Improving antimalarial outcomes

Tackling malaria in large, cross-border regions is a complex and challenging task. Dr Jaishree Raman’s recent project has contributed to malaria control within the Lubombo region of southern Africa by monitoring antimalarial drug resistance and the effectiveness of control programmes.

Prior to joining the National Institute of Communicable Diseases this year, you spent 10 years at the Malaria Research Unit in Durban, South Africa. Could you give an insight into some of the achievements of this remarkable research unit?

During its 25 year existence, the Malaria Research Unit played a very influential role in advancing existing knowledge and reducing the malaria burden, not only in South Africa, but throughout the continent. The Unit has been instrumental in implementing effective malaria control programmes as well as building capacity to ensure the sustainability of these initiatives.

One of the Unit’s greatest achievements was the establishment of the first African multi-country malaria control programme, as part of the Lubombo Spatial Development Initiative (LSDI). The success of the initiative, which aimed to develop the Lubombo region into a globally competitive economic zone by promoting regional cooperation and service delivery, was guaranteed only once malaria was effectively controlled in the region.

How can malaria be specifically diagnosed and treated?

As the symptoms of uncomplicated malaria are non-specific and very similar to a number of other common illnesses, it cannot be diagnosed by symptoms alone. The detection of either malaria parasites in a blood smear or malaria antigens by a rapid diagnostic test (RDT) are two of the most commonly used methods to confirm infection. Following diagnosis, a patient is required to take a course of antimalarial drugs, which generally target blood-stage malaria parasites. Until very recently, most of the recommended antimalarials killed those responsible for the malaria symptoms (asexual parasites) but were largely ineffective against the parasites associated with onwards transmission (sexual gametocytes). This has partially been addressed by the introduction of artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated malaria infections. The artemisinin component of ACTs are effective against asexual parasites and all but the very mature stage gametocytes.

A two-pronged method for effective malaria control was adopted by the LSDI. Can you outline the approaches that were used?

Given the complexity of the malaria life cycle, the driving forces behind the LSDI malaria control programme, Drs Brian Sharp and Dave Le Sueur, felt sustained effective malaria control within the Lubombo region would require an integrated approach – incorporating both vector and parasite control. To this end, the LSDI malaria intervention in southern Mozambique consisted of two main strategies: vector control using insecticide-based indoor residual spraying; and effective case management comprising definitive diagnosis with RDT kits and treatment with efficacious antimalarials. Following the remarkable successes of the LSDI malaria control initiative, the LSDI model has been replicated on Bioko Island and mainland Equatorial Guinea with equally impressive results.

What are the key methodological features of the work you have recently completed on antimalarial drug resistance?

In response to recent drug resistant malaria epidemics, the World Health Organization (WHO) recommends regular drug efficacy testing as a means of ensuring effective antimalarials are in place. The gold standard for drug efficacy assessments – in vivo efficacy trials – are unfortunately expensive, time consuming and very labour intensive. A more cost-effective alternative, the routine surveillance for known molecular markers of antimalarial drug resistance (genetic mutations), was employed in this study. Finger prick capillary blood samples from children aged between two and 15 years were collected on filter paper during annual malaria prevalence surveys. Once in the laboratory, parasite DNA extracted from the filter paper blood was subjected to molecular analyses (polymerase chain reaction and endonuclease restriction cleavage) to detect mutations associated with reduced antimalarial efficacy.

Should Africa receive more global support for improvement of malaria treatment, care and prevention?

A very resounding yes! The unprecedented increase in funding for malaria control initiatives in Africa over the past decade has significantly contributed to the dramatic decrease in the incidence of malaria on the continent. In fact, the decreases have been so impressive in two African countries – South Africa and Swaziland – that they have embarked on elimination agendas. In order for the gains made against malaria to be sustained and elimination to become a reality on a continental scale, it is essential that funding for malaria research and control continues. A decline or cessation in support could allow malaria to rebound with serious human and economic consequences.
IN SOUTHERN AFRICA, the high incidence and long-term debilitating effects of malaria have impeded socioeconomic development of the region. Malaria increases the burden on health systems, already over-stretched by infectious diseases like HIV/AIDS and TB, meaning resources available for effective malaria detection and treatment are limited. This is further compounded by the complex geographic distribution of malaria. Badly afflicted and disease-free regions often exist in close proximity, making addressing malaria in a country-specific manner very challenging. Additionally, the endemic malaria situation in many southern African areas is exacerbated by a lack of sustained financial support, skilled malaria experts and essential infrastructure.

