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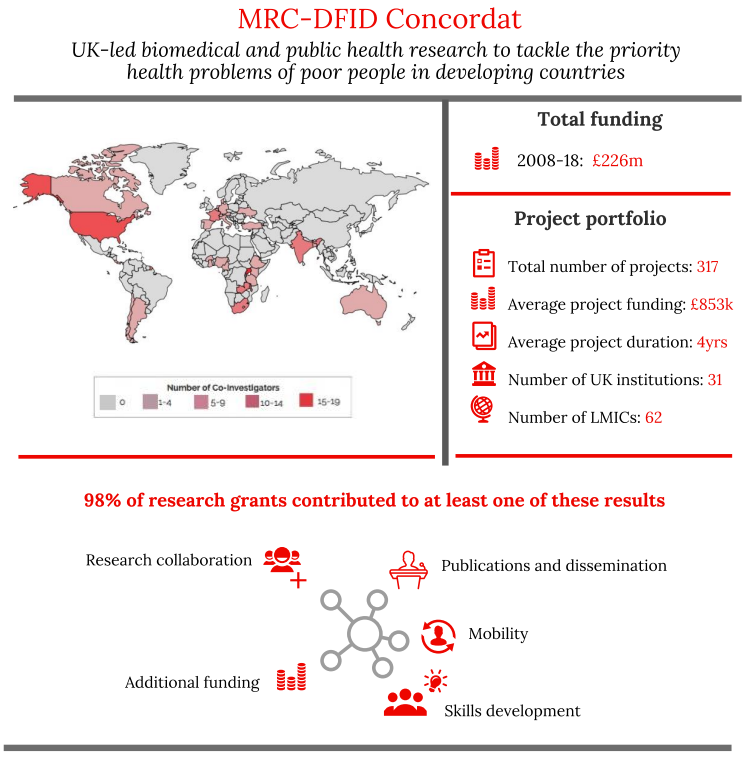
Review of the MRC-DFID Concordat

CASE STUDIES



Appendix C Case studies

C.1 MR/JO12483/1 - Transfusion and Treatment of severe Anaemia in African Children: a randomised controlled trial (TRACT)

C.1.1 Description of the scheme/project/initiative

The project Transfusion and Treatment of severe Anaemia in African Children: a randomised controlled trial (TRACT), was funded by the Concordat grant MR/JO12483/1. It was an MRC Global Health Trial and the total awarded amount was £3,046,319. The study dealt with 3,700 children who suffered from severe anaemia (SA) in a multicentre randomised controlled trial in Uganda and Malawi and the Principal Investigator (PI) was Dr. Kathryn Maitland from Imperial College London.

According to the 2010 Malawi Demographic and Health Survey, Malawi alone has a 63% prevalence of childhood anaemia. [151] In Uganda it is estimated that 50% of children under five years have anaemia.[152] Anaemia is a condition in which the body cannot produce enough healthy red blood cells to carry oxygen to tissues and organs. Consequences of childhood anaemia are poor cognitive development for mild and moderate anaemia and death for severe anaemia.[153] Blood transfusions can be used to rapidly replace the missing blood cells and deter or reduce the consequences of anaemia.

The trial was set up to respond to these poor outcomes of SA, including high rates of in-hospital mortality, 6-month case fatality and chronic morbidity.[154] Factors associated with these outcomes include potentially treatable co-morbidities such as recurrent infection and multiple vitamin deficiencies, which were not addressed in current guidelines.[155] Moreover, existing policies guiding clinical management are in general fragmented, based on weak evidence and often impractical.[156] TRACT is designed to probe each of these contributing factors directly and add to the slim evidence base for blood transfusions in paediatric SA cases.[157]

C.1.2 Mode of implementation

The project started in the first quarter of 2013 and is currently still ongoing, until 2019. For a period of two years, 3,700 African children, aged two months to twelve years, were enrolled at admission in the hospitals and followed for six months after. In order to ensure proper ethical conduct, the researchers created a verbal consent process that was two-staged. Verbal assent was sought from parents or guardians on admittance to the hospital whereas full consent was sought once the child's clinical condition was stabilized.

All involved medical staff was trained on the practicalities of conducting randomised controlled trials and medical doctors were trained on triage. Knowledge sharing took place over the course of the project execution through formal and informal exchanges between the different project members.

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[151] Kazembe, Lawrence and A Ngwira. "Analysis of severity of childhood anaemia in Malwi: A Bayesian ordered categories model." *Journal of Open Acces Medical Statistics*. (2016).

[152] Kuziga, Fiona, Yeka Adoke, and Rhoda K. Wanyenze. "Prevalence and Factors Associated with Anaemia among Children Aged 6 to 59 Months in Namutumba District, Uganda: A Cross- Sectional Study." *BMC Pediatrics* 17 (2017): 25. *PMC*. Web. 5 June 2018.

[153] Kazembe, Lawrence and A Ngwira. "Analysis of severity of childhood anaemia in Malwi: A Bayesian ordered categories model." *Journal of Open Acces Medical Statistics*. (2016).

[154] Calis, Job CJ, et al. "Severe anemia in Malawian children." *New England Journal of Medicine* 358.9 (2008): 888-899.

[155] Ibidem

[156] Mpoya, Ayub, et al. "Transfusion and Treatment of severe anaemia in African children: a study protocol for a randomised controlled trial." *Trials* 16.1 (2015): 593.

[157] Ibidem

Since the results of the research were still under embargo at the time of writing this case study, there are no presentations or publications available on the final results as yet.

In Malawi, there was intensive collaboration between the different actors involved on the ground, such as the researchers from the Malawi Liverpool Wellcome Trust laboratories[158], Malawi blood transfusion services, other medical units outside the paediatric unit at the Queen Elisabeth Hospital, and the scientific team. This type of inter-organisational collaboration focused on Malawi only, while international collaboration engaged the different members of the project team in Malawi, Uganda, the UK and the Netherlands.

C.1.3 Main achievements, results of the project (so far) and expected impact

To appraise the achievements and expected impacts of the TRACT project it is necessary to distinguish between the different objectives of the project.

Scientific results

Although the results are not yet known, whatever the final results will be, they will be able to inform policies and guidelines by attending conferences and getting in touch with the WHO on how to use blood transfusion in treating children suffering from SA. Namely, if the intervention shows that following current WHO guidelines yields the best results for patients, it would imply that they have to keep blood for the very sick only but stick to the current conservative transfusion guidelines. If, the intervention approach of administrating blood transfusion in a more liberal manner and with follow-up multi-vitamin and mineral treatment will prove more successful, policy and guidelines should be changed, and more blood should be collected. This would in the long run improve the treatment of patients. In either case, this project significantly broadens the scientific evidence base on how to treat SA and what the effects are of blood transfusions in children. The high relevance of the project was one of the features that was reiterated throughout interviews with co-investigators and local staff as rendering the project a scientific success.

Results for participants

On the patient-level, participants received good care, better than other patients outside of study would receive, due to the additional resources availability. Some of the co-investigators indicated that there were children who received blood that would otherwise not have been made available to them. As such, participating children had a much better chance of survival. The emphasis on a well-informed consent and the study having as few exclusion criteria as possible, made the study inclusive to many children with SA.

Results concerning research capacity

On a very practical level, the skills and procedures pertaining to the labelling of blood and subsequent transfusion were also improved both in the participating clinics and hospitals in Uganda and Malawi. In Uganda blood was initially not or poorly labelled. According to the PI , this procedure was improved after a presentation for the Ugandan Medical Conference, also beyond the participating clinics and hospitals.

Regarding research capacity, there were a number of different outcomes and achievements. The interviewed co-investigators were in agreement about the added value of the study for their own career development. They identified different pathways of impact for personal capacity building. The first one was through interaction with the PI throughout the implementation of the project, including the discussions on the study design, responding to impromptu challenges and in the general running the trial. A second pathway was through collaboration with the PI on (upcoming) scientific peer-reviewed

[158] The MLW Trust is an affiliate of the Malawian College of Medicine. It has a Memorandum of Understanding with the University of Liverpool and the Liverpool School of Tropical Medicine.

publications and presentations at conferences. One of the five co-investigators was made full professor on the basis of the published works related to the research project.

Research capacity development is also apparent for support staff. Nurses in Malawi and Uganda were trained to improve their skills set, including medical training as well as training on documenting project results and research management. As a result, they were asked to participate in other (RCT) studies at the clinics and hospitals where they were working. In Malawi, medical students were trained in the hospital where the trial took place, so there is a potential for further knowledge transfer to a new generation of physicians once the results of the study are made available.

Results concerning policies, follow-up studies

Once the results are finalised there is a possibility that they will be included in new guidelines and standards. Dissemination of the results is already under preparation through session organised on how best to communicate the findings, engage with the WHO and attend large paediatrics conferences.

The co-investigators are also in the process of identifying follow-up studies from the TRACT project. However, this has only recently been set into motion as the project is still ongoing.

C.1.4 Lessons learnt

Co-investigators were in overall agreement that the project had run smoothly and collaboration between the members of the project team had gone well. The scientific relevance of the project was repeatedly cited as an important success factor as it was relatively easy to mobilise support internally at the clinic sites and with crucial partners such as laboratories and blood banks. Another enabling factor was that the management/organisation of the study was done professionally; all resources came in on time: money, medicines, blood, lab results, etc. Good communication and onboarding staff from the start were considered factors that benefited the project.

At the same time interviewees identified a few points of improvement, especially concerning the sustainability of the achievements. These concerns pertained most namely to the development of local research capacity. Although co-investigators did gain new skills and knowledge, the level of involvement in research design and subsequent capacity to carry out similar studies (more) independently remained limited. An unforeseen change in the PI in Malawi also meant that at a certain point there was a lack of ownership over the study design and implementation which, despite not compromising the project scientifically, did result in a large budget overrun in Malawi.[159]

C.1.5 Transferability of the scheme

The trial was unique in the way it dealt with a difficult issue with a relatively small existing evidence base and used a complex approach of a multi-centre randomised controlled trial. This elevates both the relevance of the study as well as the robustness of the findings, and thus serves as an example for future studies. Moreover, the development of a well-informed consent process is also notable as the study included children and posed an alternative treatment to an otherwise standard and regular treatment. As such, the consent process had to be of high standards in order to avoid ethical missteps.

Two key recommendations surfaced from the interviews with the different stakeholders. First of all, that there is a need to involve local investigators[160] as PIs from the start of projects to ensure sustainable local capacity building and execution of the projects. Secondly, more attention should be paid to policy follow-up by both the research team and the funder. Part of the grant should be allocated towards

[159] This had less impact on the research process in Uganda.

[160] By 'local' interviewees meant researchers who worked and lived for a long period of time in the host-country. As a rule of thumb one could consider a criterion of paying taxes in the host-country to be qualified as a 'local' researcher.

sharing the results and ensuring engagement with policymakers. Although this engagement has been set in motion in the project, this could be more heavily embedded in the requirements of the grant

C.2 MR/L002515/1 Lung health and exposure to household air pollution in rural Malawi (CAPS)

C.2.1 Description and relevance of the scheme/project/initiative

The MRC-DFID Concordat Grant MRL25151 on Lung Health in Malawi (484,680 GBP) was a young investigator grant that provided protected time for the Principal Investigator, Dr Kevin Mortimer at the Liverpool School of Tropical Medicine, to dedicate his time to the larger MRC-Wellcome Trust Joint Global Health Trial project Cook stoves and Pneumonia (CAPS). Since these were essentially twin grants, and have resulted in a single big research project, we will describe here the overall impact of the project, henceforth referred to as CAPS, drawing out specific impact of the support grant where relevant. The CAPS project aimed to address the lack of systematic evidence regarding the relationship between smoke and childhood pneumonia. Childhood pneumonia is among the major causes of childhood morbidity in developing countries[161], and exposure to household air pollution, mainly from cooking, was often assumed to be a major driver. This assumption was one of the main reasons behind the global investment in 'clean cook stoves', which reduce smoke and hazardous gasses. The CAPS study aimed to investigate this assumption through a randomised control trial in Malawi, building on insights from respiration science as well as more sociological studies.

In terms of local relevance of these activities, it is clear that pneumonia is recognised as a major burden of childhood disease in Malawi and similar developing countries[162]. However, it should be noted that some local study participants, as reported in a focus group with field officers, felt that the study did not address their health priorities (which were hernias and elephantiasis), nor was the local population consulted on the study design. The importance of clean cook stoves in Malawi is evidenced by the creation of a government appointed task force for the introduction of clean cook stoves and partners such as the Global Alliance for Clean Cook stoves who promotes the use of these cook stoves, not only for health reasons but also because of reduced fuel consumptions (helping to combat deforestation)

C.2.2 Mode of implementation

The project was implemented as an exposure-incidence study by randomly distributing clean cook stoves in rural Malawi. The main study group focused on children up to five year of age, across 52 villages in the Chikwawa and Karonga districts in rural Malawi. The goal was to determine whether the reduced exposure to open fire thanks to the cleaner cook stoves would result in lower incidence and mortality due to pneumonia. The project used modern electronic data collection tools. The project worked closely with the government health services in these districts to ensure the follow-up of patients. The main trial data collection took two years (2014-2016), with regular follow-up by field officers every three months, to prevent the common reversion to traditional cooking methods seen with clean cook stove projects. The project team existed of the PI (remote, based in Kenya), a research manager (in Malawi) and a team of field research officers and support staff. The project appointed an advisory board that included representatives from the Ministry of Health, and local healthcare research partners (Malawi-Liverpool Wellcome (MLW) Trust in particular) and the KPS (Karonga Prevention Study), which were all collaborators on the study. The main study was complemented by a cross-sectional support study among adults to determine the prevalence of obstructive lung disease in adults in the same grant.

A particularly noteworthy aspect of the project was its strong focus on community engagement and science communication, supported through the local science communication team of MLW. All villages

[161] http://www.who.int/features/2013/malawi_pneumonia_diarrhoea/en/

[162] Ibidem

appointed a local advisory group, and the field officers ensured proper consent of village and household heads before engaging the women in the studies.

C.2.3 Main achievements, results of the project (so far) and expected impact

The main impact pathway of the project was to contribute to more effective policy making and reduced childhood mortality through improved scientific insight into the relationship between smoke and pneumonia. Secondary benefits were sought in the area of capacity building, and direct benefits to the study population.

