Strategic Plan

KEMRI–Wellcome Trust Research Programme

2016–2021
# Table of Contents

1. Introduction .......................................................................................................................... 1
2. Management .......................................................................................................................... 2
3. Vision and Mission .................................................................................................................. 3
4. Established Scientific Themes .............................................................................................. 4
   4.1 Vaccines .......................................................................................................................... 4
   4.2 Genomics and infectious disease transmission ............................................................... 6
   4.3 Clinical Research ............................................................................................................. 7
   4.4 Population Health: Malaria, Malnutrition and Mortality ............................................... 9
   4.5 Health Systems and Research Ethics .............................................................................. 10
5. Developing Themes ............................................................................................................... 11
   5.1 Neonatal health ............................................................................................................... 12
   5.2 Anti-Microbial Resistance ............................................................................................. 12
   5.3 Biobank .......................................................................................................................... 12
6. Training and Development of Long-term Capacity ............................................................... 13
7. Public Engagement ............................................................................................................... 14
8. References ............................................................................................................................ 15
1. Introduction

The KEMRI-Wellcome Trust Research Programme has delivered internationally competitive research and capacity building for 26 years. We renewed core funding for our next 5-year cycle starting October 2016. Our strategic plan is based on the review process and internal consultative meetings, laying our vision and strategy for the next five years. Our scientific themes draw together researchers from different disciplines to work on high priority areas and enhance the rapid dissemination and uptake of findings into policy and practice. Work within and between themes is highly inter-disciplinary and interaction between themes is common.

We have 850 employees and work across 3 main hubs in Kenya and Uganda; Nairobi, Kilifi and Mbale with international reach through collaborating sites (Figure 1, below).

From Nairobi we coordinate health systems research including networks of hospitals for pragmatic trials, undertake international and national epidemiological work and coordinate malnutrition surveillance. From Kilifi we undertake work across the spectrum of disciplines with a unique resource of linked demographic surveillance of 0.25M residents, clinical phenotyping and molecular biology. From Mbale we coordinate multi-centre clinical trials on malaria and its consequences. Clinical research and social science cut across all three hubs.

Figure 1: Geography of Hubs and Collaborations
Core funding provides the basic platform for research and our scientific outputs are supported by additional project funding including Fellowships from the Wellcome Trust and other funders. Historical data on funding is shown in figure 2, below.

Figure 2: a) Funding utilized over 5 years b) new awards by year

2. Management

The Kilifi and Nairobi hubs operate as part of a KEMRI centre (the Centre for Geographic Medical Research – Coast). The Programme Director is based in Kilifi and there is a Nairobi Director, both working with the KEMRI – CGMRC Centre Director. In Mbale, Uganda we collaborate with the Mbale Clinical Research Institute, with a Scientific Director for this collaborative work based in the Programme. Our Operational Platform is led by our Chief Operating Officer.

Kilifi, our largest hub, divides into four Scientific Departments, each led by a Departmental Chair. Each Scientific Department has a responsibility for an aspect of the core research platform, managed by a Head, with joint line management from the Departmental Chair and the Programme Director. Our three hubs integrate via the Scientific Themes
which run across the Programme (see below). Our Scientific committee, which includes Directors and Chairs of Departments, determines and oversees scientific strategy. The Executive Management Committee, chaired by the Programme Director, oversees our operational governance, financial and risk management. Designated PIs act as Scientific Theme Leads for coordinating across departments and hubs, and will regularly update management on progress and plans.

Figure 3: Management Organogram

3. Vision and Mission

Our **vision** is to establish sustainable capacity for research that improves global health and our **mission** is to deliver high quality research that is relevant to global health and to build local capacity for undertaking research. We **aim**; 1) To conduct research to the highest international
scientific and ethical standards on the major causes of morbidity and mortality in the region in order to provide the evidence base to improve health and 2) to train internationally competitive Kenyan and African research leaders. Specific scientific aims for the next 5 years are detailed below.

4. Established Scientific Themes

4.1 Vaccines

We will develop a major scientific theme on vaccines including Phase I, II and III trials and post-licensing evaluations. Our aim is to contribute to the clinical development and evaluation of vaccines that improve global health. We will accelerate progression through early testing by undertaking first-in-human studies in Kenya, providing critical immunogenicity and efficacy data to support licensing and inform health policy with post-vaccination evaluations of effectiveness.

