Improving **parasite eradication**

Dr Edwin Michael explains how a model under development at the Univeristy of Notre Dame's Department of Biological Sciences could transform the way lymphatic filariasis is tackled on a global scale

Could you start by outlining the key aims of your study into lymphatic filariasis (LF) in Papua New Guinea?

Our research is ultimately premised on the fact that effective planning and evaluation of community-level parasitic control programmes must accommodate and address the key biological and social complexities that underlie parasite transmission in the field. For LF, this required tackling the questions of how infection dynamics are affected by the different mosquito species involved in its transmission, how local ecological conditions may influence persistence and extinction dynamics, and what these imply for the World Health Organization (WHO)-led initiative to achieve the global eradication of this vector-borne parasitic disease. We set out to develop and analyse the first mosquito genus-specific transmission models for LF rooted in detailed field data from Papua New Guinea in order to investigate these critical questions.

What is LF? Could you explain the repercussions of the disease in affected communities and how it is spread?

LF, commonly known as elephantiasis, is a profoundly disfiguring parasitic disease caused by thread-like nematode worms. It is spread by several mosquito species and is endemic in all developing tropical countries. Some 120 million people are estimated to be infected worldwide currently, with about 40 million suffering from overt clinical disease manifested as severe swelling due to lymphedema (arising generally from accumulation of lymphatic fluid in the limbs) and hydrocele in men (fluid accumulation in the scrotal sac). Apart from this physical burden, the disease also imposes immense social and economic burdens on at-risk communities, which essentially confines many of these communities to hard-to-break health/poverty traps.

The current WHO recommended strategy for filariasis control is based on the expectation that six annual doses of drug treatment could eliminate LF from a community. Has your research demonstrated this to be true?

Our modelling results, now increasingly backed by field observations, have shown that the current top-down fixed WHO mass drug administration (MDA) strategy with a predefined globally invariant design – which also assumes high certainty in knowledge of how the LF system will respond to perturbations – needs to be changed if LF elimination is to be successfully accomplished in all endemic settings. In particular, our results show that the duration and frequency of mass treatments will vary between sites as a result of baseline endemicity levels, and will be strongly affected by the capacity of programmes to achieve high drug coverage. More fundamentally, we have shown that transmission dynamics, and hence eradication thresholds, will also differ significantly between communities as a result of variations in the local ecological conditions that affect LF transmission.

How are you developing models of lymphatic filariasis transmission? Has this proven difficult with regard to variations between different communities?

Our model of LF transmission is complex although it is essentially based on a hybrid coupled partial and ordinary differential equation system. The challenge for building this type of model lies in the formulation and analysis of the simultaneous effects of multiple positive and negative density dependent processes acting at different stages of the parasite life cycle. We use a diverse range of data sources from the published literature and from field trials in order to quantify, estimate and parameterise model functions and parameters.

Although we have begun to make some headway in investigating the impact of between-site heterogeneities, including derivation of the data-driven inferential frameworks that can reliably allow determination of model states and structures by calibration against local data, the next stage of work will require the development of platforms that can jointly couple spatially distributed data on key ecological conditions, including climate and weather variables, that affect parasite transmission with spatio-temporal data on human and vector infection prior, during and following interventions.

What are the next steps in the project?

Our work has shown that parasite systems are inherently variable entities, and that to manage such systems, it is ultimately necessary to adopt practices that allow for the precise estimation of transmission and control dynamics according to localised conditions. We are beginning to address this problem by developing and testing a spatial Bayesian modelling framework that melds our LF models with sparse vector abundance and human infection data from field surveys to deliver location specific posterior predicted distributions of prevalence, impact of interventions, and associated unobserved spatially varying model parameter inputs. This would allow managers and policy makers to select intervention approaches that combine good outcomes with high reliability for any given endemic setting.

Modelling the end of lymphatic filariasis

Research into lymphatic filariasis in Papua New Guinea has deepened understanding of the complex and interrelated variables behind infection rates. By incorporating this knowledge into new models, scientists at the **University of Notre Dame**, USA are helping policy makers find effective paths to eliminating the disease

FOR YEARS INFECTIOUS diseases like HIV, polio, malaria, tuberculosis and the neglected tropical diseases (NTDs) have been responsible for high levels of morbidity and mortality in developing countries. Now, a renewed global effort coordinated by the World Health Organization (WHO) aims to prevent and eradicate these diseases. Lymphatic filariasis (LF) is one of the NTDs under fire and is infamous for its distinctive symptoms of severe lower body swelling. The disease places a major burden on vulnerable communities, so finding the optimal strategy to combat it is essential.

Research by Dr Edwin Michael and his colleagues at the Department of Biological Sciences at the University of Notre Dame, USA is making a crucial contribution to the debate about how best to tackle LF. WHO currently advocates a regular set of doses of drugs to susceptible communities, but Michael's findings suggest that this one-size-fits-all approach is not the most effective path to eradication. Informed by the models the team has developed, he believes a more flexible approach, accommodating the complex underlying factors of the disease, is necessary: "More locally relevant but variable intervention strategies based on locality-specific eradication targets will need to be developed and applied if we are to successfully accomplish the goal of LF eradication," he explains.