In terms of scientific and policy impact, the study had the unexpected result that no link was found between household smoke and pneumonia. These significant results were published in the Lancet peer reviewed journal, and have strongly boosted Dr Mortimer's career, who now leads a small team at LSTM and has won several subsequent grants (MRC JRF, NHI Global Health) to engage in new, larger studies in the field of lung health. He was also invited into the editorial board for several leading journals. The findings benefitted from attention from major media outlets (BBC[163], The Economist[164]), and have caused a renewed debate into the value of global investment in cook stoves as evidenced by the discussions in these articles. Academically, the new debate is moving towards a more holistic investigation of smoke and air pollution and the relationship with lung health, moving away from cooking only[165]. In terms of policy, the results of the study were integrated into the WHO Guideline for Indoor Air Quality. Currently, the policy direction of the MoH and the Global Clean Cook Stove alliance has not changed in a major way, as they are repositioning the benefit claims towards reduced fuel consumption. However, it is likely that this project has contributed to preventing a potentially large opportunity cost of misdirected public investment.

In terms of capacity building, the project had a significant impact on the team members involved in Malawi. A number of field officers (at least two out of 20) followed a Bachelor course, funded through the programme, while the others received other types of training. All medical staff involved in the project were also trained to improve their lung function evaluation skills. Senior members of the local team saw their career take off with international and national opportunities in research management. Training was also provided to local community members, and local field officers indicate that the local population in the target districts have become more supportive of research in general, possibly benefitting future studies. However, capacity building was less developed in terms of local research capacity. No local researchers were involved in the design, implementation and analysis of the study which were carried out at LSTM, and as such the project had only indirect effect on the Malawian health research capacity, i.e. exclusively on research support functions.

In terms of direct health benefits, the target population benefitted from improved access to medication during the trials, which is otherwise often problematic in Malawi. Furthermore, participating villages benefitted from the access to the cook stoves (the control group was also given a unit at the end of the study), which has other benefits such as fuel savings and reduced burns. However, since no local suppliers exist for cook stoves nor their parts, the sustainability of the latter benefit is minimal.

C.2.4 Lessons learnt, changes over time

Key success factors for this project included the very strong local research support capabilities of MLW and KPS, with a strong presence of field offices and good relationships with local populations. Furthermore, a highly developed science communication strategy ensured high-quality implementation of the project and a positive outlook of the local participants towards science. The science communication team of MLW is currently organising screenings of a movie that showcases the results

[163] https://www.bbc.co.uk/news/magazine-38160671

[164] https://www.economist.com/international/2018/04/05/household-smoke-may-be-the-worlds-deadliest-environmental-hazard

[165] http://www.environment-health.ac.uk/news/professor-majid-ezzati-editorial-lancet-do-smoke-free-stoves-really-save-lives

of the trials in each of the 52 villages. Another key success factor was the attitude of the MRC-DFID Concordat fund management, which was relatively light touch, allowing the scientists to focus on their research due to the low administrative burdens.

Key barriers during the trial included ensuring the continued use of the cook stoves by the trial population, as women sometimes find them unpractical, or they might break down and no spare parts are available. This challenge was addressed through improved training of the local population. Field officers noted the difficulties in mobilising women to use the cook stoves without compensation, and the solution which was found (giving T-shirts) was in hindsight not considered an appropriate gift by the target population (they do not need these). Finally, a key barrier was the lack of initial engagement with the MLW due to the limited local senior presence of the study in Malawi.

Sustainability of the project is likely to be high in terms of the academic follow-up, with major studies already underway. Policy-wise, the follow-up is less certain as there is no systematic engagement from the study team with policy makers post-project. The extent of local health benefits due to the cook stoves, training and medicine received, is likely to be very limited. In terms of capacity building, the local research support staff all managed to find relevant further positions, showing good sustainability for these results.

C.2.5 Transferability of the scheme

The transferability of the study approach is high in terms of the way the project dealt with community engagement and science communication. Working with an established centre like MLW, using good research support facilities, are other positive lessons.

C.2.6 Suggestions, recommendations

Increasing the local research involvement at a more senior level for large trial studies could ensure smoother engagement and increased capacity building. More intensive training of participating government health staff in terms of Good Clinical Practise could have been also helpful to ensure lower drop-out rates and higher consistency of care during the trial. Furthermore, more attention could be paid by the research designers to the sustainability of the local health interventions (e.g. better to use locally produced/available cook stoves, as was initially proposed in the proposal).

C.3 MR/L004623/1- MRC/UVRI Uganda Research Unit on AIDS - Mental health among HIV infected CHildren and Adolescents in KAmpala, Uganda (CHAKA) - African Research Leader Award

C.3.1 Description of the scheme/project/initiative

This case study describes the impact achieved by projects supported by the Concordat grant MR/L004623/1- MRC/UVRI to the Uganda Research Unit on AIDS. The grant (£706,133), an African Research Leadership award was given to Prof Kinyanda to support research done on mental health among HIV infected children and adolescents in Kampala, Uganda (CHAKA). The research built on the result generated by predecessor MRC funded projects in Uganda. The study was carried out with a lead PI, Prof Patel from the London School of Hygiene & Tropical Medicine, between 2014 to 2017. The project sought to investigate the impact of Psychiatric Disorders (PD) on HIV infected children and adolescents in Uganda and the implications for service provision. Studies have shown that PD is an issue with children and adolescents infected with HIV,[166] however, few of such Psychiatric studies have been conducted in Africa.[167] The CHAKA study was one of the first of its kind, dealing with children and

[166] Mellins CA, Malee KM. Understanding the mental health of youth living with perinatal HIV infection: lessons learned and current challenges. J Int AIDS Soc. 2013;16:18593. doi: 10.7448/IAS.16.1.18593.

[167] Erica Breuer, Landon Myer, Helen Struthers & John A Joska (2011) HIV/AIDS and mental health research in sub-Saharan Africa: a systematic review, African Journal of AIDS Research, 10:2, 101-122, DOI: 10.2989/16085906.2011.593373

adolescents, HIV and mental health in Uganda. The study addressed gaps in terms of knowledge deficiency and provided funding for areas where there was a need for certain expertise such as psychiatric epidemiology, psychiatric genetics as well as knowledge of qualitative research methodology in mental health. It comprised of epidemiologic, genetic and qualitative components with the objectives to:

- Determine the prevalence, 12-month incidence and predictors of PD (including neurocognitive impairment) among HIV infected children and adolescents
- Investigate the relationship between differences in the serotonin transporter gene and depressive disorder
- Examine the impact of PD on HIV disease progression
- Examine the impact of PD on social and academic functioning and risky behaviours (i.e. treatment adherence, alcohol use, sexual behaviour and suicidal behaviour)
- Investigate help-seeking behaviour and identify service delivery gaps in Ugandan HIV services.[168]

C.3.2 Mode of implementation

The project was one of the first longitudinal studies that have been conducted in Uganda and Sub-Saharan Africa, on the impact of Psychiatric Disorders on HIV disease progression in 1339 HIV infected children and their caregivers. During the three years of the study, data was collected at baseline, six and 12-months. The study collaborated with local institutions, Mbarara University and Kyambogo University in Uganda. It also benefitted from international collaborations through the involvement of Prof Kenneth D. Gadow from Stony Brook University, USA, who is a renowned researcher in the study field and provided the child and adolescent symptom Inventory-5 (CASI-5) to assess psychiatric disorders. The inventory was adapted for use in Uganda for the study. Furthermore, the ARL through the study collaborated with research partners from Norway, India, Ghana and South Africa.

C.3.3 Main achievements, results of the project (so far) and expected impact

Scientific results

The main impacts of this grant so far have been in the academic sector, informing and contributing to future research through scientific publications. The members of the international study team are writing articles169 to publish, and the study has also served as a basis for further studies of its kind. Four publications in peer reviewed journals have resulted from the study. The ARL has gone ahead to publish nine papers, out of which eight are under review, and one is submitted to date.

Another member of the study team has submitted a publication to BMC psychology as first author, got trained in behaviour activation programme as a result of working on the CHAKA study and is now using this in the management of depression in adults.

There was also a significant progression from presenting at conferences locally, to regionally and internationally over the years, including a presentation at the 28th World Congress of the International Association of Suicide prevention in Montreal Canada, June 2015; 8th Annual Pan-African PCAF Psychotrauma Conference, Nairobi, July 2015; the Africa- Norwegian Mental Health Research Group workshop at Ghana university, November 2015; 6th Annual Malawi Mental Health Research and Practice Development Conference, College of Medicine, University of Malawi, March 2016.

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[168] UK research and innovation- http://gtr.ukri.org/projects?ref=MR%2FL004623%2F1

[169] For example: Kinyanda E, Nakasujja N, Levin J, Birabwa H, Mpango R, Grosskurth H, Seedat S, Patel V. Major depressive disorder and suicidality in early HIV infection and its association with risk factors and negative outcomes as seen in semi-urban and rural Uganda. J Affect Disord. 2017 Apr 1;212:117-127

Results for participants

The research was regarded as beneficial and would for the first time lead the way for a comprehensive psychosocial management of emotional and behavioural problems in children affected by or infected with HIV in Uganda. The qualitative research revealed that care givers with HIV and their infected children could support each other and this was suggested as a possible form of social support that could be built on and explored further.

Results concerning research capacity

The profile of mental health research at the MRC/UVRI research unit on AIDS has been raised as a result of this funding. The MRC/UVRI has for the first time included funding for mental health in its next quinquennial review period (2017-2022) to the established mental health research group. This includes salary support for five years for the ARL and research funding for two pilot studies that are expected to lead to future clinical trials applications. The ARL grant enabled the provision of support to two PhD students and to one Master's student as well as the supervision of eight research assistants under the CHAKA study. One of the PhDs and the Master's degree student have finished their studies and both are engaged in different research work. The ARL, Prof Kinyanda has been promoted to Senior Scientist and is now on the research leader track with the MRC.

Results concerning policies, follow-up studies

The CHAKA study has contributed to the child mental health policy that is already being used in the country. The Ministry of Health of Uganda launched the Child and Adolescent Mental Health Policy Guidelines at the 2nd Annual Ugandan Conference of Child and Adolescent Mental Health that was held in March 2017. Furthermore, there is now a plan to develop an intervention as a result of the study with plans to implement and integrate it into the Uganda Health system in the future. This formative work for intervention is using the same contacts and networks and collaborators to go to next level. The research team from the study are now working on another study and their capacity to deliver results has improved from the experience of working on CHAKA.

The ARL successfully applied for a Senior Fellowship in Public Health and Tropical Medicine from the Wellcome Trust to undertake a study entitled, 'Integrating the management of depression into routine HIV care in Uganda (the HIV+D trial)' worth 2.02 million pounds for 5 years and is the first Ugandan to get such an award. In this new ongoing study, the research team is working to make sure that interventions are in line with polices and programme from the Ministry of Health.

C.3.4 Lessons learnt, changes over time

The African Leadership award is considered a prestigious scheme, which provides sufficient funding for the research that was envisaged. It allowed the awardee dedicated time to undertake research. Having an encouraging mentor, Prof Patel from LSHTM and a well written proposal were positive elements that helped guide the study. Working within the research environment of MRC/URVI was regarded as conducive as it already had certain structures in place such as financial, accounting, procurement, storage services that could be used.

One of the main challenges cited was the fact that the funding lasted for two years only, which was a bit rushed especially when taking into consideration the duration for PhD studies and the much-needed funding for their projects. Another challenge was that funds specifically for capacity building were not included in the proposal by the ARL. The timetable of two years for the study was set by the ARL and the research team in spite of the MRC/DFID allowing for a period of up to five years for the grant. It is however a lesson learned and more study time and stronger inclusion of capacity building elements would be included in any future grant applications.

C.3.5 Suggestions, recommendations

Overall the study was a pioneer study on mental health among adolescents and children. This African Research Leader award demonstrated that in addition to supporting the ARL a broad range of impacts can be delivered. The project contributed to the body of knowledge in mental health in children, established strong international networks, built the capacity of other African scientists and served as the basis for other studies in future. As a future suggestion, the provision of a wider range of schemes that would address early career and intermediate level researchers to develop their research capacity would be very helpful to have.

C.4 Developing methods to assess the impact of malaria interventions upon transmission and the progress towards elimination

C.4.1 Description of the scheme/project/initiative

Malaria is a major cause of morbidity and mortality in Kenya with over 70 per cent of the population at risk of infection.[170] Areas in Western Kenya around Lake Victoria and the coast present the highest risk, and children less than 5 years of age and pregnant women are most susceptible to infection. A study using data from 2012 to 2013 in Kisumu County found the prevalence of malaria in adults to be 28 per cent, with women being 50 per cent more likely to have malaria than men.[171] Since 2012, the WHO has recommended the use of insecticide-treated nets and intermittent preventive treatment in pregnancy.[172] Measuring progress towards elimination requires an estimate of the reduction in transmission that has occurred over time. Mathematical modelling in infectious diseases provides a framework for understanding the dynamics of disease transmission.[173] With the advent of new treatment options and control strategies, and concerns of climate change, mathematical models are necessary to better understand the impact of these factors on malaria epidemiology and transmission.

This case study[174] describes the impact achieved by projects supported by the Concordat fellowship MR/L012189/1 (£299,834) - *Developing methods to assess the impact of malaria interventions upon transmission and the progress towards elimination*, awarded in 2013, to Dr Patrick Walker, an infectious disease epidemiologist whose work is focused on conducting mathematical modelling of malaria in view of informing control and prevention strategies in various settings.

Using available data gathered by the Kenya Medical Research Institute (KEMRI) and the U.S. Centers for Disease Control and Prevention (CDC)'s Research Centre in Kisumu, Dr Walker was able to build and calibrate models of malaria transmission accounting for local ecology and epidemiology in Western Kenya and integrate interventions aimed at curbing malaria transmission. The models capture the progress being made by various control strategies as well as informing on optimal combinations of interventions in the region.

C.4.2 Mode of implementation

The mathematical modelling studies undertaken by Dr Walker allowed estimation of the control strategies required to achieve elimination in an area of intense transmission with high long-lasting

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[170] Republic of Kenya Ministry of Health.2016. *Kenya. Malaria Indicator Survey 2015. National Malaria Control Programme*.. Nairobi: Ministry of Health. accessed June 6, 2018. https://dhsprogram.com/pubs/pdf/MIS22/MIS22.pdf.

[171] Jenkins, Rachel, Raymond Omollo, Michael Ongecha, Peter Sifuna, Caleb Othieno, Linnet Ongeri, James Kingora, and Bernhards Ogutu. 2015. "Prevalence of Malaria Parasites in Adults and Its Determinants in Malaria Endemic Area of Kisumu County, Kenya." *Malaria Journal* 14: 263. https://doi.org/10.1186/s12936-015-0781-5.

