points between 2012 and 2015 to isolates collected before 2012. This led to the identification of new genetic mutations that may be related to tolerance to certain antimalarial drugs such as Lumefantrine. The mechanism by which these genetic markers mediate drug tolerance is the focus of the PhD thesis research of Haddijatou Mbye, funded by the Wellcome Trust DELTAS programme.

The monitoring of the response of malaria parasites to antimalarial drugs will continue at least until the end of 2018. Two new approaches based on advanced technologies will be implemented. The first approach will involve NextGeneration sequencing to characterise all the genetic markers in parasite isolates

tolerant to antimalarial drugs. The second approach by flow cytometry will precisely determine the stage at which parasite isolates adapt to drugs. This work would allow us to characterise the mechanisms of antimalarial drug resistance and identify genetic markers. We will then establish their occurrence among clinical malaria cases and in the general population.

DISEASE CONTROL AND ELIMINATION THEME



Malaria parasites at Schizont stage

Delivering an Action Agenda for Nutrition Interventions Addressing Adolescent Girls and Young Women

Given their important relationships with medium- and long-term outcomes, adolescent nutritional behaviours are assuming considerable importance in nutrition interventions.



Girls ploughing in Keneba

A study on delivering an action agenda for nutrition interventions addressing adolescent girls and young women: priorities for implementation and research, was recently published in the Annals of the New York Academy of Sciences. The study describes evidence-based nutrition recommendations and the current global guidance for nutrition actions for adolescents as young

people undergo major anatomical and physiological maturational changes in preparation for adulthood.

Despite the limitations of available information, researchers believe that a range of interventions are feasible to address outcomes in this age group, although some would need to start earlier in childhood.

Findings show that nutritional requirements are higher during adolescence than during the prepubescent stage and during adulthood. A significant proportion of adolescents also become parents, and hence the importance of their health and nutritional status before as well as during pregnancy has its impact on their own health, fetal well-being, and newborn health.

NUTRITION THEME

The need for delivery platforms and strategies, relevant to low- and middle-income countries was highlighted with a clear need to translate evidence into policy, for the implementation of key recommendations and addressing knowledge gaps through prioritized research.

Researchers propose packages of preventive care and management comprising nutrition-specific and nutrition-sensitive interventions to address adolescent under nutrition, over nutrition and micronutrient deficiencies. The study concluded that compromised health among young people also affects the health of future generations; therefore, strategies that can improve their health are good investments in both the short and longer terms. The recent pledges on sustainable development goals have provided a renewed agenda to improve the health of adolescents and young people by strengthening the delivery mechanisms of healthcare interventions.

Professor Andrew Prentice commented, "There have never been more adolescents in the history of our planet than there are now. They will soon become parents and therefore are the gateway to our future. Caring for their nutrition will play a significant part in creating an optimum start for the next generation, and will likely have an impact for generations that follow."



Healthy growth and nutrition among today's adolescents holds the key to the future health of nations. Photo: Felicia Webb

MRCG awarded highly competitive Medical Research Council Foundation Award

Award to pursue Evaluating novel diagnostics and enabling preventive measures for childhood tuberculosis between the United Kingdom (UK) and partners in Sub-Saharan Africa

MRC Unit The Gambia's Professor Beate Kampmann, Theme Leader, Vaccines and Immunity and co-investigator Dr Uzochukwu Egere have recently been awarded a highly competitive Medical Research Council (MRC) Foundation Award to pursue translational research on "Evaluating novel diagnostics and enabling preventive measures for childhood tuberculosis between the United Kingdom (UK) and partners in Sub-Saharan Africa".

