PATH Malaria Vaccine Initiative outlines new strategy to eliminate and eradicate malaria

At the recent Fifth Multilateral Initiative on Malaria Pan-African Malaria Conference (held November 2–6, 2009, in Nairobi, Kenya), the PATH Malaria Vaccine Initiative (MVI) outlined an aggressive strategy that aims to achieve the long-term goals set in 2006 by the international community for elimination and eradication of malaria.

According to the WHO, there were 247 million cases of malaria in 2006, and it is estimated that a child dies of this preventable and curable disease every 30 seconds.

Malaria is caused by parasites of the species *Plasmodium*. There are four types of human malaria, of which *Plasmodium falciparum* is the most deadly. The PATH MVI was set up in 1999 through a grant from the Bill & Melinda Gates Foundation with the aim of identifying vaccines against *P. falciparum* and aiding them through the development process.

The MVI strategy aims to build on the recently reported success of GlaxoSmithKline Biologicals' RTS,S vaccine candidate, which has now reached Phase III clinical trials, and is therefore the worlds most advanced malaria vaccine candidate. The trial, being carried out in partnership with the Malaria Clinical Trials alliance and 11 African clinical trial sites, aims to ultimately enroll up to 16,000 children aged 6 weeks to 17 months.

The RTS,S antigen in the vaccine is produced in yeast and consists of the circumsporozoite protein and the hepatitis B surface antigen. The vaccine is designed to target the pre-erythrocytic stages of *P. falciparum* by eliciting a strong neutralizing antibody response against surface-exposed sporozoite proteins. The sporozoite stage is part of the asexual reproduction of the malaria parasite. Sporozoites develop in mosquitos that have fed on infected humans and migrate to the salivary glands of the insect. When mosquitos feed on humans the sporozoites are passed on and infect the hepatocytes of the host liver, after which the infection spreads to the blood.

The RTS,S vaccine is designed on the rationale that antibodies raised against the circumsporozoite protein of the RTS,S antigen will either bind to and neutralize invading parasites or opsonize them, labeling them for macrophage-mediated destruction.

In a Phase II study of the vaccine, the efficacy rate of protection against development of clinical malaria in young children was found to be 53%. If Phase III testing is successful and the vaccine is licensed, RTS,S could reach the landmark achievement of being a 'first-generation' malaria vaccine. As set out in the international community's 2006 Malaria Vaccine Technology roadmap, the goal of this vaccine is to induce immunity that lasts longer than 1 year and is at least 50% effective.

Many of the feasibility studies being undertaken by MVI focus on providing the vaccinated individual with immediate protection against the parasite while it is still in the pre-erythrocytic stage. MVI plan to continue with investments in the area of blood-stage infection but note that they will be limited and aim more towards yielding results that could be useful in development of a pre-erythrocytic vaccine.

MVI plan to aggressively target malaria through research into a variety of vaccines and vaccine boosters and the technology needed to develop these.

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"Our new strategy will build, efficiently and aggressively, on the incredible knowledge generated in MVI's first decade of operation," explains Dr Christian Loucq, director of strategy and operations for MVI. "We are looking both inside and outside the malaria research community, towards investing aggressively in approaches and technologies that are at an earlier stage of development."

As part of their new strategy, MVI hope to identify and develop:

- Vaccine candidates that block the transmission of malaria from mosquitoes to humans, thus limiting the spread of infection;
- Vaccines against *Plasmodium vivax*, the widespread malaria parasite that is less severe than *P. falciparum* but still capable of affecting humans;
- Laboratory tools and methodologies for the evaluation of these vaccine candidates in humans.

Loucq emphasizes that this strategy is a work in progress that cannot be fruitful without the aid of the international community.

"Our plan is to maintain sufficient flexibility so that if one or more of our approaches is highly successful, we will be able to realign budget and strategy to accelerate its development," said Loucq. "But what is still as true today as 10 years ago is that we cannot achieve our goals without the sustained commitment of partners, including national governments, industry, other researchers, and donors."