[172] World Health Organization Global Malaria Programme. 2012. *Intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP): updated WHO Policy recommendation*. 2012. Accessed June 6, 2018. http://www.who.int/malaria/iptp_sp_updated_policy_recommendation_en_102012.pdf?ua=1.

[173] Antao, Tiago, and Ian M. Hastings. 2011. "ogaraK: A Population Genetics Simulator for Malaria". *Bioinformatics* 27, no. 9: 1335–36. https://doi.org/10.1093/bioinformatics/btr139.

[174] The case study relies on experiences shared by six researchers who are familiar with the projects supported by the Concordat grant MR/L012189/1 and is supported by additional desk research. For purposes of respecting informed consent, individuals and their organisations are not named.

insecticidal nets coverage. It provided insights into the effects of insecticide-treated nets and estimated the impact of different control strategies involving mass administration of artemisinin combination therapy on transmission.

Dr Walker continues to develop his model in collaboration with the KEMRI/CDC Research Centre which houses researchers from KEMRI, CDC, and the Liverpool School of Tropical Medicine (LSTM). In particular, Dr Walker is working closely with Professor Feiko ter Kuile head of the Malaria in Pregnancy Consortium based in Kisumu.

The MRC-DFID Concordat offers a three-year fellowship with the benefit of flexibility allowed in managing the research. This administering enables grant holders to engage in dissemination and networking activities, which were highlighted as important enablers to both personal development and achieving research impact. This flexibility allowed Dr Walker to respond to the Ebola crisis, studying the effects of the outbreak on health systems and how this affected malaria prevalence, and evaluating the effect of mitigation strategies developed by the WHO Global Malaria Programme in response to the Ebola outbreak.[175]

The fellowship provided opportunities for Dr Walker to engage with important actors in malaria research and policy. Dissemination activities allowed interactions with the U.S. CDC, the WHO and the Program for Appropriate Technology in Health (PATH) as well as representatives from the national malaria control programmes from Kenya, Zambia, El Salvador, Gambia and Senegal.

C.4.3 Main achievements, results of the project (so far) and expected impact

Scientific results

Dr Walker's research used a combination of data analysis and mathematical modelling to evaluate the impact of a variety of strategies on the prevalence, incidence, and elimination of malaria. Studies focused on the sensitivity of available diagnostic tests at detecting malaria infection and how by increasing sensitivity, these could contribute to improving the prospect of malaria elimination through test-and-treat strategies.[176,177] A separate study explored data obtained from six cohort studies in West Africa and an individual-based malaria transmission model to evaluate seasonality, transmission intensity, and the interval between malaria episodes as factors influencing the success of post-treatment prophylaxis.[178] Results suggested seasonality and the overall intensity of transmission should be considered when deciding between artemisinin-based combination therapies. Further work focused on estimating the efficiency of malaria interventions at reducing malaria burden and transmission, and found that an initial intervention consisting of long-lasting insecticide-treated nets, followed by seasonal malaria chemoprevention or indoor residual spraying, was generally the most cost-effective intervention. [179]

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[175] Walker, Patrick G. T., Michael T. White, Jamie T. Griffin, Alison Reynolds, Neil M. Ferguson, and Azra C. Ghani. 2015. "Malaria Morbidity and Mortality in Ebola-Affected Countries Caused by Decreased Health-Care Capacity, and the Potential Effect of Mitigation Strategies: A Modelling Analysis." *The Lancet. Infectious Diseases* 15, no. 7: 825–32. https://doi.org/10.1016/S1473-3099(15)70124-6.

[176] Slater, Hannah C., Amanda Ross, André Lin Ouédraogo, Lisa J. White, Chea Nguon, Patrick G. T. Walker, Pengby Ngor, et al. 2015. "Assessing the Impact of Next-Generation Rapid Diagnostic Tests on Plasmodium Falciparum Malaria Elimination Strategies". *Nature* 528, no. 7580: S94–101. https://doi.org/10.1038/nature16040.

[177] Wu, Lindsey, Lotus L. van den Hoogen, Hannah Slater, Patrick G. T. Walker, Azra C. Ghani, Chris J. Drakeley, and Lucy C. Okell. 2015. "Comparison of Diagnostics for the Detection of Asymptomatic Plasmodium Falciparum Infections to Inform Control and Elimination Strategies". *Nature* 528, no. 7580: S86–93. https://doi.org/10.1038/nature16039.

[178] Cairns, Matthew E., Patrick G. T. Walker, Lucy C. Okell, Jamie T. Griffin, Tini Garske, Kwaku Poku Asante, Seth Owusu-Agyei, et al. 2015. "Seasonality in Malaria Transmission: Implications for Case-Management with Long-Acting Artemisinin Combination Therapy in Sub-Saharan Africa". *Malaria Journal* 14: 321. https://doi.org/10.1186/s12936-015-0839-4.

[179] Walker, Patrick G. T., Jamie T. Griffin, Neil M. Ferguson, and Azra C. Ghani. 2016. "Estimating the Most Efficient Allocation of Interventions to Achieve Reductions in Plasmodium Falciparum Malaria Burden and Transmission in Africa: A Modelling Study." *The Lancet. Global Health* 4, no. 7: e474–484. https://doi.org/10.1016/S2214-109X(16)30073-0.

Research also focused on modelling malaria in pregnancy.[180,181] This work combined maps of the current risk of malaria in pregnancy with maps of the level of drug resistance across Africa to estimate the impact of scaling up intermittent preventive treatment of malaria in pregnancy, and found evidence supporting preventive treatment in pregnancy. The cost-effectiveness of introducing the RTS,S[182] malaria vaccine in sub-Saharan Africa in addition to existing interventions was also investigated.[183] Results showed that implementing the RTS,S malaria vaccine was only optimal once very high coverage of the existing interventions had been achieved.

In the duration of this fellowship, the Ebola crisis in West Africa occurred, which overwhelmed healthcare systems in the affected countries from 2014. During this time, Dr Walker focused his work temporarily on the impact of decreased healthcare capacity and mitigation strategies on malaria as a result of the Ebola outbreak.[184,185] Dr. Walker estimated the number of cases and deaths due to malaria, and estimated additional deaths caused by reduced healthcare capacity as a result of the Ebola outbreak. Results showed that reduced healthcare capacity led to a higher number of untreated cases of malaria, which likely contributed to morbidity during the Ebola crisis. This burden could have been mitigated by mass drug administration, reducing the number of non-Ebola fever cases within healthcare systems.

Overall, the fellowship allowed Dr Walker to contribute to 12 publications with the majority of them being published in high impact journals such as the Lancet Global Health, Nature, the Lancet Infectious Diseases and PLoS Medicine.[186]

Results concerning research capacity

The research undertaken by Dr Walker has brought about benefits to the malaria research field and in particular to the West Kenyan setting, and has helped researchers at the KEMRI/CDC Research Centre by informing their thinking around the type and combination of interventions that would be most promising to curb transmission. This allowed these researchers to formulate successful proposals for further funding into malaria transmission, including the Joint Global Health Trial Scheme and the European and Developing Countries Clinical Trials Partnership (EDCTP) for work on large-scale trials expected to have important policy impacts.

Dr Walker was able to attract further funding from PATH's Innovation Fund to investigate changes in transmission of malaria in pregnant women attending antenatal services and the effect of various interventions aimed at limiting transmission in this population.

Dr Walker was also asked to deliver a short course to PATH on the basics of malaria modelling and was able to obtain funding for one of his collaborators in Western Kenya to attend a course on mathematical modelling at Imperial College London. Dr Walker's presence at the Research Centre in Kisumu facilitated other junior African researchers to become better acquainted with modelling, which is important as there are few Kenyan statisticians or mathematicians engaged in research.

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[180] Walker, Patrick G. T., Jessica Floyd, Feiko Ter Kuile, and Matt Cairns. 2017. "Estimated Impact on Birth Weight of Scaling up Intermittent Preventive Treatment of Malaria in Pregnancy given Sulphadoxine-Pyrimethamine Resistance in Africa: A Mathematical Model". *PLoS Medicine* 14, no. 2: e1002243. https://doi.org/10.1371/journal.pmed.1002243.

[181] Walker, Patrick G. T., and Matt Cairns. 2015. "Value of Additional Chemotherapy for Malaria in Pregnancy". *The Lancet. Global Health* 3, no 3: e116-117. https://doi.org/10.1016/S2214-109X(15)70081-1.

[182] RTS,S is a scientific name and represents the vaccine's composition, http://www.malariavaccine.org/files/MVI-GSK-FAQ-FINAL-web.pdf

[183] Winskill, Peter, Patrick Gt Walker, Jamie T. Griffin, and Azra C. Ghani. 2017. "Modelling the Cost-Effectiveness of Introducing the RTS,S Malaria Vaccine Relative to Scaling up Other Malaria Interventions in Sub-Saharan Africa". *BMJ Global Health* 2, no. 1: e000090. http://dx.doi.org/10.1136/bmjgh-2016-000090.

[184] Walker, Patrick G. T., Michael T. White, Jamie T. Griffin, Alison Reynolds, Neil M. Ferguson, and Azra C. Ghani. 2015. "Malaria Morbidity and Mortality in Ebola-Affected Countries Caused by Decreased Health-Care Capacity, and the Potential Effect of Mitigation Strategies: A Modelling Analysis". *The Lancet. Infectious Diseases* 15, no. 7: 825–32. https://doi.org/10.1016/S1473-3099(15)70124-6.

[185] Ghani, Azra C., and Patrick G. Walker. 2016. "Provision of Malaria Treatment for Ebola Case Contacts". *The Lancet. Infectious Diseases* 16, no. 4: 391–92. https://doi.org/10.1016/S1473-3099(15)00481-8

[186] Researchfish Data for the Concordat from 2003 until 2017

Results concerning policies, follow-up studies

Dr Walker has been able to engage with policy actors at national, regional and global levels. While direct policy impact is yet to be achieved, it has helped inform policy discussions and contributed to the wider evidence base. Participation in events such as the WHO Evidence Review Committee has been highlighted as important as in many countries national malaria policies are adapted from WHO recommendations.

C.4.4 Lessons learnt, changes over time

The data available through the KEMRI/CDC Research Centre allowed Dr Walker to rapidly build and calibrate the model. The close engagement with key scientific leaders in the field facilitated dynamic exchanges which helped researchers in Kisumu avoid research into interventions that would not have the desired benefits. The engagement with the KEMRI/CDC Research Centre also enabled interactions with the representatives of the Kenyan Malaria Control Programme. The collaboration with Prof ter Kuile and the Malaria in Pregnancy Consortium led to attending WHO Evidence Review Committee meetings on the updating of WHO's "Malaria in Pregnancy Guidelines" and delivering a presentation to CDC staff.

Due to the nature of the work, there were no major barriers highlighted in undertaking the research. In view of implementing the combination of suggested interventions predicted to have greatest impact some barriers to implementation could be related to the associated costs and the willingness from policymakers to implement.

Both the grant application process and the Researchfish reporting were perceived as valuable and positive experiences. In particular it was appreciated that Researchfish captures a range of activities including the ones pertaining to dissemination.

The results have already informed additional interventional research projects led by Prof ter Kuile and allowed Dr Walker to undertake follow-on research on transmission of malaria in pregnant women attending antenatal services. Engaging with the WHO, the U.S. CDC, the Malaria in Pregnancy Consortium and various representatives of malaria national programmes in a range of African countries represent meaningful milestones towards policy change.

C.4.5 Transferability of the scheme

Mathematical modelling is a highly specialised and relatively new field when compared to traditional epidemiology. The models that have been developed can be transformed and adapted to the ecology and epidemiology of different settings; however, this research endeavour is dependent on a skilled modeller.

C.4.6 Suggestions, recommendations

This case study describes how a Concordat fellowship led to research findings which directly informed interventional research avenues, while contributing to the recipient's career development.

Analysis of the case study suggests the following recommendations:

- Maintain the flexibility in administering the fellowship funds by the recipient.
- In view of helping with translating research findings and engaging with policymakers there could be an opportunity for DFID to become more engaged and potentially help organise workshops for program managers from various institutions to discuss use of evidence in policy.
- With regards to the Joint Global Health Trials, there were suggestions to specify if there is a funding limit for the applications. Reflections were offered on the potential to further contribute to capacity building in developing countries by allowing financing of PhD students as part of projects undertaken through this funding scheme.

C.5 Defining the merozoite targets of protective immunity against *Plasmodium falciparum* malaria through multi-centre cohort studies

C.5.1 Description of the scheme/project/initiative

The development of an effective malaria vaccine remains an important research priority as the global malaria control agenda moves from reductions in morbidity and mortality towards elimination. Whilst our understanding of the molecular complexity of *Plasmodium falciparum* has grown tremendously in the last decade, this has not been paralleled with equivalent strides in deciphering the underlying mechanisms and the targets of naturally acquired immunity.

This case study[187] describes the impact achieved by projects supported by the Concordat African Research Leader (ARL) award MR/L00450X/1 (£738,228)- *Defining the merozoite*[188] *targets of protective immunity against* Plasmodium falciparum *malaria through multi-centre cohort studies*, awarded in 2013, to Prof Faith Osier, a researcher from Kenya working on malaria paediatric immunology. All ARLs have a mentor within a UK University, who is officially the PI on the grant. The PI for Prof Osier's grant is Prof Kevin Marsh from the University of Oxford. Prof Osier is currently a visiting Professor of Malaria Immunology at the University of Oxford (since 2013), and a Group Leader at Heidelberg University Hospital, Germany and at the Kenya Medical Research Institute (KEMRI) Wellcome Trust Centre for Geographic Medical Research (Coast) (CGMR-C) in Kilifi, Kenya.

The projects supported by the ARL award aimed at identifying the immune response in children infected with malaria, to aid in designing better malaria vaccines. To achieve this, Prof Osier used four approaches: i) systematically analyse antibody responses to a number of parasite proteins; ii) conduct a cohort study, using previously collected serum samples and epidemiological data from established cohorts in Africa, to analyse the vast repertoire of responses; iii) standardise the protocols used for antigen testing; and iv) assess antibody-dependent mechanisms of action to specific antigens.

C.5.2 Mode of implementation

The first study funded through this award was conducted in Burkina Faso and Senegal, looking at the immune response in children in two settings with different intensity of malaria transmission.[189] Antibody levels to parasite proteins were measured and compared with the protective thresholds established in Kenyan children. The antibodies measured were not found to provide protection against severe malaria in young infants.