4.1.1 Pre-licensing development

We engage with national regulatory agencies and with the community to facilitate early-phase vaccine trials including first-in-human studies and have recently conducted Phase 1 Ebola vaccine trials [1]. The capacity to conduct first-in-human studies in Africa will accelerate vaccine development by removing the need for prior Phase I studies in Europe. Our near-term early phase plans include Phase I and II trials of vaccines against Rift Valley Fever, malaria, Shigella, Non-Typhoidal Salmonella, Respiratory Syncytial Virus and whole-cell pneumococcal vaccines. Our Head of Laboratories will work with London School of Hygiene and Tropical Medicine (LSHTM) staff on Phase II Ebola Vaccine trials in Sierra Leone and Mwanza, Tanzania.
4.1.2 Immunological studies

4.1.2.1 Malaria

Over the next 5 years, in collaboration with the Wellcome Trust Sanger Institute (WTSI), we will develop chip-based methods for screening several hundred full-length antigens simultaneously [2] and conduct these assessments in a) experimental studies using controlled human malaria infection and b) large multi-centre immuno-epidemiological studies with partners in 13 West and East African sites to provide the largest post-genomic integrated assessment of P. falciparum vaccine candidates to date [3]. We are also studying the acquisition of immunity in children who experience recurrent malaria episodes. We will look for evidence of patterns of cellular activation that reproducibly predicts multiple malaria episodes in different cohorts.

4.1.2.2 HIV

We collaborate with the International AIDS Vaccine Initiative (IAVI) to conduct surveillance for acute HIV infection and seroconversion. We have developed operational and epidemiological surveillance in high-risk cohorts and key populations. We will compare the functional properties of T cells early in infection with the host’s ability to subsequently control virus, and in addition we aim to conduct Phase II HIV vaccine trials with immunological and clinical assessments of response to vaccination.

4.1.3 Post-licensing evaluation

Post-licensing effectiveness studies at population-level offer an opportunity to evaluate herd immunity (which augments the effectiveness of vaccination) and serotype or strain replacement (which may offset early benefits). Our epidemiological surveillance is uniquely well-suited to examine these effects, having demographic surveillance of 280,000 residents with fully linked prospective monitoring of clinic vaccinations, phenotyping of cases and mortality monitoring, and a legacy of 25 years of data and samples to contextualize long-term trends and variations in genotype.

An example evaluation is pneumococcal conjugate vaccine that was introduced into the vaccination schedule in Kenya in 2011 at a cost of £10M per year [4]. Our data on effectiveness and herd immunity demonstrate indirect benefits, supporting assessments of cost effectiveness. We will expand this work to analyse the effectiveness and population-level impact of rotavirus vaccine and other anticipated new vaccinations such as the candidate malaria vaccine RTS, S [6]. We will conduct modelling and cost-effectiveness studies and communicate with policy makers including the Kenya National Immunization Technical Advisory Group.
4.2 Genomics and infectious disease transmission.

Our objectives are to use genomic tools a) to describe the transmission of infectious disease in order to inform infectious outbreak control policy and b) to provide an immediate view of the evolution of resistance to host immunity and drug pressure.

4.2.1 Emerging Infections

We will use our collection of samples to rapidly assemble the epidemiology of infections which have not been well studied, focusing initially on arboviruses; Rift Valley Fever Virus, Dengue, Chikungunya and Zika Virus.

4.2.2 Respiratory Viruses

We will select common respiratory pathogens and undertake detailed analyses of the networks of relatedness of respiratory viruses to determine transmission networks. We will use genomics to infer who infects whom [7]. Studies will be undertaken on fine spatial scales within Kilifi and also national and international scales using samples from 5 African and 2 Asian sites.

4.2.3 Malaria

We will work with WTSI to sequence 1000 falciparum isolates spread through space and time in Kilifi County, to provide a resource for studying local networks of transmission, parasite evolution and genetic variation over 25 years of continuous sampling. We will use this resource to identify the emergence of mutations leading to escape from host immunity, fine-scale transmission dynamics and determinants of pathogenicity.

4.2.4 Host Genomics

We have a major interest in host genetic resistance to malaria (in particular red cell polymorphisms) with a long-standing collaboration with WTSI [8]. We will now investigate the functional significance of mutations in the red cell, their impact on cellular invasion by parasites and their ability to select sub-populations of parasites. These functional studies will bridge the critical gap between genetic associations and knowledge of pathophysiology to inform the design of therapeutic agents. We have previously used Mendelian Randomization to demonstrate that malaria causes bacteraemia [9]. We will now study; a) whether malaria leads to hypertension in later life and b) whether iron status changes the risk of malaria or bacteraemia.