The Foundation Award represents the MRC's first phase of research funding anticipated from the £1.5bn Global Challenges Research Fund. The 41 Foundation Awards led by the MRC, and supported by Arts and Humanities Research Council (AHRC), Biotechnology and Biological Sciences Research Council (BBSRC), Economic and Social Research Council (ESRC) and North American Electric Reliability Corporation (NERC), have been

allocated to support ambitious, novel and distinctive research in non-communicable diseases and infections. The award will enable Prof Kampmann's team at MRCG to build upon the research conducted during her MRCG Program Grant "Reach 4 Kids" and will additionally involve new partners in Africa and their respective national TB control programs- "Reach4Kids Africa". The ultimate aims are to validate promising new diagnostics and to



MRCG's Reach 4 Kids Team

HIGHLIGHT

VACCINES AND IMMUNITY

extend much needed preventative measures to protect young children exposed to TB. It will lay the foundations for a network of dedicated paediatricians, public health personnel and researchers in our region. According to Declan Mulkeen, MRC's Chief of Strategy, "The five research councils involved in the Foundation Awards have been working collectively to provide new and broader approaches to meet global research challenges. It's encouraging to see these projects tackling the broader environmental and economic factors affecting health, as well as using new technologies to bring cost-effective treatments within reach." Furthermore "The MRC has a strong track record in Global Health research, often in partnership.

Infectious disease has been the main focus and remains the largest area of funding, but as countries develop, their health needs change. The Global Challenges Research Fund will enable us to tackle a broader range of health problems, for local and global benefit. These awards represent a significant win for global research. We hope that many of the research partnerships being supported will move on to even more ambitious work over the coming years", he added.

Commenting on the award Professor Kampman said "TB in children is a much-neglected condition worldwide. I am absolutely delighted that our Reach 4 Kids program of work has been rewarded with this grant, which will enable us to reach

out beyond The Gambia to new partners in Mali, Nigeria and Tanzania in order to improve the management of children affected by TB, and to create a larger network for science and advocacy".

When asked to comment on the award Professor Umberto D'Alessandro, Unit Director said, "This is an extremely prestigious award that will allow us to expand our research activities related to TB in children to other countries in West Africa. It also shows The Unit's ability to compete for funding with some of the best academic institutions in the world. I would like to congratulate Prof Kampmann and her team for this wonderful achievement."



Community Sensitisation on Childhood TB

Genomics Sequencing in The Gambia

MRCG to pilot sequencing samples directly in the field: at the heart of outbreaks

MRC Unit The Gambia recently acquired two portable sequencing devices to pilot on field samples in the recently established Genomics Facility. These were provided as part of the continued collaboration between Oxford Nanopore and the Francis Crick Institute. The Oxford Nanopore MinION Sequencer is unique in its ability to directly sequence DNA/RNA in the field, yielding rapid, high-quality sequence data for downstream analysis in real time.

A Portable Sequencing device is ideal for field studies and outbreak situations, where genetic information on pathogen strains can help map disease transmission and inform treatment strategies. The long sequencing reads generated with this platform improve the data accuracy, which is beneficial when sequencing highly repetitive pathogen genomes. The MinION device has the potential to offer relatively low-cost genotyping, high mobility for testing, and rapid processing of samples with the ability to display results in

Abdul K Sesay, Manager, Genomics Facility, was selected to be part of the MinION Access Program (MAP) in 2014. He successfully

negotiated with The Francis Crick Institute and the team at Oxford Nanopore, to bring the devices and necessary computing hardware to the MRC Unit The Gambia. Laboratory Services currently have eight flow cells that will be used in the coming months to sequence a range of organisms in proof of principle experiments with this new device. The MinION works as follows: tiny protein pores are embedded in a synthetic membrane, one in each well. A potential is applied across the membrane and, as a result, a small current runs through the pore. As the (charged) DNA/ RNA molecules traverse the pore they reduce the



Penda Suso, Scientific Officer at The Genomics Core, displaying the MinION devices

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current. These reductions depend on the shape of the DNA or RNA that is a tell-tale sign for the base identity. Single molecules are sequenced as they pass through the pore and because there is no interaction there is no limit to the length of the molecule that can be sequenced.