UNDERSTANDING TRANSMISSION AND EXTINCTION

LF is caused by filarial parasites; the adult nematode worm resides in the human lymphatics and blocks the flow of lymph through the body. When they reproduce their larvae enter the blood stream. If a mosquito bites the human host in order to feed, the larvae are ingested along with the blood and begin the next phase of their development. The next time the mosquito, or vector host, feeds, the larvae are transmitted into a new human host and the cycle begins again. Understanding this complex ecological cycle and how the size and type of mosquito population in a local area influences rates of LF infection is essential to improve management of the disease and this principal underpins Michael's research projects.

To understand how the rates of transmission and extinction of the parasite vary between locations, the impact of local ecological factors on transmission and infection thresholds must be calculated. The threshold biting rate (TBR – the biting rate below which transmission is interrupted in a population) and the worm breakpoint (the prevalence of host parasites below which local extinction occurs) both vary according to location. The researchers investigated several underlying factors of this variability; vector biting rate, host immunity, exposure/infection aggregation in societies and the prevailing mosquito species.

Michael was especially interested in discovering the importance of the mosquito species: "In pure anopheline areas, eradication thresholds may in general be higher than in pure culicine areas, in sites, such as in many endemic localities in Africa, with mixed anopheline-culicine transmission, the ratio of culicines in the system can dilute or decrease overall transmission if it is high and vice versa," he reveals. Discovering the importance of this and other location specific variables and uncertainties, reinforced Michael's conclusion that they must be incorporated into modelling frameworks to develop successful of strategies for LF elimination.

PUTTING THE THEORY INTO PRACTICE

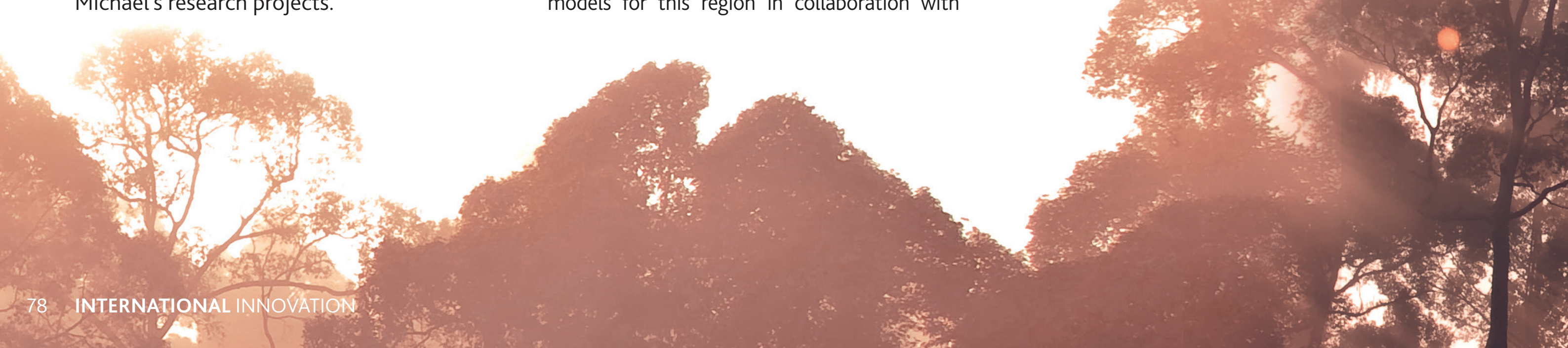
Michael and his team thus set about developing the necessary models of LF transmission. Working with vast and diverse data from the field, the researchers use partial and ordinary differential equations to build these models. They are using data from Papua New Guinea (PNG) because this country suffers from some of the highest levels of LF infection in the world; a solution here would represent a major breakthrough in the fight to eradicate the disease. In PNG, LF is only transmitted by anopheline mosquitoes, but previous models used to manage the disease in this area were based on transmission by culicine mosquitoes and population data from Southern India and were therefore in desperate need of updating.