As a continuation of this work, with the aim of identifying protective antibody responses, the researchers made use of data from an ongoing cohort study known as the Kilifi Birth Cohort which is part of the Kilifi Health and Demographic Surveillance System, a well-established community surveillance framework that covers an area of 900 km^2 around Kilifi Country Hospital. One study used data collected between 2001 and 2010 and provided evidence that protective immunity is a result of multiple antibody-dependent mechanisms with distinct targets.[190] A second study used data from the same cohort collected

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[187] The case study relies on experiences shared by 6 researchers who are familiar with the projects supported by the Concordat grant MR/L00450X/1 and is supported by additional desk research. RAND Europe has also taken into account contextual knowledge gathered through the set of 12 interviews that were conducted in relation to Concordat supported projects undertaken in Kenya for the purposes of the wider Concordat evaluation project. For purposes of respecting informed consent, individuals and their organisations are not named.

[188] The merozoite is a form in the parasite's life cycle once this enters the human (host) organism, following its asexual division (schizogony). The next form the parasite takes after being a merozoite is the gametocytes which is the only form in which the parasite can infect the mosquito.

[189] Kangoye, David Tiga, Victorine Atanase Mensah, Linda Muthoni Murungi, Irene Nkumama, Issa Nebie, Kevin Marsh, Badara Cisse, et al. 2016. "Dynamics and Role of Antibodies to Plasmodium Falciparum Merozoite Antigens in Children Living in Two Settings with Differing Malaria Transmission Intensity". *Vaccine* 34, no. 1: 160–66. https://doi.org/10.1016/j.vaccine.2015.10.058.

[190] Murungi, Linda M., Klara Sondén, David Llewellyn, Josea Rono, Fatuma Guleid, Andrew R. Williams, Edna Ogada, et al. 2016. "Targets and Mechanisms Associated with Protection from Severe Plasmodium Falciparum Malaria in Kenyan Children". *Infection and Immunity* 84, no. 4: 950–63. https://doi.org/10.1128/IAI.01120-15.

from 2002 to 2010 and evaluated the role of special antibodies (cord blood IgG) in protection against severe malaria during the first year of life.[191] Results showed that antibody activity reduced the probability of developing severe malaria in the first 6 months of life, and identified targets of antibodies which could contribute to the development of vaccine candidates against severe malaria in infants.

Throughout her ARL award, Prof Osier was able to use the resources available at KEMRI CGMR-C – both researchers and infrastructure – and build a network that would allow knowledge sharing with other African scientists and attract additional funding from entities such as the Wellcome Trust and the European and Developing Countries Clinical Trials Partnership (EDCTP.)

Using the ARL award, Prof Osier built the South-South Malaria Antigen Research Partnership (SMART) in 2013, a virtual South-South network which brings together African scientists to share resources and expertise towards producing malaria vaccines and increasing research capacity in Africa. The network shares serum samples and epidemiological data on malaria gathered through prospective cohort studies. Initially envisaged as a network with three partner countries – Burkina Faso, Tanzania and Kenya, SMART has grown to seven countries expanding to Ghana, Senegal, Uganda and Mali.[192] The network took the SMART name under an EDCTP Senior Fellowship which Prof Osier won in 2016.[193]

C.5.3 Main achievements, results of the project (so far) and expected impact

Scientific results

Using the ARL award, Prof Osier designed a protein microarray to measure a variety of malaria proteins. The platform enables antigen discovery by mapping new proteins that can be further investigated in terms of immunity and vaccine development. Prof Osier's group has used it to run a multi-centre and multi-country study with over 10,000 data points from the seven SMART countries. The development of this platform has attracted a small grant from the Cambridge/Alborada Research Fund which fostered technology transfer of the protein expression array from the Wellcome Trust Sanger Institute in Cambridge, UK to KEMRI CGMR-C laboratories,[194] as well as funding from the Wellcome Trust, EDCTP, and the Humboldt Award.[195]

In regard to publications supported by the ARL award, Prof Osier has published five articles in journals such as Infection and Immunity, Vaccine, International Journal for Parasitology, and Trends in Parasitology.

Results concerning research capacity

The ARL award has brought about new scientific knowledge in the field of paediatric protective immunity against the malaria parasite and has contributed to the professional development of the ARL as well as that of members of her research group which in 2017 consisted of three Post Docs, seven PhD students, one statistician, three assistant research officers and two research interns all from various African countries.[196]

By building the SMART network, the award has led to greater South-South knowledge exchange between African researchers and has enabled early career researchers to continue engaging in research and pursuing PhD degrees by securing funding for research activities.

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[191] Murungi, Linda M., Klara Sondén, Dennis Odera, Loureen B. Oduor, Fatuma Guleid, Irene N. Nkumama, Mark Otiende, et al. 2017. "Cord Blood IgG and the Risk of Severe Plasmodium Falciparum Malaria in the First Year of Life". *International Journal for Parasitology* 47, no. 2–3: 153–62. https://doi.org/10.1016/j.ijpara.2016.09.005.

[192] SMART includes the following centres: Malaria Research and Training Centre (MRTC), Bamako, Mali, Kintampo Health Research Centre, Kintampo, Ghana, Institut Pasteur Dakar, Dakar, Senegal, Centre Nationale de Recherche et de Formation sur le Paludisme, Ouagadougou, Burkina Faso and KEMRI-CGMRC in Kenya.

[193] SMART. n.d. [Homepage]. Accessed June 6, 2018. https://www.smartpartnership.net/.

[194] MRC/DFID African Research Leadership Awards Annual Progress Report Year 1 – F. Osier dated 9th May 2015

[195] SMART. n.d. [Homepage]. Accessed June 6, 2018. https://www.smartpartnership.net/.

[196] MRC/DFID African Research Leadership Awards Annual Progress Report Year 3 – F. Osier dated 22 May 2017

For the ARL, the award has been the catalyst of rapid professional development allowing her to pursue her own research ideas, obtain prestigious awards and a professorship as well as mentor other researchers.

Dr Osier was able to build on the Concordat award and go on to attract other prestigious awards such as receiving the 1st EVIMalaR African Scientist Award from the European Virtual Institute of Malaria Research in 2014, obtaining the 5th Merle A. Sande Health Leadership Award from the Accordia Foundation, USA in 2014, receiving the Royal Society Pfizer Award from the Royal Society, UK in 2014, being the Sofja Kovalevskaja Award Winner from the Alexander von Humboldt Foundation, Germany in 2016, and lately being appointed a TED Fellow by Technology, Entertainment, Design (TED), USA in 2018. Currently she holds the following funding: a Sofja Kovalevskaja Award, a Wellcome Trust Strategic Award for Controlled Human Malaria Challenge Infections, a Wellcome Trust DELTAS award for capacity building, an MRC/DFID African Research Leader Award, an EDCTP Senior Fellowship, and a Tackling Infections to Benefit Africa (TIBA) Award.[197] She routinely gives presentations at conferences throughout Africa and Europe[198].

For her peers and junior staff, Prof Osier is seen as an inspirational trailblazer with another ARL recipient commenting that interacting with Prof Osier gave her more confidence to apply for this award.

For the KEMRI CGMR-C, ARL awards including that of Prof Osier have expanded the work pursued in the centre and contributed to developing research capacity building by inspiring African researchers and building links with other groups such as the one at Heidelberg University, which facilitates access to German facilities and knowledge transfer between groups. The ARL award has also led to technology transfer to Kenya, with the KEMRI CGMR-C now being the one centre in Africa with the skills and technology to express proteins and protein microarray facilities.

Results concerning policies, follow-up studies

The work of Prof Osier and her team is contributing to regional research capacity development. This is particularly important due to the small number of existing African-based scientists compared to the size of continent -there are only 79 scientists per million Africans, compared to 4,500 per million in the US.[199]

It is also making important strides towards a malaria vaccine; however, the full effects of such basic research are expected to materialise in a wider timeframe.

C.5.4 Lessons learnt, changes over time

Several interviewees highlighted mentorship as a key facilitator to undertaking the research and building research capacity. The relationship between the PI and the ARL was seen as beneficial for providing advice on the strategic direction of the research and helping with networking and identifying additional opportunities. However, it was noted by both recipients of ARL and PIs on ARL grants that the PI terminology does not accurately represent their role, as the African researcher decides the funding allocation and leads the projects. It was suggested "mentor" would be a more appropriate title.

Prof Osier is a leader and mentor to members of her group who feel encouraged and empowered to conduct research, engage in dissemination activities such as presentations at conferences (e.g. the April 2018 Multilateral Initiative on Malaria in Senegal), pursue independent funding (e.g. one PhD student was able to attract a small grant from the EDCTP) as well as engage in mentorship activities of their own with Post Docs supervising master students and interns at KEMRI CGMR-C. She also has established a

[197] Osier, Faith. n.d. "Prof. Faith Osier CV". Accessed June 6, 2018. https://docs.wixstatic.com/ugd/ad1f32_1efc4f466aef416c84ed1a88f2ebb7d4.pdf.

[198] MRC/DFID African Research Leadership Awards Annual Progress Report Years 1,2 and 3 – F. Osier

[199] Kariuki, Tom. 2015. "Africa produced just 1.1% of global scientific knowledge – but change is coming". *The Guardian*, October 26, 2015. Accessed June 6, 2018. https://www.theguardian.com/global-development-professionals-network/2015/oct/26/africa-produces-just-11-of-global-scientific-knowledge

close collaboration between the two groups she is currently heading in Kilifi and Heidelberg, organising virtual group seminars.

The experiences shared by interviewees highlighted barriers pertaining to obtaining ethical clearances and handling the logistics around international sample transport which were noted as particularly time consuming.

In general, when it comes to wider capacity building in the African context, the interviewees mentioned the following barriers: limited career structure and mentorship opportunities, few centres that provide the physical and intellectual environment needed to compete internationally, and limited networking opportunities. However, it was also stated that the ARL award does address several of these challenges to a certain degree.

The current monitoring and reporting system used by MRC has been appraised as beneficial. In particular, the limited bureaucracy and its annual periodicity were appreciated (as opposed to reporting every six months or filling in timesheets). Researchfish was also considered effective at capturing a range of outputs and impacts and communication with the project officers was seen as straightforward and helpful.

A key element of the sustainability of results is the SMART network which provides samples from various settings leading to more generalisable results. As the work conducted is dependent on the latest technologies, it is important to secure further sources of funding in view of maintaining a steady research stream and developing SMART further. The ARL award has been particularly instrumental. However, as it is a one-time award, funders could also consider the possibility of establishing a structured fellowship scheme that could allow African researchers to move from the early to the late stages in their careers.

C.5.5 Transferability of the scheme

The ARL was seen to provide enough flexibility that would allow researchers from various settings to apply. However, it is dependent on the willingness of the UK-based PI to accompany the African researcher in the process. The grant administration is also done by the UK institution, although the way the money is used is decided by the ARL award recipient. There were mixed views on the potential to change this way of administration as there were views that while some African institutions have the capacities to administer the award, others may not. Some interviewees did feel that there are existing capacities to allow for African institutions to begin to solely manage the award.

C.5.6 Suggestions, recommendations

This case study highlighting Prof Osier's and her team's activities resulting from the ARL award provide an example of how such an award can contribute to knowledge generation towards developing future malaria vaccines, to Kenyan and regional research capacity building, and how it can help a mid-career African researcher transition to a further stage in her career.

The case study would suggest the following recommendations:

- The ARL award is seen as an extremely helpful award and from the interviewees perspective it would be beneficial to increase the number of available awards throughout Africa.
- Consider articulating a structured fellowship scheme that could allow African researchers to move from the early to the late stages in their careers.

C.6 Studies to understand the response of the infant's immune system to infectious diseases and vaccines (long version)

C.6.1 Description of the scheme/project/initiative

Despite world efforts to reduce child mortality under the age of 5 years as part of the Millennium Development Goals, in 2016 4.2 million deaths still occurred within the 5 years of life, meaning 30.5

deaths per 1,000 live births.[200] In the African region, the risk of a child dying before 1 year of age was 52 per 1,000 live births.[201] In The Gambia, the infant mortality rate was 60.2 deaths per 1,000 live births in 2017.[202] Although there are various causes of newborn mortality, over 25 per cent of deaths in this period occur as a result of infections.[203] Understanding the way in which infants develop their immune system in response to vaccines and infections is therefore a global health priority. Research into infant immunology could ultimately inform the development of novel interventions to protect newborns and infants.

The projects funded through grant MC_UP_A900_1115 (from 2013 to 2018) characterised key elements of the immune response to given pathogens, described the immune response generated as a result of vaccination, and established the optimum regimes for the use of current vaccines. This aimed to provide insight into the development of natural and vaccine-stimulated immunity, facilitating the development of novel protective strategies in order to guide future rational vaccine development and maximise the protection of infants. The grant served as core funding for the activities of the Vaccines and Immunity Theme, including building a core team by covering their overheads. Projects under this grant made use of core facilities at the MRC Unit in The Gambia (hereafter referred to as the Unit) rather than receive direct funding for specific projects. Therefore, we found it relevant to highlight cases where additional funding was obtained.

C.6.2 Mode of implementation

The projects funded through this grant investigated the immune response generated in infants through vaccination of pregnant women and infants in order to understand age-dependent immune development in the context of vaccination, infection, and important epidemiological and pathogen-derived factors. In addition to clinical trials, the projects made use of observational cohorts of mother/infant pairs as platforms to investigate host responses in different age groups and determine the interactions between host and pathogen under vaccine or infection pressures.

In explaining the rationale for choosing areas of research, one of the main researchers explained that the research questions driving these projects are aligned with global health priorities, including those identified through the WHO SAGE Committee, and are relevant for the needs of West African populations. The guiding principle of whether a certain type of research is justified in the West African context is used by the Unit to decide whether or not to undertake private sector sponsored research. The MRC/DFID/Wellcome Trust Global Health Trial Scheme has been found to be a particularly rapid and responsive mechanism in view of conducting research on urgent needs.

Conducting these types of projects relies on the Unit's established research platform, meaning the availability of core staff with particular expertise in conducting immunological studies in children as well as laboratory skills.

Over the last 10 years there has been a change in the funding model of the Unit, from core funding to more project-specific funding. This has attracted several projects to the Vaccine and Immunity Theme team, primarily financed through the Global Health Trial Scheme but also through donors such as the MRC, Wellcome Trust, Bill and Melinda Gates Foundation and industry (e.g. Merck, Novartis).