Two projects will be used to evaluate the MinION. The first project is, in collaboration with Martin Antonio, Director of World Health

Organisation Regional Reference Laboratory for Invasive Bacterial Diseases, and will re-sequence Cerebrospinal fluid specimens collected from suspected meningitis cases during a historical outbreak/ epidemic in the region. The second project to be done in collaboration with Andrew Prentice, Nutrition Theme Leader, will sequence samples and evaluate the differences in the gut microbiome of malnourished children. Head of Laboratory Services, Davis

Nwakanma, said "In-house capacity for field deployment of the MinION sequencer, will facilitate MRCG's research in a significant way. Bringing DNA sequencing close to where disease outbreaks occur, should make it possible to identify the responsible pathogens in real-time and to more quickly implement appropriate interventions. Abdul's commitment to this important project is commendable and has led to the significant progress made to-date."



The Genomics Core team at work in the new facility

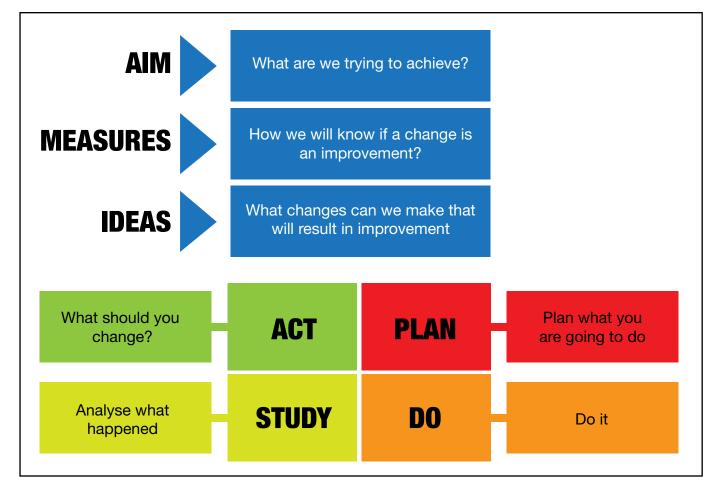
Clinical Services Department (CSD) embarks on Quality improvement in healthcare delivery

Transforming Healthcare delivery

Renowned for providing high quality care, the CSD recently launched a quality improvement programme, to continuously provide systematic changes to work that enables health care to be safe, effective, patient-centered, timely, efficient and equitable.

The improvements covers several aspects, including a patient satisfaction survey, the production of guidelines to standardize care and two specific projects - one to introduce sepsis alerts and early treatment; and the other to introduce usage of an Early Warning Score (EWS) to highlight deteriorating patients.

Headed by Dr Karen Forrest, Head of Clinical Services, together with the medical students, doctors, ward nurses and staff in the Gate Clinic, the model adopted by CSD is the commonest model used to guide quality improvement projects.



CSD Improvement model

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From March 2017 onwards, Sepsis alerts were introduced to provide up to date and relevant care to our patients. Simultaneously, the first set of guidelines for the Gate Clinic were published. In anticipation of introducing a scoring system over the last month, the observation sheets on the ward were changed. The patient satisfaction survey in Fajara and Keneba was piloted in May and has being rolled out in Fajara.

The interviewing of patients about their experiences on the ward (and not just in OPD) commenced in October and will be headed by a visiting doctor who will be responsible for collecting the next round of data on the sepsis alerts and take the EWS project forward.

CSD staff were encouraged to join the online training programme through the Open School at www.ihi.org - which is free to MRCG staff to enable CSD staffs to suggest ways of improving their own area of work.

With this project, it is envisioned that the training programme will provide the possibilities of using these methods to introduce operational research into the department. It will further enhance collaboration with other healthcare providers in The Gambia in rolling out successful projects from CSD into the wider health service.



Gate Clinic at MRCG

PROFILES

Fatou Jaiteh currently pursuing a 4 year PhD in Medical Anthropology

Fatou a 2016 recipient of the ITM Scholarship



Fatou Jaiteh Social Scientist

Fatou Jaiteh started working as a Social Scientist within the Disease, Control and Elimination Theme of the Medical Research Council Unit The Gambia in April 2015. With a background in biomedical science, public health, international development and medical anthropology her work involves conducting mixed methods (qualitative and quantitative) research as part of transdisciplinary projects focused on malaria.