4.2.5 Vector Biology

Our vector biology group is focusing on integrated vector management of anopheles mosquitoes for malaria control on the Coast and other regions of Kenya, operational assessments of insecticide resistance, characterization of residual transmission in areas of high treated bed net use (including examinations of indoor versus outdoor biting and changing species compositions), genomic studies of mosquito evolution during periods of expansion in the use of bed nets and bed net effectiveness work to determine the effect of resistance and outdoor biting on malaria control.
4.3 Clinical Research

Our aim is to answer questions of immediate translational importance, focusing on inpatient care of sick children and neonates. To achieve this, we will operate a “pipeline” approach with progression through a) investigation of pathophysiology and b) early phase clinical trials in preparation for larger trials and c) multi-centre trials to influence policy.

4.3.1 Critical Care

Some of the most common treatments given to critically unwell children admitted to hospital in Africa include fluids, oxygen and blood transfusions. Surprisingly, treatment decisions in these areas are supported by very little clinical trial data.

4.3.1.1 Fluids

We provided the only high quality data on fluid management in large multi-centre trials, showing that fluid boluses increase the mortality of children admitted with fever and shock [10].

In order to generate a new ‘treatment algorithm’ for shock management that would be suitable for further clinical trials, we have an active international collaboration currently studying critical care management in an ovine model of sepsis in Brisbane University.

4.3.1.2 Severe Anaemia

Severe anaemia is a common cause of admission to hospital in Africa. The “TRACT” trial will be used to examine the haematological and mortality outcomes of three different randomizations - i.e. (i) liberal transfusion (30ml/kg whole blood) versus conservative transfusion (20ml/kg) versus no transfusion (control); (ii) post-discharge multi-vitamin multi-mineral supplementation (including folate and iron) versus routine care (folate and iron alone) for 3 months; (iii) post-discharge co-trimoxazole prophylaxis for 3 months versus no prophylaxis.

4.3.1.3 Hypoxia

Oxygen is a basic element of hospital care, but in Africa provision is costly and supplies are inadequate. The “COAST” trial is designed to determine which children would benefit from receiving oxygen and whether there is a benefit from high flow oxygen. We will randomize children in two strata; a) children with mild hypoxia will be randomized to Oxygen or room air; b) children with more severe hypoxia will be randomized to high versus low flow oxygen.

4.3.1.4 Severe Malaria

We have two developing initiatives in the area of severe malaria. We are leading a consortium of clinicians, epidemiologists and trialists to accelerate interventional research on severe malaria including the Malawi and the Thai Wellcome Programmes. In addition, we plan a trial targeting bacterial co-infection in severe malaria (predominantly gram-negative...
bacteraemia including non-typhoidal salmonellae) [11].

4.3.2 Sickle Cell Disease and Blackwater Fever

Approximately 1% of children in East Africa are born with sickle cell disease and 20% have G6PD deficiency. We have registered a cohort of 700 children with sickle cell disease in Kilifi and over 1,000 children are registered in clinics in Mbale, Uganda. A randomized trial on hydroxyurea is underway, recruiting in both Kilifi and Mbale. Black water fever is increasingly recognized in Eastern Uganda as a distinct syndrome and appears to be a recently (re-)emerging condition in Uganda and other parts of Africa. It is characterized by haemolysis, haemaglobinuria and recent malaria infection. We will examine possible aetiologies through case-control and observational haematological studies.

4.3.3 Malnutrition

We are leading an international consortium to study the pathophysiology of acute malnutrition. The network includes Kenya (3 sites), Malawi, Uganda, Bangladesh and Pakistan. We plan to expand this network and conduct clinical trials using mortality as an endpoint and to undertake demographic, clinical, laboratory and social phenotyping to identify potentially modifiable pathways that may prevent mortality [12]. We will conduct studies on interventions to support breast feeding and re-lactation for mothers of wasted young infants admitted to the ward. We will assess the social acceptability and feasibility of a peer-support intervention to promote re-lactation. Based on these data we then apply for funding for definitive multi-centre trials.

4.3.4 Neuro-cognitive Health and Mental Health

We will conduct assessments of the impact of HIV infection or exposure on executive functioning in adolescence, studies of the epidemiology and consequences of seizures and other neurological disorders, including host genetics. We have established a unique position in neuro-cognitive assessments in Africa, having pioneered the use of the Kilifi Development Assessment scale (now used across Africa) [14]. We will develop systematic monitoring of neuro-cognitive outcomes of severe illness.
4.4 Population Health: Malaria, Malnutrition and Mortality

We aim to understand changing epidemiology of malaria, understand the determinants of health transitions and vulnerabilities at fine scales, and to embed the use of data for decision-making by national ministries.