Sources: Bejon P, Lusingu J, Olotu A et al.*: Efficacy of RTS,S/AS01E vaccine against malaria in children 5 to 17 months of age.* N. Engl. J. Med. *359, 2521–2532 (2008); http://www.who.int/mediacentre/factsheets/fs094/en/index.html http://www.malariavaccine.org/index.php http://www.denniskunkel.com/DK/Protozoa/281001C.html*

Malaria, TB and HIV/AIDS tests require better assessment

Scientists have recently emphasized the poor quality of studies that assess the accuracy of three of the main infectious killers: TB, HIV and malaria.

Fast and efficient diagnosis is crucial for the treatment of infectious diseases, and a team led by Dr Madhukar Pai at the Research Institute of the McGill University Health Centre and McGill University (Quebec, Canada), in collaboration with researchers at the TDR (Special Programme for Research and Training in Tropical Diseases) and the WHO, have suggested that scientific papers frequently use low-quality methods. In addition to this, the researchers report that bias and variation were present in all of the papers studied.

"The necessary methodological elements, such as patient selection criteria, recruitment methods or blinded test interpretation, were poorly reported," explained Pai, who is the senior author and principal investigator of the study. "Moreover, only a small percentage of these studies accurately described the manner in which the tests were conducted and whether they are reproducible."

Approximately 3.5 million deaths world wide are a result of TB, malaria and HIV/AIDS infection and early diagnosis is key to keeping the rate of infection under control. Dr Pai noted the dangers of poor assessment of low-quality commercial diagnostics. "Poorly designed studies can lead to premature or misguided adoption of tests that may have little or no clinical and public health relevance, resulting in incorrect diagnosis and adverse consequences for the patient."

Researchers must strive to make a concerted effort to improve the quality of diagnostic studies during design and implementation. "Whether it is for cancer testing, TB or even the flu, we must report the study results in a clear and transparent manner in order to validate the accuracy of the test and ensure it is properly used at the clinical level," stated Pai.

Source: McGill University Health Centre, http://www.muhc.ca/media/news/item/?item_id=112214

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Could sterile male mosquitoes eliminate malaria?

Sterile insect technique (SIT) is the release of sexually sterile male insects into a pest population in the hope that they will eradicate the pest. In a supplement, published in BioMed Central's open access *Malaria Journal*, Dr Mark Benedict proposes that the technique could be applied to the malaria problem in Africa.

"In the context of elimination, SIT could play a unique role. As part of an area-wide integrated pest management programme, the SIT may be able to minimize problems due to insecticide resistance to antimalarial drugs. Because it is uniquely effective at low mosquito densities, SIT might be just the thing to deliver the final blow to mosquito populations and to completely remove malaria from a given area".

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SIT was developed by Dr Benedict and his colleagues at the International Atomic Energy Agency in Vienna, Austria, and involves generating male mosquitoes that are sexually active but unable to produce offspring. Female mosquitoes only mate once in a lifetime and so a single mating with one of the sterile males will ensure that she never produces young. In contrast to insecticides, which eliminate a fraction of the insect population, SIT produces a steady decline in insect numbers over time.

Benedict highlighted the strengths of the technique, "The SIT has proven highly effective over large areas when used against other insects. We produced this supplement because we believe that the technique has been overlooked as an anti-mosquito method. Its efficiency in low vector-population settings precisely complements insecticide-treated bednets, indoor residual spraying and larval control: when they are at their weakest, SIT is at its strongest."

Source: *Benedict MQ, Robinson AS, Knols BGJ (Eds): Development of the sterile insect technique for African malaria vectors.* Malaria J. *8 (Suppl. 2) (2009).*

New method for more accurate antimalarial dosing

A method for age-based dosing for malaria drugs has been developed by researchers at Liverpool School of Tropical Medicine (LSTM, Liverpool, UK). Weight-based dosing has become difficult in several malaria-endemic countries owing to restricted formal health services.

Adequate scales are in short supply, and treatment is most often administered at home using drugs bought from shops and street vendors. For this reason, doses are tailored to the patient using their age to estimate body weight.

