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2.5 Groundbreaking Research into the Treatment of Severe Malaria that Lead to Changes in the World Health Organization's Official Guidelines

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Established in 1967, SEAMEO TROPMED/Thailand, which is based at the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, offers training in endemic tropical diseases, parasitology, community and preventive medicine. It also conducts research into alternative control measures of diseases and the promotion of healthy lifestyles, including trials of new chemotherapeutic compounds and new vaccines. It also provides clinical care to patients suffering from tropical diseases.

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I. Abstract

Malaria remains a critical global health challenge in tropical countries worldwide, particularly in the Southeast Asian region. Severe malaria infection is a major cause of childhood mortality and a leading cause of paediatric hospital admissions in both sub-Saharan Africa and Asia. Consequently, the disease has been a major focus of intensive clinical research conducted at the SEAMEO TROPMED Regional Centre of Tropical Medicine (SEAMEO TROPMED/ Thailand), at Thailand's Mahidol University's Faculty of Tropical Medicine, since 1950.

Over the past decade, efforts to reduce malaria fatalities have focused on two large multi-centre clinical trials that compare parenteral treatment with either artesunate, or quinine treatments in patients with severe malaria. The first research study, conducted in four Southeast Asian countries, focused on adult test patients. The second study was conducted in nine African countries on children under 15 years old.

The two studies revealed that artesunate medical treatment substantially reduces both adult and child malaria infection mortality rates. This data, together with a meta-analysis of all trials comparing artesunate and quinine treatments, strongly suggests that parenteral artesunate should replace quinine as the treatment of choice for severe falciparum malaria infection worldwide.

II. Project Description

1. How does the project link to the needs of the region?

Severe malaria is a life-threatening disease. Patients suffer high fever, coma, acidosis (excessive acid in the blood), severe anaemia, renal failure and/or failure of other organs. Once the disease has passed this critical stage, the patient can die within 24 hours. Immediate medical intervention, with an injectable antimalarial drug, is essential to save the patient's life. For centuries, the drug of choice was quinine. In the early twentieth century, a group of Chinese scientists developed a new class of antimalarial drugs called artemisinins containing a more potent action against the malaria parasite Plasmodium falciparum.

This drug also kills the parasites at an earlier stage than quinine, preventing young ring forms developing into the much more dangerous advanced trophozoite and schizont stages. However, trials in the 1990s that compared quinine with an oil-based derivative of artemisinin called artemether for the treatment of severe malaria did not show any advantage of artemether in preventing death. It became clear this was because the oily substance was not absorbed well at the intramuscular injection point. This ineffectiveness was especially noticeable in very sick patients who needed the drug the most.

Subsequent trials were therefore performed with a water-soluble derivative of the drug called artesunate, which can be absorbed directly into the blood stream. This solution is better absorbed into the patient's circulation when given via intramuscular injection. Recent figures indicate that half of the world's population is at risk of malaria infection, with 109 malarious countries identified in four continents. This accounts for an estimated 200-300 million cases of malaria infection per year, which claims an average one million fatalities per year. An estimated 85-90 percent of global malaria cases where identified in Africa and Asia respectively.

2. How does the SEAMEO TROPMED/ Thailand address this urgent need?

SEAQUAMAT Study

The Faculty of Tropical Medicine and the Mahidol-Oxford Tropical Medicine Research Unit collectively coordinated a major trial in four Southeast Asian countries to compare artesunate with quinine in the treatment of severe malaria. The patients in this trial, with the acronym SEAQUAMAT, came from Bangladesh, India, Myanmar and Papua Indonesia, and were mainly young adults.

The data safety committee who monitored the trial stopped the study after 1,461 patients had been selected because the number of deaths was 35 per cent lower in patients treated with artesunate, compared to those treated with quinine. The study was published in the world's leading general medical journal The Lancet in 2005 and as a result of the trial, the WHO changed their guidelines regarding the treatment of severe malaria in adults to recommend the use of artesunate.

However, the results were not sufficient to modify the treatment of severe malaria in African children, who account for up to 90 per cent of all global malaria fatalities. It was argued that the disease has more rapid detrimental effects in children compared to adults, so the more effective antimalarial drug might not have as much time to exert its life-saving properties. Also, in comparison to Asia, Africa has less quinine resistance. An additional issue is that many children diagnosed with severe malaria in Africa also have an additional severe bacterial infection which an antimalarial drug is ineffective in treating.

SEQUAMAT study sites: Artesunate versus quinine for the treatment of severe falciparum malaria: A random trial in:

- Bangladesh: Chittagong;
- India: Rourkela;
- Myanmar: several sites;
- Papua Indonesia: Timika.