4.4.1 Epidemiology of Malaria in Africa

We established regional leadership in the spatial epidemiology of malaria in 1996. Since 2013, this scientific development has evolved into a programme of support to national governments in the Africa region. Through a consortium including LSHTM, the African Regional Office of the World Health Organization and the Programme we now provide epidemiological support to over 20 sub-Saharan African countries to generate data-driven, geo-spatial profiles to guide malaria control.

Our country-specific epidemiological work is owned by National Ministries and was used by 14 of these Ministries in their applications to fund malaria control. These countries have now attracted almost £1.5B for malaria from the Global Fund, representing a significant return on the programmes scientific investment to African countries over the last five years. We also work on the use of routine data to monitor trends in malaria.

4.4.2 Malaria epidemiology beyond the Africa Region

We provide technical and scientific support the WHO’s Eastern Mediterranean Region (EMR) malaria endemic and eliminating countries, notably Somalia, Sudan, Yemen, Afghanistan and Saudi Arabia. This collaboration aims to unravel the complexities of the malaria transition in the region and the threats posed by conflict, human population movement and vulnerable sectors of society.

4.4.3 Hospital and health service mapping

Universal access is fundamental to health care systems, but many LMICs are unable to map their population’s access to health services. We will create indices for accessibility to hospital care and develop methods for defining catchment areas. We will also develop work on referral to hospital, for instance examining possible interventions in the pathway to hospital care.
4.4.4 Mortality, malnutrition and health vulnerabilities

There has been a sustained decline in child mortality across much of Africa since the 1970s, yet there remains substantial international and subnational variation in the levels and rates of decline. Working with colleagues at the University of Kwa Zulu Natal we will use small area estimation techniques to provide credible estimates of U5M at county levels in Kenya from 1990 to explore the impact of changing malaria parasite prevalence and other factors on child mortality.

We are piloting mapping of malnutrition, providing a basis to expand to international mapping of malnutrition in sub Saharan Africa to begin investigations into broader health vulnerabilities including access to hospital care and socio-economic status. We will develop maps of prevalence of malnutrition, and also of the differing causes of malnutrition by geographical area.

4.5 Health Systems and Research Ethics

Well-functioning health systems are essential to the delivery of a diverse range of current and future health interventions. Our aim is to conduct studies describing means of improving the quality, efficiency and accessibility of health care through studies on health care financing, governance, management, human resources, health information and community perspectives and practice. This theme brings together a multidisciplinary group including clinicians, anthropologists, economists, ethicists, and policy analysts. Our strategy is to conduct both high quality, high impact stand-alone health policy and systems studies, as well as to feed into and value add to multi-disciplinary disease specific studies being conducted across the programme.

4.5.1 Learning Health Systems

“Learning Health Systems” integrate research and evaluation into the structure of health systems with the aim of improving outcomes for patients [16]. Low and middle income countries have the opportunity to leapfrog decades of development by taking advantage of the new digital economy, specifically the rapid introduction of electronic medical record systems. We have developed the critical collaborations with the Kenyan Ministry of Health, Kenyan Paediatric Association and a network of 14 hospitals participating in a clinical information network to support the evolution of a learning health system in Kenya.

We will collect data on 35,000 paediatric admissions and 5,000 neonatal admissions per year across the network. We will improve the design of electronic medical records to allow the data collected by health workers as part of the routine electronic medical record to support research. Our ambition is to nest observational comparative effectiveness studies that will lead rapidly to efficient pragmatic randomized trials within routine healthcare.

4.5.2 Health Economics

We will carry out research aimed at informing policy choices and debates on health systems reforms for Universal Health Coverage (UHC) in Kenya [17]. The Kenyan government has made a commitment to UHC and has initiated health-financing reforms. Programme researchers in health economics have established close working relationships with the Kenyan Ministry of Health to explore key health financing questions aimed at providing the evidence base for policy making for UHC.
4.5.3 Governance under devolution

Working with colleagues in South Africa we have developed an innovative approach to conduct action-orientated health systems research in which health managers at district/county level are active participants in the research [18]. Research findings are fed back to managers and others in the system in real time, and any governance changes made are tracked over time as the system evolves and researchers and managers learn together.

We will scale up this work to three counties across Kenya. This work will continue to offer insights into opportunities and challenges for strengthening health system governance across sub-Saharan Africa.

4.5.4 Case management

We will evaluate the translation of treatment policy into practice and innovative ways to strengthen health systems such as SMS messaging systems to promote adherence to treatment and follow-up.

We will build on our early successes in pragmatic trials on malaria management in Kenya [19] to develop international work including Tanzania and Malawi including other paediatric diseases such as pneumonia and diarrhoea.