The projects have led to collaborations with pharmaceutical companies involved in vaccine development. These include: research on the meningococcal vaccine ACWY in collaboration with

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[200] World Bank. Mortality rate, infant (per 1,000 live births). https://data.worldbank.org/indicator/SP.DYN.IMRT.IN

[201] World Health Organization. Global Health Observatory (GHO) data –infant mortality. http://www.who.int/gho/child_health/mortality/neonatal_infant_text/en/

[202] Central Intelligence Agency. The World Factbook-infant mortality rate. (2017). https://www.cia.gov/library/publications/the-world-factbook/fields/2091.html

[203] The Republic of The Gambia, Department of State for Health & Social Welfare. The Gambian road map to accelerate the reduction of maternal & newborn morbidity & mortality (2005). http://www.nationalplanningcycles.org/sites/default/files/planning_cycle_repository/gambia/gambia_mnh_road_map_2005-2015.pdf

Novartis;[204] funding from Pfizer Vaccine Research for studies on pneumococcal PCV-13 in children;[205] and assistance in protocol preparation from GSK for work on Group B *Streptococcus*.[206] Collaboration with industrial partner PharmaJet facilitated research into vaccine delivery using needleless devices.[207,208]

C.6.3 Main achievements, results of the project (so far) and expected impact

Scientific results

The Unit is building a diverse portfolio in the field of infant immunology. One major stream of research focuses on vaccination during pregnancy. This has led to vaccines for influenza, tetanus and pertussis being recommended for use during pregnancy, and new vaccines being developed to prevent important neonatal infections in the future, including Group B *Streptococcus*[209] and pneumococcal vaccine PCV-13.[210]

Another major study used Concordat core support to evaluate the use of needleless devices to deliver vaccines. The system was set up to deliver inactivated poliovirus vaccine using disposable syringe jet injectors (DSJI) provided by PharmaJet.[211] The efficacy of DJSI was evaluated for intradermal vaccination rather than intramuscular vaccination in a nested clinical trial funded by the Bill & Melinda Gates Foundation and the MRC. DSJI were then used to deliver inactivated poliovirus vaccine in combination with measles-rubella and yellow fever in a study funded by the Bill & Melinda Gates Foundation from 2013-2014.[212] Results from these studies revealed the importance of training vaccinators for campaign and routine intradermal vaccination, as well as providing evidence to support the co-administration of inactivated poliovirus, measles-rubella, and yellow fever vaccines within the Expanded Programme on Immunisation (EPI) schedule at 9 months. Moreover, DSJI are being tested for delivery of other vaccines. Another study focusing on needleless vaccination is ongoing, funded by the Wellcome Trust, evaluating intranasal live attenuated influenza vaccine (LAIV). The Gambia does

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[204] Clarke, E. T., N. A. Williams, P. M. Dull, J. Findlow, R. Borrow, A. Finn, and R. S. Heyderman. 2013. "Polysaccharide-Protein Conjugate Vaccination Induces Antibody Production but Not Sustained B-Cell Memory in the Human Nasopharyngeal Mucosa." Mucosal Immunology 6 (2): 288–96. https://doi.org/10.1038/mi.2012.70.

[205] Trück, Johannes, Amber Thompson, Begonia Morales-Aza, Elizabeth A. Clutterbuck, Merryn Voysey, Ed Clarke, Matthew D. Snape, Dominic F. Kelly, Adam Finn, and Andrew J. Pollard. 2017. "Memory B Cell Response to a PCV-13 Booster in 3.5year Old Children Primed with Either PCV-7 or PCV-13." Vaccine 35 (20): 2701–8.

[206] Le Doare, Kirsty, Amadou Faal, Mustapha Jaiteh, Francess Sarfo, Stephen Taylor, Fiona Warburton, Holly Humphries, et al. 2017. "Association between Functional Antibody against Group B Streptococcus and Maternal and Infant Colonization in a Gambian Cohort." Vaccine 35 (22): 2970–78.

[207] Clarke, Ed, Yauba Saidu, Jane U. Adetifa, Ikechukwu Adigweme, Mariama Badjie Hydara, Adedapo O. Bashorun, Ngozi Moneke-Anyanwoke, et al. 2016. "Safety and Immunogenicity of Inactivated Poliovirus Vaccine When given with Measles-Rubella Combined Vaccine and Yellow Fever Vaccine and When given via Different Administration Routes: A Phase 4, Randomised, Non-Inferiority Trial in The Gambia." The Lancet. Global Health 4 (8): e534-547.

[208] Bibby, Jack, Yauba Saidu, Ama Umesi, Ngozi Moneke-Anyanwoke, Adedapo O. Bashorun, Mariama Badjie Hydara, Ikechukwu Adigweme, et al. 2017. "The Immunogenicity of Fractional Intradermal Doses of the Inactivated Poliovirus Vaccine Is Associated With the Size of the Intradermal Fluid Bleb." Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America 65 (5): 851–54.

[209] Le Doare, Kirsty, Amadou Faal, Mustapha Jaiteh, Francess Sarfo, Stephen Taylor, Fiona Warburton, Holly Humphries, et al. 2017. "Association between Functional Antibody against Group B Streptococcus and Maternal and Infant Colonization in a Gambian Cohort." Vaccine 35 (22): 2970–78.

[210] Trück, Johannes, Amber Thompson, Begonia Morales-Aza, Elizabeth A. Clutterbuck, Merryn Voysey, Ed Clarke, Matthew D. Snape, Dominic F. Kelly, Adam Finn, and Andrew J. Pollard. 2017. "Memory B Cell Response to a PCV-13 Booster in 3.5year Old Children Primed with Either PCV-7 or PCV-13." Vaccine 35 (20): 2701–8

[211] Bibby, Jack, Yauba Saidu, Ama Umesi, Ngozi Moneke-Anyanwoke, Adedapo O. Bashorun, Mariama Badjie Hydara, Ikechukwu Adigweme, et al. 2017. "The Immunogenicity of Fractional Intradermal Doses of the Inactivated Poliovirus Vaccine Is Associated With the Size of the Intradermal Fluid Bleb." Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America 65 (5): 851–54.

[212] Clarke, Ed, Yauba Saidu, Jane U. Adetifa, Ikechukwu Adigweme, Mariama Badjie Hydara, Adedapo O. Bashorun, Ngozi Moneke-Anyanwoke, et al. 2016. "Safety and Immunogenicity of Inactivated Poliovirus Vaccine When given with Measles-Rubella Combined Vaccine and Yellow Fever Vaccine and When given via Different Administration Routes: A Phase 4, Randomised, Non-Inferiority Trial in The Gambia." The Lancet. Global Health 4 (8): e534-547.

not have an influenza vaccination policy despite WHO recommendations for influenza vaccination to be considered in high-risk populations, including pregnant women and children under the age of five.[213]

A project funded by the MRC-DFID Concordat looked at the acceptance of intranasal LAIV in The Gambia using a cross-sectional survey in Gambian women whose children had or had not received the vaccine.[214] Results revealed that the acceptance of intranasal LAIV was higher in women whose children had already received the vaccine, but overall intent to vaccinate was very high, suggesting that it is feasible to include seasonal vaccination in the childhood vaccination schedule.

Other ongoing research at the Unit is investigating the immunogenicity of several doses of human papillomavirus (HPV) vaccine and the possibility of administering it to a younger age group, with the aim of understanding whether fewer doses could provide the necessary protection. Another ongoing research project focuses on the effectiveness of the rotavirus vaccine and understanding why it is less effective in African populations compared to European populations.

Academic impact has been achieved through 28 publications in scientific journals on topics ranging from natural immunity to challenges and opportunities for childhood immunisation in The Gambia.[215]

Results for participants

The studies provide important information in view of enabling decision makers to make evidence-informed decisions. For example, research into PCV vaccines, conducted from 2008 to 2010 found the Gambian PCV programme reduced the incidence of invasive pneumococcal disease in children by approximately 55 per cent.[216] Further research from the Unit on PCV-13 conducted from 2013 to 2014 generated data for the licensing and WHO pre-qualification of the vaccine.[217] Previously mentioned research on the effectiveness of the rotavirus vaccine in African populations compared to European populations could potentially inform the development of vaccines that are better suited for this population.

Studies on finding better ways of administering vaccines (e.g. the DSJI studies or the HPV studies) or on the acceptance on certain vaccines by the population (e.g. LAIV) could lead to greater efficiencies within vaccination campaigns as well as better vaccination experience for the population.

Results concerning research capacity

In addition to producing high impact publications, the research brought about professional development opportunities for researchers. The opportunity to work at the Unit in this field has enabled several researchers to develop critical skills needed to conduct high quality clinical research. In addition to engaging in project work, staff members were also encouraged to pursue distance learning courses and gain research-specific qualifications. For example, one researcher, in addition to getting on-the-job training, was able to diversify his expertise from clinical diagnostics to immunology, attend relevant conferences, and pursue independent research (on cellular components of breast milk).

The PI, Dr Ed Clarke, has become a leader in the field of immunology, and is frequently involved with the WHO SAGE Committee.

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[213] Meeting of the Strategic Advisory Group of Experts on immunization, April 2012 – conclusions and recommendations. Wkly Epidemiol Rec 2012;87:201–16.

[214] Armitage, Edwin P., Janko Camara, Sulayman Bah, Alice S. Forster, Ed Clarke, Beate Kampmann, and Thushan I. de Silva. 2018. "Acceptability of Intranasal Live Attenuated Influenza Vaccine, Influenza Knowledge and Vaccine Intent in The Gambia." Vaccine 36 (13): 1772–80.

[215] Research Fish Data for the Concordat from 2003 until 2017

[216] Mackenzie, Grant A., Philip C. Hill, David J. Jeffries, Ilias Hossain, Uchendu Uchendu, David Ameh, Malick Ndiaye, et al. 2016. "Effect of the Introduction of Pneumococcal Conjugate Vaccination on Invasive Pneumococcal Disease in The Gambia: A Population-Based Surveillance Study." The Lancet Infectious Diseases 16 (6): 703–11. https://doi.org/10.1016/S1473-3099(16)00054-2.

[217] Medical Research Council. WHO Prequalification of pneumococcal vaccine based on MRC Unit The Gambia study. http://www.mrc.gm/prequalification-pneumococcal-vaccine-based-mrc-unit-gambia-study /

In addition to MRC-DFID Concordat funding, this project attracted funding from other sources including the Bill & Melinda Gates Foundation, MRC, Wellcome Trust and National Institute for Health Research, UK.

The core team at the Unit has also focused on building relationships with colleagues from the government in The Gambia. As described by one interviewee, the government delivers antenatal care for some of the maternal vaccination trials and the Unit was able to deliver several training courses to government staff in relation to this research (e.g. emergency obstetric care, best practice for record keeping for delivery, midwifery training).

Results concerning policies, follow-up studies

This research has had an impact on policy, academic research, and in the public and private sectors. Data from the Unit showing that rotavirus made a significant contribution to morbidity and mortality in children in The Gambia, led to the introduction of a new rotavirus vaccine in The Gambia's EPI.[218,219]

Research from the Unit has been highlighted in the report *Maternal Immunization Safety Monitoring in Low- and Middle-Income Countries: A Roadmap for Program Development*.[220] This includes work done on maternal immunisation with *Haemophilus influenzae* type b (Hib) polysaccharide-tetanus protein conjugate vaccine in The Gambia,[221] work on Group B *Streptococcus* colonisation and disease,[222] and two ongoing trials to study the impact of conjugated pneumococcal vaccination on pneumococcal carriage and prevention of neonatal pertussis.

C.6.4 Lessons learnt, changes over time

A key element for success of the research pathway has been the availability of clinician researchers – generally paediatricians or obstetricians who understand the clinical field and epidemiological traits as well as the core research processes. These researchers are generally West Africans – often Nigerians and increasingly Gambians.

The Unit's good reputation was another key element facilitating impact, and was credited with enabling the recruitment of mothers and their children into clinical trials. Field coordinators also play an instrumental role in ensuring good relationships with the community by explaining the trials' procedures and obtaining permissions from the heads of communities to approach different populations in view of recruitment.

Another key element across the impact pathway has been the availability of skilled staff that understand processes in the lab including receiving, handling, storing, labelling and shipping of samples.

The experiences shared in relation to this case study suggest one main barrier which pertains to the continuity of funding for core staff. The interviewees highlighted that the main enabler for continuing to do this type of research pertains to the existence of the core team and therefore a perceived barrier was an eventual shrinkage of the team due to a loss of funding, which could affect the existing capacities.

The current reporting system using Researchfish was seen as positive. It was suggested that it would be beneficial for the MRC to provide feedback to the researchers on the information that is reported in order to better understand how the reporting of outcomes is being considered.

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[218] Medical Research Council. Outputs, outcomes and impact of MRC research: 2013/2014 report. https://mrc.ukri.org/publications/browse/outputs-outcomes-and-impact-of-mrc-research-2013-14/

[219] Researchfish Data for the Concordat from 2003 until 2017

[220] Bill & Melinda Gates Foundation and the Global Alliance to Prevent Prematurity and Stillbirth. Maternal Immunization Safety Monitoring in Low- and Middle-Income Countries: A Roadmap for Program Development. 2017. Available at: http://apps.who.int/medicinedocs/documents/s23275en/s23275en.pdf

[221] Mulholland, K., R. O. Suara, G. Siber, D. Roberton, S. Jaffar, J. N'Jie, L. Baden, et al. 1996. "Maternal Immunization with Haemophilus Influenzae Type b Polysaccharide-Tetanus Protein Conjugate Vaccine in The Gambia." JAMA 275 (15): 1182–88.

[222] Le Doare, K., S. Jarju, S. Darboe, F. Warburton, A. Gorringe, P. T. Heath, and B. Kampmann. 2016. "Risk Factors for Group B Streptococcus Colonisation and Disease in Gambian Women and Their Infants." The Journal of Infection 72 (3): 283–94. https://doi.org/10.1016/j.jinf.2015.12.014.

C.6.5 Transferability of the scheme

Conducting this type of research is highly dependent on the existence of the Unit's staff and lab capacity as well as community readiness and willingness to participate in this type of research. This can be in part attributed to the Unit's efforts of conducting research in The Gambia for the past 70 years.

C.6.6 Suggestions, recommendations

The projects conducted under the Intramural Infections and Immunity Board grant provide an example of how research can contribute to the generation of vaccines, which are one of the world's most important global public goods.

The case study suggests the following recommendations:

- Maintain core funding for the Unit and an open dialogue on potential adjustments that may be needed to support an increasing body of work in the area of vaccines and immunology.
- Create opportunities for the Unit to disseminate their research funding for projects that are not solely funded by the Concordat.
- Communicate to researchers about the use of Researchfish data and the type of analysis the Unit could potentially undertake in-house in order to produce materials that may be used to showcase their achievements. This in turn could attract additional research which would be in line with the current funding model that relies to a lesser extent on Concordat core funding.