Specifically, she has worked on a 3-year EU-funded project (COSMIC), a community-based intervention for malaria control in pregnancy involving the screening and treatment of malaria in pregnant women in The Gambia, Burkina Faso and Benin. Her role in the trial has been exploring perceptions of malaria in pregnancy and their influence on adherence to treatment in rural Gambia. She has recently published her results of this study which show that women in rural Gambia have good biomedical knowledge of malaria, but adherence to anti-malarial treatment was perceived to be low. Pregnant women discontinued the provided anti malarial treatment after one or two days mainly due to non-recognition of symptoms, perceived ineffectiveness, perceived risks of medication and advice received from their mother-in-law.

As the 2016 recipient of the ITM sandwich PhD scholarship, she is currently pursuing a 4 year PhD in medical anthropology through the Institute of Tropical Medicine, Antwerp, Belgium, MRCG and

the University of Amsterdam. The PhD work focuses on understanding illness perceptions towards asymptomatic malaria and adherence to targeted mass drug administration (MDA) within the context of malaria elimination in The Gambia. She points out that "Understanding the human factor in medical research is crucial for the appropriate delivery of interventions which best addresses the needs of the targeted communities".

After a few years of working in the Unit, Fatou has shown her hard work and inquisitive mind and has moved forward to conduct her PhD in this important are of research. It is recognized that the Unit needs to strengthen Social Science. PhD students working in the field with co-supervision with external collaborators is the way forward for this to happen.

Dr Ramatoulie Janha is navigating nutrition research towards bone health of older people

Dr Ramatoulie Janha is a Postdoctoral Scientist working in the Calcium, Vitamin D and Bone Health (CDBH) group of the Nutrition Theme at MRCG Keneba



Dr Ramatoulie Janha Senior Research Associate

She is interested in nutrition research for optimal growth and development. She has experience in an African setting where poverty and the prevalence of micronutrient deficiencies is high and the impact on the quality of life is evident. She is leading on the 20-year follow-up study of the double-blind randomised controlled trial of calcium carbonate versus placebo in pregnant women, the primary objective of which was to prevent high blood pressure during pregnancy. The main outcomes in the follow up study are bone mineral content, fragility fractures, biomarkers of bone metabolism, kidney function and high blood pressure. Dr Janha is involved in several other on-going and planned CDBH studies and is the Gambian lead for the next round of the Gambian Bone Ageing Study, including characterising osteoarthritis in elderly urban dwellers.

Dr Janha joined the Nutrition Theme in July 2014. She was one of the first African female recipients of a PhD fellowship from the European and **Developing Countries Clinical Trials** Partnership in 2006, and enrolled at the UK Open University. Her PhD research investigated the relationship between host genetic factors, pharmacokinetics and therapeutic effectiveness of the antimalarial chlorproguanil formulated into chlorproguanil-dapsone. Her PhD work is published in the journals Pharmacogenomics and BMC Evolutionary Biology. She has a BSc

in Biochemistry from the University of Ghana.

Under the leadership of Prof Ann Prentice (Director of MRC Elsie Widdowson Laboratory Cambridge and Head of CDBH) and mentorship of senior scientists Dr Gail Goldberg, Dr Kate Ward and Landing Jarjou, Dr Janha also manages the state-of-the-art bone imaging facilities of CDBH. She has attended several international conferences and workshops to present her work, and was selected to participate in the recent 17th African Nutrition Leadership Programme in South Africa, and has spent time in Cambridge. She hopes her research output in nutrition will guide national and international policies for calcium supplementation in pregnancy for women living in rural parts of Africa, policies that will impact throughout the life-course.

Breaking the Glass Ceiling for Female Researchers

Dr Jayne Sutherland advocates the support of young female researchers in order to access top level positions



Dr Jayne Sutherland, Head of the Tuberculosis Research

Dr Jayne Sutherland is currently Head of the Tuberculosis (TB) Research group at MRC Unit The Gambia, which provides a unique opportunity for multi-disciplinary research on TB using the long-running TB case-contact (TBCC) platform. The TBCC platform is run in close collaboration with the national TB program to promote health systems strengthening and public engagement. Underpinning all our studies is fundamental science to determine mechanisms, risk factors, host-directed therapies and prognostic markers for TB infection and disease.