4.5.5 Research Ethics

Health systems include research systems, and an important element of this theme will be to explore the ethics and biosocial aspects of research across the programme. Our work informs biomedical research within the programme and supports national and international research ethics discussions that shape the research environment in which we operate.

Research ethics studies cross all other scientific themes and support institutional and (inter)national policy and practice [20]. This support is essential to a programme of our size and reach (including work conducted in MRC Gambia, South Africa, Malawi, Thailand and Vietnam).
5. Developing Themes

5.1 Neonatal health

Government policies are resulting in increasing numbers of mothers delivering in hospital leading to increased neonatal admissions and survival following severe neonatal illness including neonatal ischaemic encephalopathy [13]. The recent identification of an apparently high incidence of microcephaly emphasises the need for clinical and neuro-psychological follow up of neonates.

5.2 Anti-Microbial Resistance

Antibiotic resistance is an increasing problem among children admitted to hospital with malnutrition, and antibiotic stewardship decisions should be guided by evidence. In Kilifi and Nairobi, we are conducting a multi-centre trial to determine the utility of broad spectrum versus standard-of-care antibiotics for children admitted with acute malnutrition. This provides an opportunity to examine initial faecal carriage and prevalence of antibiotic resistant organisms (i.e. coliforms with ESBL) and in admission invasive isolates, and an opportunity to survey this in other trial sites outside Kilifi (i.e. Mombasa, Malawi and Uganda). We plan further studies on alternative antibiotic strategies, particularly for treating ESBL infections in neonates who are at high risk. We have recently begun work on metagenomics surveillance, examining rectal swabs as population surveillance for invasive resistance organisms and on infection prevention and antibiotic stewardship based in Nairobi.

5.3 Biobank

We have 1.2 million biological samples stored from 1989 to 2014, including plasma, DNA, peripheral mononuclear cells, malaria parasites, invasive bacterial isolates, nasopharyngeal fluid and others. An illustration of the utility of the biobank are our developing plans to determine the epidemiology of Zika virus in Kilifi. Our stored samples include DNA from tens of thousands of acute undifferentiated fever cases over 20 years, maternal and foetal cord blood samples from >300 neonates with severe microcephaly and CSF samples from 20 neonates with microcephaly (and matched controls). The biobank will be a strategic resource to rapidly assemble epidemiological profiles of (re)-emerging infections in the future.

The first steps in this developing theme are; a) to undertake community and stakeholder engagement work to establish the feasibility of support for this activity and b) to produce a proposal for the scientific value of our datasets. The former will be led by a Bioethics Fellow (already funded) and the latter led by a Biobank Fellow from a laboratory background using short-term funding, with plans to develop a longer-term funding application.
6. Training and Capacity

Our training strategy is to emphasize the full career path with a progressive and long term outlook in the development of local research leadership. We aim to build a critical mass of African researchers who are technically proficient, able to independently lead internationally competitive science, engage with funders and policy makers and act as supervisors and mentors for the next generation.

Our conceptual framework “Attract, Train and Retain” outlines a systematic approach for enhancing the progression of individuals along the research career path. We will provide 36 attachments and internships per year (including Masters projects from local universities), and recruit from this pool and from external applications to 5 PhD studentships per year. We will support transition from PhD to independent researcher for 2 Early Post-Doctoral researchers per year, and support 4 Mid-Career Fellowships during the next 5 years. A successful outcome will comprise 80% of interns remaining in science at 5 years follow up, 95% of PhD students completing in 3.5 years with 80% of PhD students remaining in science at 5 years and the establishment of a further 5 independent research leaders at 5 years.
7. Public Engagement

Our community engagement strategy includes working with networks of community representatives, programme open days and outreach events. We will enhance ethical aspects of research via training and supporting consenting processes and materials, and provide research feedback to local, national and international health policy makers and stakeholders.

We will strengthen our schools engagement programme in Kilifi and develop engagement in Nairobi with multi-school science competitions; science cafes; attachment schemes; on-line engagement; and school-based research ethics panels to debate contemporary science issues. Participatory video will provide a dynamic means of communicating student views and priorities to researchers, policy makers and research funders.

We will undertake formative assessment and develop a radio programme, including a detailed evaluation of its impact and reach. The radio will communicate on health and science with audience participation.

We will conduct specific engagement around the biobank initiative, including community members, research participants, ethics review committees and researchers to: i) foster learning about key concerns regarding bio-banks; ii) explore community voices in biobank governance; and iii) provide systems for regular feedback to stakeholders and the community on guidelines, policy implementation and activity. Other initiatives will include strengthening the capacity of science journalism, international training for field-workers and developing information films, publications and training curricula to advance the field.
8. References