Currently, there are no standardized procedures to formulate treatments based on age, but malaria control programs require recommendations based on both age and weight. Because there is no comprehensive guidance regarding age-based dosing, there is a large amount of variation in treatment strategy, which leads to poor regimens that are broadly utilized.

"A weight-for-age reference data set was compiled and modeled specifically for this purpose using nutritional data that was shared with us by institutes and scientists from over 35 malaria-endemic countries"

In collaboration with the World Health Organisation TDR programme, the Drugs for Neglected Diseases Initiative (DNDi) and the Netherlands Organisation for Applied Scientific Research, Dr Anja Terlouw and a team of researchers from LSTM developed the new tool that aids with the determination of age-based regimens, and minimizes the number of patients who are dosed above or below the effective treatment range.

"A weight-for-age reference data set was compiled and modeled specifically for this purpose using nutritional data that was shared with us by institutes and scientists from over 35 malaria-endemic countries. This allowed us to develop a modeled reference distribution that reflects the variation in weight by age of populations in malaria endemic regions of Africa, Asia Pacific and Latin America, and can therefore provide the optimal translation of weight-based to age-based dosing regimens," explained Dr Anja Terlouw.

Dr Terlouw's group are now searching for opportunities to work on drugs for other neglected diseases, as it is becoming more and more obvious that there is a requirement for similar aged-based dosing regimes in areas where there is restricted healthcare access.

Source: *Liverpool School of Tropical Medicine, www.liv.ac.uk/lstm/about/communications/press_releases/new_tool.htm*

Screen-based malaria prevention: cheap and effective

A total of 500 homes in The Gambia, Africa, were included in a trial to determine the effectiveness of screen-based prevention of malaria. A 50% decrease in malaria transmission and anemia in children was observed.

Malaria is a potentially fatal disease and, in Africa, a child dies from malaria every 30 seconds. Malaria infection also leads to an increased risk of anemia, which can also prove deadly.

The research, undertaken by researchers from Durham University (Durham, UK), the London School of Hygiene and Tropical Medicine (London, UK), and Medical Research Council The Gambia, and funded by the Medical Research Council, was carried our in the homes of 1085 children living in the town of Farafenni. Two types of screen were tested – one saw screens attached to windows and doors, and holes in the eves closed; the other involved putting a net ceiling into the house.

Traps were installed for both methods so that the researchers could count the amount of mosquitoes that got through the screens. Hemoglobin concentration was measured in children at the end of the malaria season to assess the prevalence of anemia and parasitemia (where parasites are present in the blood).

Up until now, screens have taken a back seat to the use of drugs and insecticides, but both methods used in the current study were found to substantially reduce transmission of malaria and caused a 50% decrease in anemic children in the screened group compared with those who lived in homes that were not protected by the screens.

Professor Steve Lindsay, MRC researcher and Chair in Disease Ecology at Durham University, explained the significance of the study: "Our findings show that screening homes is a cheap, simple public health intervention that can save lives. Mosquito-proofing homes is one of the principal tools that has been associated with protection against malaria, yet it has been ignored during long-term anti-malarial drug- and insecticide-driven campaigns."

"For the first time in a generation, malaria is declining in many parts of tropical Africa, and this has led to renewed calls for malaria elimination. Our findings show that screening homes is extremely effective and could play a major role in the elimination of malaria."

Because screening protects everyone in the house for several years, it may be a cheaper long-term solution than the nets. The average cost per fully-screened individual in the trial was US$9.98.

Overall, participants welcomed the screens, with nine out of ten people hoping to obtain or keep full screening. Despite some problems such as rats making holes in the screens and mosquito entrance owing to open doors, the trial participants were hopeful, their comments including, "We are ready to maintain the screening even without the MRC", "If it would cost selling a goat to repair our screening, we would do it as we know they are very useful", and "Screened ceilings are like a bednet for the whole house".

Source: Durham University: http://www.dur.ac.uk/news/research/?itemno=8628