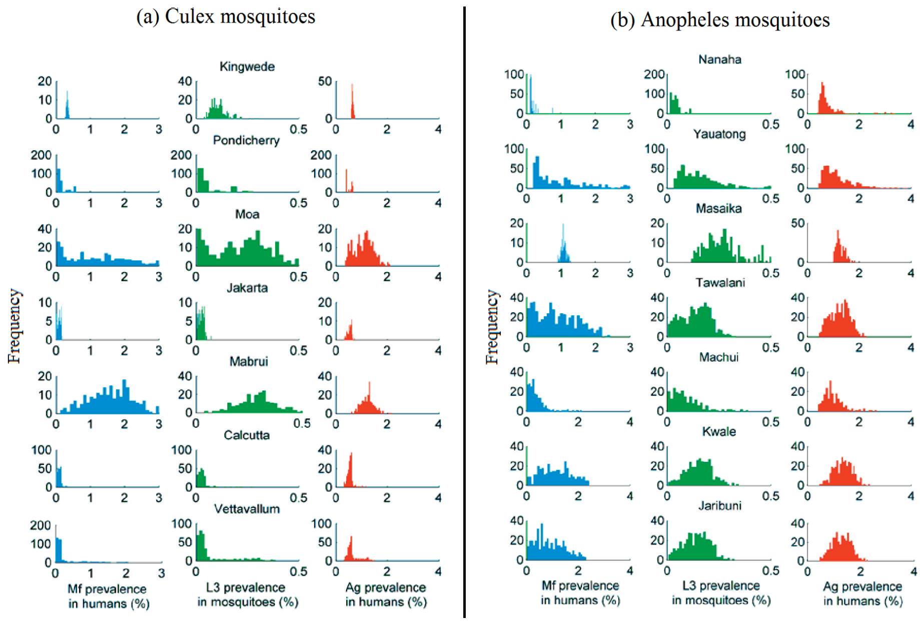
Thanks to the wealth of data available, the team has made great progress in developing models for this region in collaboration with Case Western Reserve University, USA and the PNG Institute for Medical Research. Based on this success they have gone on to incorporate the effects of transmission by both anopheline and culex vectors, as well as other variables, into the model. A key innovation is the development of data-model fusion frameworks that allow reliable representation of local dynamics using site-specific data. This is a major breakthrough in the field and paves the way for comparisons of LF-transmission and infection dynamics across all affected regions of the world.

Despite this promising progress, Michael recognises that implementing effective elimination strategies based on the models remains a huge challenge: "While adaptive management strategies, whereby data from each site or from endemically homogeneous regions could be used to develop and apply local strategies, would provide the optimal solution, this is unlikely to be practically possible in most endemic settings currently," he states. The scale of the problem and the need for reliable data means that reaching all effective communities will still require innovative approaches.

THINKING AHEAD

The models, however, point to some potential alternatives. By working from a bottom-up perspective, designing flexible local initiatives everywhere to meet appropriate elimination targets would result in global elimination of LF. This approach to ending parasite transmission would take time and control of the disease would need to be established before focusing on its complete eradication. Another option could be to focus on improving the resiliency of the approach to achieve elimination, by using, for example, several control options together to make transmission interruption





Frequency distributions of transmission break or endpoints obtained by Bayesian Melding model fits to age infection prevalence from communities exposed predominantly to culicine (a) or anopheline (b) mosquito vectors. The results show that breakpoints whether measured by microfilariae (mf) infection, infective L3 larvae or antigen (Ag) prevalence are highly variable within- and between-villages as a result of stochasticity and uncertainty in parameter values. In general, however, for a given endemicity level, LF endpoints for all the shown three infection indicators are found to be lower in culicine compared to anopheline-transmitted LF.

more likely. However it is approached, the researchers are certain that combining vector control with mass treatments is the most effective way to achieve LF elimination in the long term.

To facilitate this, the researchers are now working on a Bayesian spatial-prediction tool to bring together their LF models with local data about vector abundance and human infection from field surveys. By reaching out to policy makers, this tool could transform the way LF interventions are planned and implemented. WHO has shaped its previous policy on LF elimination strategy according to their work and the team are hopeful that their latest findings will also be taken on board. "For parasite control, an ecologically and socially resilient approach must ultimately not only tackle integration of diverse technical control options, but also place control within the broader human developmental context of enhancing investment, likelihoods, education, infrastructure, governance and innovation in endemic settings," Michael explains, emphasising the importance of a rounded approach to NTD control. "Developing such a transformative framework is crucial if we are to avoid the partial solutions that have characterised the outcomes of most previous global parasite control programmes."

The work has received a great deal of interest from influential organisations in the field; Michael has been invited to work with WHO, Centers for Disease Control, the Carter Center and the Bill and Melinda Gates Foundation. Thanks to this thorough research and the innovative new models and control approaches it has spawned, the eradication of LF is likely to occur sooner rather than later. For the millions of people currently living with the infection this would mean a better chance of escaping poverty-driven health problems, and would provide the next generation with a healthier start in life.

INTELLIGENCE

MODELING LYMPHATIC FILARIASIS TRANSMISSION AND ERADICATION IN PAPUA NEW GUINEA

OBJECTIVES

The project focuses on the control and elimination of the vector-borne disease, lymphatic filariasis, to show how mathematical models of parasite transmission can provide a quantitative framework for aiding the design of parasite elimination and monitoring programmes.

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EDWIN MICHAEL is an epidemiologist who studies the spread and control of important tropical infectious diseases. He is currently working as Professor at the University of Notre Dame. The overriding objective of Michael's research is to address the next generation of critical questions regarding the population ecology, epidemiology, and control of neglected tropical and vector-borne diseases, including lymphatic filariasis and malaria.

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