C.7 Studies to understand the response of the infant's immune system to infectious diseases and vaccines (short version)

Despite world efforts to reduce child mortality under the age of five years, in 2016 4.2 million deaths still occurred, meaning 30.5 deaths per 1,000 live births.[223] In the African region, the rate of a child dying before one year of age was 52 per 1,000 live births.[224] Although there are various causes of newborn mortality, over 25 per cent of deaths in this period occurred as a result of infections.[225]

Vaccination is a key tool in early prevention of childhood infections. It is however vital to understand to whom to give the vaccine (either pregnant mother or the baby), when (at what age) and how frequently to give each vaccine such that it generates good, long lasting, protective immune response.

Through the Concordat, the MRC and DFID funded projects undertaken in the MRC Unit in The Gambia between 2013-18 to investigate the immune response generated in infants through vaccination of pregnant women and infants. The research helped understand age-dependent immune development in the context of vaccination, infection, and important epidemiological and pathogen-derived factors. The research questions (including the choice of infection/vaccine studied) were aligned the work of the WHO Strategic Advisory Group of Experts (SAGE) on Immunisation, while providing high levels of local relevance to West African countries. The projects made use of core facilities and research teams at the MRC Unit in The Gambia and involved cohorts of mother/infant pairs recruited through strong community engagement.

The projects have led to collaborations with pharmaceutical companies involved in vaccine development and resulted in 28 publications published in scientific journals on topics ranging from (biomedical knowledge of) natural immunity to more implementation related challenges and opportunities for childhood immunisation in The Gambia.[226] Research from the Unit has been highlighted in the report Maternal Immunization Safety Monitoring in Low- and Middle-Income Countries: A Roadmap for

[223] World Bank. Mortality rate, infant (per 1,000 live births). https://data.worldbank.org/indicator/SP.DYN.IMRT.IN

[224] World Health Organization. Global Health Observatory (GHO) data –infant mortality.

[225] The Republic of The Gambia, Department of State for Health & Social Welfare. The Gambian road map to accelerate the reduction of maternal & newborn morbidity & mortality (2005)

[226] Research Fish Data for the Concordat from 2003 until 2017

Program Development.[227] This includes work done on maternal immunisation with Haemophilus influenzae type b (Hib) polysaccharide-tetanus protein conjugate vaccine in The Gambia,[228] work on Group B Streptococcus colonisation and disease,[229] and two ongoing trials to study the impact of conjugated pneumococcal vaccination on pneumococcal carriage and prevention of neonatal pertussis.

The research also brought professional development opportunities for the researchers involved. The opportunity to work at the MRC Gambia Unit in this field has enabled several researchers to develop critical skills needed to conduct high quality clinical research through online learning and training provisions. The PI, Dr Ed Clarke, has become a leader in the field of immunology, and is frequently involved with the WHO SAGE Committee.

Government health care workers delivered antenatal care for some of the maternal vaccination trials and the Unit was able to provide these staff with several specific training courses (e.g. emergency obstetric care, best practice for record keeping for delivery, midwifery training). This not only improved the skills and capabilities of individual staff but reinforced the beneficial relationship with The Gambia Ministry of Health centrally.

A key policy impact is that based on evidence from the Unit showing that rotavirus made a significant contribution to reduction in morbidity and mortality in children in The Gambia, has led to the introduction of a new rotavirus vaccine in The Gambia's national Expanded Programme of Immunisation EPI.[230,231]

A key element for success of the research has been the availability of clinician researchers – generally paediatricians or obstetricians who understand the clinical field and epidemiological traits as well as the core research processes in the lab including receiving, handling, storing, labelling and shipping of samples. Field coordinators played an instrumental role in ensuring good relationships with the community by explaining the trials' procedures and obtaining permissions from the heads of communities to approach different populations. The MRC Unit's good reputation was credited with enabling the recruitment of mothers and their children into clinical trials.

The MRC Unit's good reputation and close working relationship with Ministry of Health, National immunization programmes both centrally and individually with staff was a key element facilitating impact.

Summary project information

PI: Dr Ed Clarke, MRC Unit, the Gambia

LMIC partners: MRC Unit, the Gambia

Project funding: £3,437,905

Project implementation: 2013-2018

Project ID: MC_UP_A900_1115

[227] Bill & Melinda Gates Foundation and the Global Alliance to Prevent Prematurity and Stillbirth. Maternal Immunization Safety Monitoring in Low- and Middle-Income Countries: A Roadmap for Program Development. 2017. f

[228] Mulholland, K., R. O. Suara, G. Siber, D. Roberton, S. Jaffar, J. N'Jie, L. Baden, et al. 1996. "Maternal Immunization with Haemophilus Influenzae Type b Polysaccharide-Tetanus Protein Conjugate Vaccine in The Gambia." JAMA 275 (15): 1182–88.

[229] Le Doare, K., S. Jarju, S. Darboe, F. Warburton, A. Gorringe, P. T. Heath, and B. Kampmann. 2016. "Risk Factors for Group B Streptococcus Colonisation and Disease in Gambian Women and Their Infants." The Journal of Infection 72 (3): 283–94.

[230] Medical Research Council. Outputs, outcomes and impact of MRC research: 2013/2014 report.

[231] Research Fish Data for the Concordat from 2003 until 2017

C.8 *Plasmodium falciparum* anti-malaria drug resistance in The Gambia: Identification of potential genetic markers by retrospective whole genome approaches

C.8.1 Description of the scheme/project/initiative

Globally, malaria is one of the main public health problems in terms of morbidity and mortality, with over 200 million cases and an estimated 500,000 deaths each year.[232] In The Gambia, the most represented species of the malaria parasite is *Plasmodium falciparum*, with an incidence of 85 per cent.[233] Artemisinin-based combination therapies (ACTs)[234] are the WHO-recommended first- and second-line treatment for uncomplicated *P. falciparum* malaria and chloroquine-resistant *Plasmodium vivax* malaria.[235] Resistance to ACTs has been documented worldwide in both *P. falciparum* and *P. vivax*, and *P. falciparum* has developed resistance to nearly all antimalarials in current use. In The Gambia, artemether-lumefantrine treatment failure rates exceed 10 per cent.

This case study[236] describes the impact achieved by projects supported by the Concordat grant MC_EX_MR/K02440X/1- *Plasmodium falciparum anti-malaria drug resistance in The Gambia: Identification of potential genetic markers by retrospective whole genome approaches*, awarded in 2013. The grant represents a Concordat career fellowship award, the first to be awarded to an African scientist – Dr Alfred Ngwa – to support his research between 2013 and 2018 on projects conducted at the MRC Unit in The Gambia. The projects conducted under his leadership aimed to identify and determine the distribution of malaria drug resistance markers in The Gambia, following five years of implementation of ACT in the country.

Research conducted under this fellowship focused on genetic changes in malaria infection following ACT implementation in The Gambia. Specifically, it aimed to look at characterising microsatellite variations and single nucleotide polymorphisms (SNPs), determining the prevalence of resistance markers in endemic communities, and defining the association of these polymorphisms with treatment failure and reduced drug sensitivity.[237]

C.8.2 Mode of implementation

To achieve its objectives, the projects employed hybrid select and Illumina sequencing[238] of retrospective isolates in collaboration with the Broad Institute in the U.S., flow cytometry techniques to assess the effects of artemisinin derivatives on early developmental stages of field isolates, and genotyping of isolates from *ex vivo* and *in vivo* studies in collaboration with the Wellcome Trust Sanger Institute in the UK.

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[232] World Health Organization. 2017. *World Malaria Report 2017*. Geneva: World Health Organization. Accessed June 5, 2018. http://www.who.int/malaria/publications/world-malaria-report-2017/en/.

[233] International Association for Medical Assistance to Travellers. n.d. "Country Health Advice Gambia. General Health Risks: Malaria". Accessed June 5, 2018. https://www.iamat.org/country/gambia/risk/malaria.

[234] The most commonly used ACTs are: mefloquine + artesunate, sulfadoxine/pyrimethamine (SP) + artesunate, and lumefantrine + artemether. In The Gambia, the first-line ACT is artemether-lumefantrine (AL), with artemether being the artemisin-derivative and lumefantrine the partner drug active against the erythrocytic stages of *P. falciparum*.

[235] Ceesay, Serign J., Climent Casals-Pascual, Jamie Erskine, Samuel E. Anya, Nancy O. Duah, Anthony J. C. Fulford, Sanie S. S. Sesay, Ismaela Abubakar, Samuel Dunyo, Omar Sey, Ayo Palmer, Malang Fofana, Tumani Corrah, Kalifa A. Bojang, Hilton C. Whittle, Brian M. Greenwood, and David J Conway. 2008. "Changes in malaria indices between 1999 and 2007 in The Gambia: a retrospective analysis". *Lancet* 372, no. 9649: 1545–54.

[236] The case study relies on experiences shared by two researchers working in the MRC Unit who are familiar with the projects supported by the Concordat grant MC_EX_MR/K02440X/1 and is supported by additional desk research. However RAND Europe has taken into account contextual knowledge gathered through all the 21 interviews that were conducted in relation to Concordat supported projects undertaken in The Gambia for the purposes of the wider Concordat evaluation project. For purposes of respecting informed consent, individuals or their organisations are not named.

[237] Researchfish Data for the Concordat from 2003 until 2017

[238] Illumina sequencing is a type of next-generation sequencing that allows low-cost high throughput whole-genome sequencing. Illumina sequencing can be used to study bacteria, bacterial populations and their evolution, and bacterial virulence.

The main researcher on the project was Dr Ngwa, who also provided support to two PhD candidates through the fellowship by involving them in particular work streams of the projects and offering mentorship towards their development as researchers. A Cameroonian national, Dr Ngwa joined the MRC in 2006 where he worked for five years before the fellowship award. Through building a research portfolio of publications in his time at the MRC and acquiring skills in articulating research questions, developing research plans, and grant applications, he decided to apply for the career development fellowship in 2013. He viewed the opportunity given by the Concordat particularly valuable as it offered a degree of personal visibility in the scientific community by being able to attend various meetings and flexibility in the overall research projects that was less common in other types of funding streams, manifested through the opportunities of employing researchers and tap into resources that permitted following up on the emerging results.

The fellowship provided many opportunities for collaborations in Senegal and Nigeria,[239] which facilitated access to sample banks and sample collection opportunities. It also enabled collaborations with UK-based institutions such as the Wellcome Trust Sanger Institute which provided support to generate data and support analysis, and the London School of Hygiene & Tropical Medicine (LSHTM) which facilitated access to training in evolutionary biology.

C.8.3 Main achievements, results of the project (so far) and expected impact

Scientific results

The main impacts of this grant so far have been in the academic sector, informing and contributing to future research through scientific publications, collaborations, the generation of genomic data and the development of a new tool for genotyping. Fifteen publications in scientific journals have resulted from the work, including in high impact journals such as Nature Genetics.[240] Collaborations have been established within UK research institutes and with other international institutions in Ghana, Nigeria, and Senegal.[241] This work has generated a pipeline for genotyping microsatellites from next generation sequencing data of wild isolates, contributing to research into structural variations in the genome of the parasite, and facilitating the evaluation of population structures as infection prevalence decreases across Africa. The researchers have also provided consensus sequences from whole genome sequencing analysis to PlasmoDB –a repository for *Plasmodium* research- and proteome antibody hybridisation data from The Gambia on selected asymptomatic and clinically infected cases.[242]

This work has also contributed to the development of a new technology with potential commercial applications. The tool consists of new fragment analysis assays for 35 microsatellite loci targeting signatures of selection from drugs and interventions that reduce transmission. These are now being applied to study parasite populations across the African continent.[243]

Results concerning research capacity

One key benefit resulting from the fellowship was developing research capabilities. In this respect, the collaboration with University of Lagos in Nigeria brought about the opportunity to supervise two PhD students which were embedded in the MRC Unit's platforms and gained skills in the methods proposed by Dr Ngwa's research plan, while working with their own samples. One of the students was awarded the title of Best Student in 2015 from the University of Lagos and is currently being hosted at The Gambia

[239] Nigerian Institute of Medical Research and the University of Lagos in Nigeria, Cheikh Anta Diop University in Senegal

[240] Researchfish Data for the Concordat from 2003 until 2017

[241] The institutions are the following: University of Ghana in Ghana, Nigerian Institute of Medical Research and the University of Lagos in Nigeria, Cheikh Anta Diop University in Senegal

[242] Researchfish Data for the Concordat from 2003 until 2017

[243] Ibidem

Unit for a Post-Doctoral fellowship. Following graduation, the second PhD researcher went on to support the Nigerian government by conducting research in Abuja.

Within the Unit, the fellowship facilitated training and involvement of junior staff members, including interns. It particularly supported researchers coming from a physical sciences background who gained skills in cell biology and genomics of malaria. These researchers went on to pursue MSc studies (one of them to Harvard University) or PhD studies, with one researcher gaining a Wellcome Trust Delta PhD position at the University of Ghana (there are no PhD programmes offered by the University of The Gambia) and conducting research housed at the MRC Unit in The Gambia. One PhD student credited the mentorship of Dr Ngwa in gaining skills that allowed her to articulate the research plan which won her the Delta scholarship. Furthermore, she stated she became much more confident in public speaking, networking, and reaching out to researchers outside The Gambia as a result of the coaching she received from Dr Ngwa.

Dr Ngwa is currently supervising three PhD students, two Post Docs, and a new PhD and two more Post Doc positions have recently become available as a result of Dr Ngwa's research projects. In his view, none of these opportunities would have been possible without the fellowship grant. Furthermore, the MRC career development award allowed him to develop rapidly at a critical time in his career and establish himself as a leader in his field.

With respect to capacity development, Dr Ngwa was able to attract funding that allowed acquisition of high performing equipment, which is now housed at the Unit. Throughout his fellowship, he was able to contribute to the Developing Excellence and Leadership Training in Genomics for the Elimination of Malaria (DELGIM) where he is now co-investigator on a project partially funded by the MRC. This allowed for the acquisition of a high-performance computer unit including a high-power server which is linked to research units in Mali and Kenya. As a result, students now have the opportunity to gain theoretical skills in bioinformatics and genomics, and then apply them directly in analysis at The Gambia Unit. Dr Ngwa's research efforts also facilitated acquiring the first next generation sequencing equipment available in The Gambia, and to his knowledge in all of West Africa, a machine which is also used to analyse samples from Nigeria, therefore contributing to wider regional capacity.