Jayne is currently Principal Investigator (PI) on a European Union (EU) funded project for TB vaccine development, site-PI and member of the steering committee for a TB biomarker study (GC6-2013) and site-PI for an European & Developing Countries Clinical Trials Partnership (EDCTP) funded project seeking to develop a point of care test for TB diagnosis.

Current research projects in her laboratory include defining the role of non-classical T cells and other innate cells in the early response to Mtb infection; correlates of risk for progression to active TB; immunity at the site of infection; immune responses to M. africanum (a prevalent strain in West Africa) compared to M. tuberculosis; and immunity to TB in the context of HIV and other co-infections (including Influenza).

Jayne joined MRCG in 2006 as part of a Bill Gates multi-site consortium (GC6) looking at biomarkers for TB 'risk'. This project is just now coming to full fruition, and a 4-gene

signature to predict which of the 2 billion people infected with TB worldwide will progress to active disease has been developed. This will enable targeted therapy in a cost-effective manner. Prior to joining The Unit she worked on Cancer immunotherapy, which was her PhD topic in Melbourne, and early post-doc in London.

Moving to TB was not technically difficult but certainly posed challenges in regards to generating a track record for funding applications. The GC6 consortium provided Jayne with long-term mentorship and support, particularly from Dr Martin Ota, Prof Stefan Kaufmann, Prof Gerhard Walzl and Prof Hazel Dockrell.

In 2012 she took over as Head of the TBCC platform and TB immunology laboratory when Dr Ota took a position at WHO. "This was a monumental step for me, I had to prove my worth to the male-dominated teams I worked with and also to people who had known me as a young post-doctoral student. However, I had an excellent example of female leadership in Professor Beate Kampmann who has provided tireless support for my career trajectory." explains Dr Sutherland.

Dr Karen Forest is leading major transformational change in health care delivery

Driving successful change



Dr Karen Forrest Head of Clinical Services

Dr Karen Forrest is the Head of Clinical Services who plays a pivotal leadership role in strengthening the quality of health care delivery at the Clinical Services Department (CSD). Dr Forrest is an internal physician with a specialisation in gastroenterology. She obtained her medical qualifications at the University of Oxford and then did postgraduate training in Liverpool. She has postgraduate qualifications in medical education. She also did her Masters in theology and anthropology in Kenya, completing a research project on Gambian understandings of illness and disease.

Karen has worked in The Gambia since 2011. Before joining The Unit in 2015, Karen was previously the Doctor-in-charge of Sibanor Health Centre in Foni Bintang, Upper River Region (URR). Her passion for providing optimum care to her patients is a clear manifestation of how she quickly grasped and can fluently speak Mandinka.

Since arriving at MRCG, Karen has developed systems for monitoring and managing the Clinical Services Department. She has worked hard to learn from the expertise of other departments and managers and has sought to improve working relationships with research teams. As such, she has written a large number of clinical guidelines and has highlighted the need to improve the quality of care provided in the CSD.

Karen was also actively involved in the development of the Electronic Medical Record System (EMRS) which was initiated in March 2015. In collaboration with Data Management, Karen saw the successful completion of phase one and phase two of the deployment of the EMRS at MRCG. Over the last few years, MRCG has seen her enormous contribution towards the integration of the automation of the Gate Clinic, pharmacy, inventory of stock, in-patient clinic, Electronic Gate Clinic, E-patient card, improved Doctor Interface and Ward functions into the EMRS. Thus the CSD now have an effective, efficient and economic operational automated system to support the entire Clinical Services infrastructure of MRCG.

Leading health research in West Africa to save lives and improve health across the world

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Your Feedback Please!

Our Science – the newsletter of MRC Unit The Gambia, is for everyone who is interested in our work and community.

We are keen to receive feedback and suggestions for new features from our readers, if you have any comment please let us know.

Email: ourscience@mrc.gm

MRC Unit The Gambia

Atlantic Road, Fajara P.O.Box 273 Banjul The Gambia

Communications

\(+220 449 54 42 Ext: 2306

□ communications@mrc.gm

www.mrc.gm