LUBOMBO SPATIAL DEVELOPMENT INITIATIVE

In 1999, the Lubombo Spatial Development Initiative (LSDI) – a trilateral partnership between the governments of Mozambique, South Africa and Swaziland, aiming to develop the economic potential of the area – established a malaria control arm in response to the high malaria burden that was inhibiting socioeconomic development of the Lubombo region. The primary objective of the LSDI was to make significant reductions in malaria morbidity and mortality by developing and improving sustainable infrastructure for effective malaria control, and establishing cross-border collaboration to ensure the coordination and implementation of effective vector control interventions.

The main geographic focus of the intervention was Mozambique, since it had the highest malaria burden of the three participating countries, representing the largest parasite reservoir for the potential reintroduction of malaria into South Africa and Swaziland. The primary emphasis of the LSDI’s malaria control programme was to extend interventions into southern Mozambique. The regional expansion of successful vector control measures, while ensuring accurate diagnosis and effective treatment, was essential to the success of the initiative in all three participating countries.

MONITORING RESISTANCE MARKERS

As part of the programme, Dr Jaishree Raman has been working on a long-term project monitoring antimalarial resistance markers in both the Maputo and Gaza Provinces of southern Mozambique, following changes in antimalarial treatment policy. Genetic mutations associated with resistance to almost all commonly used antimalarials, with the exception of artemisinins, have been identified within the genome of Plasmodium falciparum, the most prevalent human malaria parasite. Raman elucidates: “In line with the World Health Organization’s (WHO’s) recommendation of regular assessment of antimalarial efficacy, our study determined the prevalence of mutations associated with resistance to antimalarials that are currently in use, or have previously been used, in Mozambique, namely; chloroquine, sulfadoxine-pyrimethamine (SP) and lumefantrine”.

Working alongside the LSDI’s malaria control programme allowed Raman to take advantage of the stringent monitoring and evaluation measures in place within the initiative; primarily the spatially enabled malaria information system (MIS) that was designed and implemented especially for the project. The two most important facets of this system were that it allowed the progress of spray...
In 2011, at the end of the initiative, the entire southern Mozambique and across the LSDI zone. and dramatic declines in malaria prevalence in Provinces were greatly strengthened, resulting in initiatives the human and infrastructural capacity were being met and corrective measures were immediately implemented in underperforming areas. “This regular monitoring and evaluation clearly demonstrated the effectiveness of the initiative as numbers of both cases of malaria and malaria mosquitoes declined markedly over the study period,” Raman enthuses.

THE ROLE OF DRUG PRESSURE

Raman’s research has highlighted the pivotal role of drug pressure on the spread of drug-resistant parasites. For example, in 2001, a peak in the quintuple mutation associated with SP treatment failure was linked to increased SP drug pressure in a neighbouring South African province, KwaZulu-Natal. Once this pressure was removed, following the introduction of the artemisinin-based combination therapy (ACT), artemether-lumefantrine in KwaZulu-Natal, the quintuple mutation prevalence in Maputo Province declined markedly. Rather unexpectedly, this mutation’s prevalence sharply increased in both Maputo and Gaza Provinces following the introduction of the ACT – artesunate and SP – as a first line treatment in Mozambique, resulting in artemether-lumefantrine becoming the antimalarial of choice in 2008.

Despite this change, prevalence of the quintuple mutation remained extremely high, raising concerns over the continued use of SP for intermittent preventative treatment. More concerning, however, was the increase in markers not associated with chloroquine sensitivity but with lumefantrine resistance. “Close monitoring of artemether-lumefantrine efficacy is therefore essential given the immense regional artemether-lumefantrine pressure, as it is the drug of choice in most southern African countries,” Raman adds. Data generated during her study have been used to inform Mozambican antimalarial drug policy and to assess the effect that antimalarial drug pressure has on the spread of resistance markers in southern Mozambique.

ENSURING FUTURE MALARIA CONTROL MEASURES

During the 12 years of LSDI’s malaria control initiatives the human and infrastructural capacity of the programmes in both Gaza and Maputo Provinces were greatly strengthened, resulting in markedly improved malaria control measures and dramatic declines in malaria prevalence in southern Mozambique and across the LSDI zone. In 2011, at the end of the initiative, the entire infrastructure acquired or developed during the programme was transferred to the relevant Mozambican provincial programmes.

Despite this investment in human and infrastructural resources, the effectiveness of the control programmes are severely hampered by the lack of adequate funding. The Mozambican and South African Governments are therefore in talks with potential funders in an attempt to secure grants to ensure the continuation of the LSDI’s malaria programme. Raman believes there is still much to do: “If malaria in Mozambique is to be effectively controlled and eventually eliminated, then considerable sustained investment into both infrastructure and human resources is urgently required,” she adds. “Funders need to ensure the long-term sustainability of interventions as the gains made against malaria are rapidly eroded once control measures breakdown.”