The DELGIM collaboration led to Dr Ngwa becoming part of another grant for the Human, Heredity and Health Collaboration in Africa (H3) amounting to a total of £3.6m awarded by NIH and Wellcome Trust across seven sites in Africa. This will allow Dr Ngwa to build further connections, expand the type of genetic research he is doing, and in his opinion propel the Unit towards becoming a widely recognised hub for genetics and genomics research in Africa.

Results concerning policies, follow-up studies

The clinical and societal applications of the research supported by the fellowship have not yet had time to deliver broader impact. However, it is anticipated that emergent research findings could inform decision makers on appropriate drug combinations which could help avoid development of resistance to malaria medications.

C.8.4 Lessons learnt, changes over time

Several key elements have been highlighted as important towards achieving the desired impact of this research. They pertain to the MRC Unit's existing platforms and governance arrangements.

Firstly, the flexibility of the fellowship allowed the PI to design his own research, support other researchers, engage in networking activities which opened doors for further collaboration, and increase his visibility as a researcher in the field of genomics.

An important facilitator to developing Dr Ngwa's career, which is one of the aims of the career development fellowships, was the opportunity to publish a significant number of articles and build a profile as a valuable researcher in the field. Dr Ngwa highlighted the importance of the MRC's policy to recommend publication in open source journals, which led to greater visibility of the research findings. The fact that the Unit attracts high quality researchers and invites high profile research leaders to deliver lectures offered in-house networking opportunities. Through the Unit's efforts, Dr Ngwa also stated that

he was able to establish good relationships with local communities and decision makers from the National Malaria Control Programme which allows him to attend regular meetings with the authorities on this topic and disseminate his findings.

The case study identified two main barriers that pertain to conducting research in The Gambia. First, the dynamic nature of research relies on having timely access to equipment and consumables which could be a challenge in this region. While the Unit has invested heavily in becoming self-sufficient which is reflected in the high number of projects they are able to conduct, purchasing remains a challenge, in particular when it comes to high-quality expensive equipment.

The second challenge is linked to researcher mobility as early career researchers can choose to relocate in pursuit of alternative opportunities overseas. This challenge is exacerbated by the small pool of Gambian researchers due to a fairly new university programme (the University was established in 2000 with the first undergraduate cohort graduating in 2006) and the absence of a PhD programme. This challenge is expected to decrease as the Unit has established a career development pathway for researchers, which is meant to lead to better retention of graduates. It was highlighted that support in the form of a bridging fund, would be beneficial to ensure funding for early Post Doc positions which in the Unit's funding model rely heavily on funding obtained from new projects, which may lead to potential employment gaps for these early career researchers.

The current system of using Researchfish as a means of reporting was seen as positive. However, potential refinement of the tool was suggested in order to ensure capturing career development activities (not only research development) such as supervising PhD students and demonstrating leadership.

Embedding the research into the Unit's research platform and a desire to establish the Unit as a regional hub in this field would suggest that this type of research has the potential to grow and inform policy decisions, and ultimately impact population health. The fellowship has already contributed to establishing a cadre of researchers, networks, and acquisition of high-quality and cutting-edge expensive equipment.

C.8.5 Transferability of the scheme

The capabilities and capacities of the MRC Unit in The Gambia have been instrumental in making the most of the fellowship funding. Therefore, fellowship plans should be mindful of regional context and leadership which would facilitate tapping into national, regional and global networks.

C.8.6 Suggestions, recommendations

Overall the study provides an example of how a fellowship grant was able to make important scientific contributions in the field of resistance to malaria medication, support both the recipient and other researchers in career development as well as lay the foundation for developing the MRC Unit in The Gambia into a regional hub in African genomic research.

The case study identified the following recommendations:

- Maintain the current degree of flexibility in administering the grant – meaning freedom to allocate the funds and pursue different research questions and engage in disseminating and networking activities.
- Emphasise the importance of career development for both recipients of the fellowship as well as researchers attracted by fellowship-related research and communicate metrics which could be used to capture this beyond academic impact with a particular focus on training and leadership development.
- Suggest the development of partners to invest more in developing country capacities that relate to medical supply and equipment delivery.
- Consider developing additional funding streams for national or regional early career researchers (considering the current Unit funding model which has decreased core capacity funding and relies predominantly on project funds to attract and retain early career researchers).

C.9 Predictive modelling to explore the policy impacts of antiretroviral therapy interventions in Africa (short version)

Since the beginning of the HIV/AIDS epidemic in the 1980s, more than 70 million people have been infected with the HIV virus and about 35 million people have died of HIV.[244] One of the highest prevalence and burden of the disease is in low- and middle- income countries, with an estimated 25 million living in sub-Saharan Africa. The management of HIV/AIDS normally includes the use of several antiretroviral drugs in combination in an attempt to control infection. One successful approach is to use multiple drugs that act on different viral targets relevant at different stages of the HIV life-cycle. This therapy is called highly active antiretroviral therapy or HAART. With ambitious new international targets to end HIV/AIDS by 2030, there is increased interest in designing strategies that help to scale-up antiretroviral therapy (ART).

Through the Concordat, the MRC and DFID funded a project under its Methodology Research Programme between 2012-2016, which explored the effects of different ART scale-up options in Uganda, using a bespoke mathematical model. Complex stochastic models are increasingly used in science and medicine to predict HIV transmission and facilitate public health decision making. The robustness of such models and thus the accuracy of predictions however rely on careful calibration with empirical data from local community settings. The project applied new methods to calibrate a model with detailed HIV/AIDS data from the community where the results were to be applied.

The Principal Investigator of the study was Richard White, currently Professor of Infectious Disease Modelling in the Centre for the Mathematical Modelling of Infectious Diseases and the TB Centre at the London School of Hygiene and Tropical Medicine and Director of the TB Modelling and Analysis Consortium. The study was conducted by a multi-disciplinary team involving UK researchers from Durham University, Universities of Cambridge, Exeter and Sheffield and the MRC/UVRI Research Unit in Uganda.

One specific application[245] of the project was to predict HIV/AIDS trends in Uganda before and after the introduction of HAART. Key data was made available from the MRC/UVRI General Population Cohort (GPC) of all residents of 25 villages in rural South West Uganda. Using the data, a detailed calibrated model was developed that was used to predict the future impact of a range of HAART strategies on HIV prevalence, incidence and mortality. The model was capable of simulating strategies that aimed at achieving the current WHO treatment recommendations and strategies of earlier treatment. In a recent report[246], the project used the model to simulate 22 ART scale-up strategies between 2016 to 2030, comprising different combinations of single interventions. Importantly, going beyond scientific modelling, the study involved the calculation of net monetary benefit (NMB) of each intervention, for a range of scenarios (e.g. different willingness/ability to pay (WTP) per DALY averted), bringing the scientific results to the real-world context of policy makers. The study was able to support the recent WHO guidelines in the Ugandan context and, dependent on resources available, recommended interventions to achieve the greatest reductions in HIV incidence.

This modelling tool can be applied in other contexts, after careful calibration, for TB/HIV control projections and costings. It can thus be used by country-level policy makers for decision making on control strategies and associated funding. The tool has now been used in workshops at global level by UNAIDS, the Global Fund and WHO, and at country level in South Africa, Vietnam, Ghana and Nigeria.

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[244] http://www.who.int/gho/hiv/en/

[245] http://cmmid.lshtm.ac.uk/mrccalib/

[246] McCreesh, N., Andrianakis, I., Nsubuga, R. N., Strong, M., Vernon, I., McKinley, T. J., ... White, R. G. (2017). Universal test, treat, and keep: improving ART retention is key in cost-effective HIV control in Uganda. *BMC Infectious Diseases*, 17, 322. http://doi.org/10.1186/s12879-017-2420-y

A new user-friendly modelling tool is now accessible through Avenir Health[247] (previously Futures Institute) a global health organization that works to enhance social and economic development by technical assistance in policy, planning, resource allocation and evaluation.

While the majority of the joint work was conducted at distance, the UK was successful in transferring knowledge and expertise on mathematical modelling to its LMIC partner. The study contributed to crucial capacity building in complex model calibration at the MRC/UVRI Research Unit in Uganda, which is now capable of conducting modelling work independently. It was reported that working with colleagues from the UK helped in gaining skills on how to run complex models as well as how to apply them. Thanks to the joint research project, one of the investigators from Uganda is now spearheading the modelling work at the MRC/UVRI Unit and was able to propose three further modelling projects in the Unit's current five-year plan. In addition, the project also contributed to training medical professionals in quantitative methods in Uganda who now use these skills in their decision making at country and global level.

Regarding national policy engagement, the research team met with Ministry of Health Officials in Uganda, and subsequently provided them with policy recommendations in the form of a policy brief entitled "Costs and effects of different ART scale-up options in Uganda". These scientific recommendations on adopting universal access to ART for all people living with HIV were underpinned by economic calculations showing that the new intervention would be highly cost effective, allowing savings on resources at the national level. Subsequent to this, the Ministry of Health revised its ART guidelines to recommend that ART be provided to all people living with HIV. This improved control and prevention of HIV should in time lead to improved survival, morbidity and quality of life, and the efficiency of health care delivery in Uganda.

One of the key challenges of successful implementation of the study results goes beyond any research project. It requires framework conditions to be in place such as a strong national health system with dedicated resources set aside for piloting, scale up and implementation of research findings. Nevertheless, the research project demonstrated that a mathematical model informed by local empirical data can provide accurate prediction of different strategies, enabling informed policy choices on the most cost-effective ways to reduce HIV infection.

Therefore, more effort should be invested in policy dialogues between researchers and decision makers, so that local and international policy makers gain sufficient trust in modelling and improved understanding to interpret results. Training more local researchers in modelling (and accurate calibration of complex models) would also strengthen the scientific field and build a critical mass so that predictive approaches can be used in other high-burden areas, including non-communicable diseases in low- and middle- income countries.

Summary project information

PI: Richard White, London School of Hygiene and Tropical Medicine

LMIC partner: MRC/UVRI and LSHTM Research Unit Uganda

Project funding: £515,607

Project implementation: 2012-2016

Project ID: MR/J005088/1

[247] http://www.avenirhealth.org/software-spectrum

C.10 Evaluating microbicides for HIV Prevention (short version)

In the early 1990s, new HIV infections increased rapidly, reaching an estimated 4.7 million new HIV infections by 1995: 2.5 million in southeast Asia and 1.9 million in sub-Saharan Africa. In order to target HIV transmission, a new range of experimental products, vaginal microbiocides were developed to potentially reduce the risk of HIV (or other sexually transmitted) infection in women. This specific target population was proposed as women are often unable to ensure the safe use of condom with their sexual partners.

Through the Concordat, the MRC and DFID initiated in 1998 the funding of the largest phase III clinical trial to test the effectiveness of microbicides in women. To help the preparations of the study, a new African-European not-for-profit partnership was established, the Microbicides Development Programme (MDP), co-ordinated jointly by the MRC Clinical Trials Unit and Imperial College London. The Principal Investigator for the study was Sheena McCormack, currently Professor of Clinical Epidemiology at the MRC Clinical Trials Unit at UCL.

The goals of the project and the MDP were multi-fold: (i) conduct social science research into the acceptability and barriers to the uptake of microbiocides; (ii) prepare clinical trial sites for a large, multi-national, randomised controlled trial; (iii) undertake early clinical studies of new microbicide products in African populations; and (iv) complete a major phase III effectiveness trial (MDP 301) of a safe, gel-based microbicide PRO2000. The MDP was funded over a 15-year period and brought together 16 research institutions or sites in Europe, South Africa, Tanzania, Uganda, Zambia and Mozambique, five not-for-profit organisations and industry to provide microbiocide gels.

While ultimately no evidence was found in the phase III clinical trial that the vaginal microbicide PRO2000 reduces the risk of HIV infection in women, it provided an important result as the trial was large enough to conclusively show the evidence for the lack of efficacy, ending scientific speculation about its clinical importance. The study however provided critical insight into social attitudes and helped create awareness about the vulnerability of women in Africa.

It was recognised early that the potential success of a vaginal product in reducing HIV transmission depends not only on clinical efficacy of the product used but also on the consistent and correct use of the product. Therefore, social science played an essential role in providing methodologies for identifying the many socio-economic and cultural factors influencing people's preferences and practices and in investigating the acceptability and the likelihood of use of such vaginal products in clinical trials and beyond.

A key success of the study that it managed to screen over 16,000 women at six research centres in four African countries to enrol over 9,000 women who were HIV negative with sexual partners who were HIV positive (i.e. sero-discordant couples). The management of the trial was led from the UK MRC Clinical Trial Unit which coordinated on the development of the trial protocol, established the central trial database, provided monitoring, analyses and oversight. This well-established infrastructure and governance model were rolled out and training about working practices and tools was given to trial co-ordinators at local trial centres. The DFID, on the other hand, contributed with its network in sub-Saharan Africa, providing a key point of entry in the communities, essential for prevention trials.

There were, however, a number of indirect benefits of conducting the MDP 301 trial:

Results for trial participants

- Awareness was raised with regards to issues related to sero-discordant couples. Many women participants reported to have been able to talk to their partners about HIV thanks to what they had learnt by participating in the trial
- An increase in the use of condoms was reported since the trial began, and the use of contraception grew in some areas. (Note that condoms were made available to trial participants.)

- The screening, which took place prior to the trial, disclosed a large number of HIV positive women. Lifelong treatment was offered to those who put themselves forward for the screening.
  - The association between screening and care was understood and created a growing demand for HIV care at local hospitals. This has an important impact on society, since earlier people did not want to know about their sero-positivity status, as they feared to be stigmatised.
  - Women participants were able to accompany their HIV positive partners to seek care.
  - Women participants who were HIV positive received a higher standard of care than they would if they had not been enrolled in the trial.
- Women who participated in the trial created a strong female community, which empowered them:
  - Trial co-ordinators reported that 1st trial participants sought permission from their partners before enrolling, whereas the same women enrolled in the 2nd trial without seeking permission.
  - Trial participation made the women 'research experienced' and more willing to read medical information.
  - There was an emerging awareness of women's rights over their bodies and there were reports of male partners being proud of their female partners, signalling the beginning of a change in local attitudes.
- Reimbursement of costs for the participants enabled some to buy essential products such as bicycles and telephones.

Results concerning research capacity

The MDP has contributed to build research capacity in its host centres in sub-Saharan Africa and established sustainable international research networks.