Photo: SEAMEO TROPMED/ Thailand

SEQUAMAT study sites

III. Significant Impacts

SEAQUMAT Study

The Faculty of Tropical Medicine and the Mahidol-Oxford Tropical Medicine Research Unit, in collaboration with a large group of investigators, also organized a large trial centered on 11 sites in nine African countries. This intensive research compared the effectiveness of artesunate to quinine in preventing death from severe malaria.

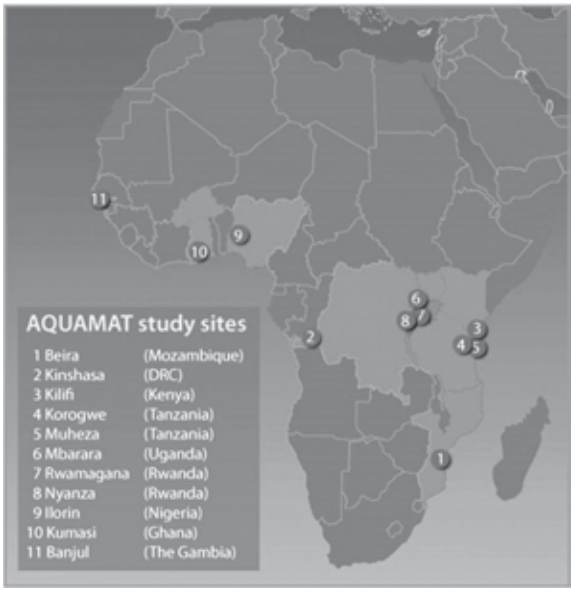

Photo: SEAMEO TROPMED/ Thailand

This open-label randomized trial, with the acronym AQUAMAT, took five years to complete and tested 5,425 children below the age of 15 infected with a confirmed diagnosis of severe malaria. Death occurred in 10.9 per cent of children given quinine treatment, compared to 8.5 per cent of children given artesunate – a 22.5 per cent reduction in mortality. Since there are an estimated 800,000 deaths from severe malaria in African children every year, a change of treatment from quinine to artesunate can potentially save hundreds of thousands of lives.

The trial showed that the higher survival rate was not at the expense of an increase in neurological sequelae in children treated with artesunate; severe neurological sequelae were observed in only between two to three per cent of children in both treatment groups. Adverse symptoms, such as convulsions or low blood sugar levels occurred less frequently in children treated with artesunate, compared to children treated with quinine. Overall, artesunate appeared to be greater tolerated in patients and with no serious adverse drug-related effects. The results were published in The Lancet on 13 November 2010.

Regarding emergency treatment administered to severely ill malaria patients admitted to clinics in Africa or Southeast Asia, in which injections could be given, six studies where recorded in which it was decided essentially on the toss of a coin, for each new patient, whether quinine or artesunate would be the main drug administered over the initial days of treatment.

Each of the studies revealed that there were fewer deaths in the section of patients who were allocated artesunate. The results of all six studies revealed that there were 488 deaths

(13.6 per cent) among the total of 3,596 patients administered quinine, but only 354 deaths (9.8 percent) among the total of 3,602 patients allocated artesunate. Also, among the group who survived the infection, their recovery from the disease was markedly faster with artesunate than with quinine. This difference (354 deaths compared to 488 deaths) is far too significant to be attributed to a play of chance. This indicates that clinics who switch from routinely using quinine to routinely using artesunate for severe malaria patients will safely prevent about 25 per cent of malaria deaths on average.

Photo: SEAMEO TROPMED/ Thailand

A press conference held at the Faculty of Tropical Medicine, Bangkok, in November 2010, to announce the results of the AQUAMAT study.

IV. Success Factors

The success of the initial research project in Southeast Asia was used as a model to conduct the same study in Africa. Through strong collaboration between interested parties and local hospitals, backed by a budget allocation and potential human recourse as the key factors, the project successfully achieved its objectives.

V. Lessons Learned and Potential for Project Expansion

At the time this report was published, there was a quality supply of artesunate for injection, available from Guilin Pharmaceuticals. This drug could be registered in all malaria endemic countries, and where applicable, be purchased with financial support from the Global Fund to Fight AIDS, Tuberculosis and Malaria.

It is expected that WHO guidelines for the treatment of severe malaria in children will be adapted according to the AQUAMAT results, yielded through the intensive research carried out by the Mahidol-Oxford collaboration and the SEAMEO TROPMED Regional Centre for Tropical Medicine, Faculty of Tropical Medicine, at Mahidol University, Bangkok, Thailand.

Photo: SEAMEO TROPMED/ Thailand

Report "Guidelines for the Treatment of Malaria"

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