- Local trial co-ordinators received training beyond the operational aspects of trial implementation. For example, after attending scientific writing workshops, they went on publishing papers.
  - They were able to supervise post-graduate research using MDP data. This was described as a rare opportunity in SSA, only made possible by the link to the MRC.
  - They obtained transferable skills about governance and management of clinical trials.
  - They were subsequently recruited because their professional skills became visible.
- The Ebola vaccine trials, USAID trials and all other important research and data collection that followed the MDP trial have benefited from the enhanced expertise resulting from conducting trials on microbicides in the same region. The local capacity and the Community Advisory Board created by the MDP trial is still being used for vaccine efficacy study.
- Some research infrastructure in the trial centres remained available for subsequent studies.

Results concerning policies

A continuous provision of HIV data coming from SSA, through the MRC, is fed to the UK Department of Health, informing their policy-making. According to interviews, results from the MDP provided evidence to argue for home testing of HIV to become legal in the UK (April 2014).

The MDP 301 trial is ultimately considered a success because it left behind a legacy in a number of areas, including skills created and social attitudes changed. It proved essential to have the buy-in of local communities and the presence of local PIs in local trial centres. The local and empowered women continue to benefit from the experience during the trial and they effectively constitute a readily available cohort of participants for clinical trials. Nevertheless, in the absence of an ex-post evaluation of such a large and pioneering clinical trial, the present case study approach has its own limitations to triangulate findings.

The recent encouraging trend regarding the decline of annual numbers of new HIV infections in southern Africa (29% decline) and western and central Africa (9% decline) may indicate that awareness and social behaviour change may play an important role in preventing the transmission of the virus and achieving public health targets. In the words of a South African trial participant: "Even though the gel proved not to be effective, we played a role in the fight against HIV. We learnt a lot about caring for ourselves, such as using condoms. We also learnt to encourage others to test for HIV and we gained confidence in helping those who were already infected."

Summary project information

PI: Sheena McCormack, MRC Clinical Trials Unit

LMIC partner: multiple

Project funding: £43 million

Project implementation: 1998-2013

Project ID: MC_U122861322

C.11 Childhood tuberculosis: Integrating tools for improved diagnosis and vaccines

C.11.1 Description of the scheme/project/initiative

Tuberculosis (TB) is one of the top 10 causes of death worldwide, and causes significant morbidity and mortality in children worldwide. In 2016, an estimated 1 million children became infected with TB and 250,000 died because of it.[248] In low- and middle-income countries, diagnosis of TB relies on microscopy for identification of the bacteria and/or clinical diagnosis of TB.[249] Using these diagnostic techniques in children can be a challenge as they have fewer bacteria in their lungs that can be recovered in a clinical sputum sample.[250] Currently, there is a lack of suitable alternative diagnostic methods for childhood TB. This represents a major obstacle to progress in identifying paediatric patients in need of treatment.

This case study[251] describes the impact achieved by projects supported by the Concordat grant MC_EX_MR/K02440X/1- *Childhood tuberculosis: Integrating tools for improved diagnosis and vaccines* awarded in 2013. This is an Infections and Immunity Board Grant awarded to the project's Principal Investigator Prof Beate Kampmann. Prof Kampmann joined the MRC Unit in the Gambia (hereafter referred to as the Unit) in 2012 when she took up the position of Vaccines and Immunity Theme Leader, while maintaining her role as Professor of Paediatric Infection, Immunity and International Child Health at Imperial College London.

[248] World Health Organization. 2018. "Tuberculosis. Key facts." Accessed June 5, 2018. http://www.who.int/en/news-room/fact-sheets/detail/tuberculosis.

[249] Tuberculosis Coalition for Technical Assistance. 2006. *International Standards for Tuberculosis Care*. The Hague: Tuberculosis Coalition for Technical Assistance. Accessed June 5, 2018. http://www.who.int/tb/publications/2006/istc_report.pdf.

[250] World Health Organization. 2014. *Guidance for national tuberculosis programmes on the management of tuberculosis in children*. 2nd ed. Geneva: World Health Organization.

[251] The case study relies on experiences shared by three researchers working in the MRC Unit who are familiar with the projects supported by the Concordat grant MC_EX_MR/K02440X/1 and is supported by additional desk research. The study team has also taken into account contextual knowledge gathered through the set of 21 interviews that were conducted in relation to Concordat supported projects undertaken in The Gambia for the purposes of the wider Concordat evaluation project. For purposes of respecting informed consent, individuals and their organisations are not named.

The projects funded through this work stream aimed at developing and evaluating new and existing tools for TB diagnosis based on both the immune response to the bacteria and the microbiological features of the bacteria.

C.11.2 Mode of implementation

The main study involved primary data collection to assess the immunological differences in three categories of children: those infected with TB, children with TB disease, and uninfected children who have been exposed to TB. The researchers tested samples from TB-affected children (infected, diseased or exposed) obtained from household cohorts in order to characterise host responses associated with protection against infection in TB-exposed children who remain uninfected. The data obtained from household cohorts were used to expand existing epidemiological databases to include the epidemiological and microbiological context of household transmission and its impact on host responses. Additionally, the researchers developed a novel statistical approach to design prediction algorithms for the diagnosis of childhood TB.

The projects built on existing expertise and infrastructure available at the Unit. Implementation also made use of the relationships built in the Gambia between MRC researchers and Gambian decision makers.

C.11.3 Main achievements, results of the project (so far) and expected impact

Scientific results

The research has resulted in 66 publications in scientific journals, including high profile journals such as The Lancet.[252] One of the main research streams supported by this grant established household cohorts to evaluate contact tracing and assess the potential of preventive therapy in childhood contacts. A total of 4,000 child contacts aged below 15 years living in the same household[253] and compound[254] with adults showing a positive microscopy test for TB were recruited for this study.[255] Research found over half of TB disease in childhood contacts was missed when contact tracing was limited to symptom screening and immediate household contacts only, emphasising the importance of expanded contact tracing. Using the same recruiting process with an age limit of 5 years, a second project evaluated the potential of isoniazid preventive treatment among childhood contacts of adults who tested positive for TB.[256] Research showed home-delivered isoniazid preventive treatment had high uptake and adherence rates, illustrating the potential of isoniazid in TB prevention.

The household cohort also enabled the researchers to conduct an evaluation of diverse diagnostic methods in TB doing a side-by-side comparison of bacterial detection assays on sputum samples of patients presenting TB symptoms, and assessing their potential as screening tests. A biosignature consisting of immune molecules showed potential as a diagnostic tool for pulmonary TB disease.[257,258]

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[252] Research Fish Data for the Concordat from 2003 until 2017

[253] A household was defined as a group of individuals living in the same building and eating from the same pot.

[254] A compound was defined as a cluster of homes or buildings often owned by the members of the same family.

[255] Egere, Uzochukwu, Toyin Togun, Abdou Sillah, Francis Mendy, Jacob Otu, Mark Hoelscher, Norbert Heinrich, Philip C. Hill, and Beate Kampmann. 2017. "Identifying Children with Tuberculosis among Household Contacts in The Gambia." *The International Journal of Tuberculosis and Lung Disease: The Official Journal of the International Union Against Tuberculosis and Lung Disease* 21, no. 1: 46–52. https://doi.org/10.5588/ijtld.16.0289

[256] Egere, Uzochukwu, Abdou Sillah, Toyin Togun, S. Kandeh, F. Cole, Adama Jallow, A. Able-Thomas, et al. 2016. "Isoniazid Preventive Treatment among Child Contacts of Adults with Smear-Positive Tuberculosis in The Gambia." *Public Health Action* 6, no. 4: 226–31. https://dx.doi.org/10.5588%2Fpha.16.0073

[257] Awoniyi, Dolapo O., Andrea Teuchert, Jayne S. Sutherland, Harriet Mayanja-Kizza, Rawleigh Howe, Adane Mihret, Andre G. Loxton, et al. 2016. "Evaluation of Cytokine Responses against Novel Mtb Antigens as Diagnostic Markers for TB Disease." *The Journal of Infection* 73, no. 3: 219–30. https://doi.org/10.1016/j.jinf.2016.04.036

[258] Chegou, Novel N., Jayne S. Sutherland, Stephanus Malherbe, Amelia C. Crampin, Paul L. A. M. Corstjens, Annemieke Geluk, Harriet Mayanja-Kizza, et al. 2016. "Diagnostic Performance of a Seven-Marker Serum Protein Biosignature for the Diagnosis of Active TB Disease in African Primary Healthcare Clinic Attendees with Signs and Symptoms Suggestive of TB." *Thorax* 71, no. 9: 785–94. http://dx.doi.org/10.1136/thoraxjnl-2015-207999

Results for participants

Research into childhood TB funded through this programme has influenced training of practitioners and researchers, facilitating national age-disaggregated notifications of the condition to the WHO and increasing reporting of childhood TB in The Gambia by 60 per cent due to better awareness and identification of childhood TB cases. It is expected that all these efforts will enable more children with TB to be identified and treated, ultimately reducing the number of lives lost to the disease.

Results concerning research capacity

Overall, the projects conducted under this grant involved approximately 30 individuals with four of these (3 African scientists and 1 UK national) obtaining their PhD as a result of the research facilitated by the grant. All of them have continued their careers in research through positions at either the Unit, or the Universities of Edinburgh and Oxford.[259]

One of the African PhD scientists attracted additional funding from the WHO's Special Programme for Research and Training in Tropical Diseases (TDR) for rolling out the contact tracing platform. In recognition of his expertise on childhood TB, which was acquired mostly through the grant cycle as he had previously worked mostly on pneumonia, he was invited by the WHO to contribute to the development of Liberia's National TB Programme.

Building on the track record and platform established through the grant, the PI was able to attract further research funding from the Global Challenges Research Fund, the EU's Innovative Medicines Initiative, the Program for Appropriate Technology in Health, and from a number of pharmaceutical companies.

Collaborations were established with institutions from both the academic and the public sector in the U.S., Canada, UK, Nigeria, Tanzania, South Africa, Senegal, Denmark and Germany. Research into a TB biosignature of childhood TB has also resulted in a patent filing for this new technology.[260]

Results concerning policies, follow-up studies

This project impacted policy by informing childhood TB guidelines and influencing healthcare and education services. Prof Kampmann was part of an external review group on WHO guidance for national tuberculosis programmes on the management of childhood TB.[4] The work raised the profile of paediatric TB in international organisations such as ECDC and WHO, leading to the inclusion of recommendations specifically for children in the TB guidelines and to the work receiving citations in clinical guidelines, policy documents and systematic reviews.[261] The researchers provided assistance to the National Leprosy and TB Programme of The Gambia in preparation for a successful application to the Global Fund, which includes additional provision of services for children.[262]

C.11.4 Lessons learnt, changes over time

The Unit's prestigious reputation has been highlighted as an important factor in being able to recruit participants to the studies. The Unit already had expertise and a track record in TB research. This was combined with expertise on paediatrics developed through the vaccine and immunology trials run by the Unit, to focus on paediatric TB. The Unit employs the greatest number of paediatricians in the country, most of them international physicians attracted to The Gambia by the Unit.

Publications and dissemination activities which helped in attaining policy impacts contributed to the career development of research staff – especially at PhD level - who were also able to attract further funding for national capacity building activities and additional projects for the Unit.

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[259] Ibidem

[260] Researchfish Data for the Concordat from 2003 until 2017

[261] Sandgren, Andreas, Luis E. Cuevas, Masoud Dara, Robert P. Gie, Malgorzata Grzemska, Anthony Hawkridge, Anneke C. Hesseling, et al. 2012. "Childhood Tuberculosis: Progress Requires an Advocacy Strategy Now." *The European Respiratory Journal* 40, no. 2: 294–97. https://dx.doi.org/10.1183%2F09031936.00187711

[262] Researchfish Data for the Concordat from 2003 until 2017

The project team ensured that community sensitisation activities were undertaken prior to commencing recruitment. These consisted of open days and communications with community leaders during which the study was explained and permissions to approach members of the community were sought. Government representatives, members of the National TB Programme, were also invited and took part in some of these activities (e.g. communications during World TB Day). Engagement with national policy makers enabled national level impacts by introducing new ways of reporting data and training of practitioners, and enhanced government expertise in the field of TB.

Interviewees stressed several barriers encountered throughout the course of the research. One pertains to the reticence of parents to engage in prophylaxis research for their healthy children (for the isoniazid prophylaxis study). This was overcome by ensuring appropriate communication and explaining to parents what the trial consists of and the evidence base and rationale for conducting the research.

Another challenge pertained to retention of staff, particularly postdocs specialised in immunology, molecular biology, and bioinformatics. The pool of qualified people is smaller for these positions, and international staff are more expensive and more difficult to attract, as these positions are not usually covered by the programme funding.

More widely, limited access to equipment was highlighted as problematic at times. The Unit engages in a yearly competitive bidding system with other UK institutions. The call is once per year which is not necessarily when the need arises. At the same time, it is difficult to justify the need to update equipment and acquire it in a competitive process, considering equipment cannot be added to project budgets as they would skew the financial proposal. As overseas units strive to be more than sample collection sites, researchers find that it is important to have some of the latest technology on site.

In view of ensuring sustainability of results, a challenge towards achieving the desired impact is represented by limited national capacity. There is an expectation from national stakeholders that the Unit would contribute more to building national capacity to deliver health services, which is currently not in the remit of the Unit.

The current reporting system was seen as positive. In particular the responsiveness of the designated programme manager was highlighted as beneficial to the overall conduct of the projects.

C.11.5 Transferability of the scheme

Several of the projects' enablers pertain to the Unit's track record and capacities, which may limit transferability in a similar setting that does not benefit from such a research institution. Lessons pertaining to community engagement and dissemination are transferable and can be taken on board by researchers operating in other settings.

C.11.6 Suggestions, recommendations

The childhood TB programme grant provides an example of how research can contribute to expanding scientific knowledge in this field, help a national TB programme improve their monitoring and reporting approach, contribute to the training of practitioners and researchers, and help develop African researchers into recognised experts in the field of childhood TB.

The case study analysis draws the following recommendations:

- The Concordat could support more capacity building elements by ring-fencing some grant finances to finance PhD studies.
- Access to equipment could be facilitated by organising specific calls for overseas units.
- Considerations by both the Unit and the Concordat should be given to incentives for postdocs, considering the challenges in attracting and retaining qualified staff.
- One interviewee suggested there could be more incentives for collaboration between different units operating in Africa including between MRC units and Wellcome Trust units.

- Collaborations with industry were described as rudimentary, partially because industry has a very set scientific agenda. Knowledge sharing on how to best engage with industry and establish agreements with provisions for capacity building could be considered.