

Editorial

Reducing Death in Malaria by Using Artemisinin Preparations

During the past 6 years, malaria has attracted unprecedented attention from policy planners, donors and scientists and, at the same time, major gains in control have been attained through wide and timely use of new strategies for diagnosis, treatment and control. Such is the excitement with these gains that malariologists now speak of the possibility and importance of malaria elimination - before the parasite again takes control. Three tools underpinning these gains are insecticide treated bednets for prevention of malaria, antigen-based rapid diagnostic tests and artemisinin derivatives for treatment of malaria. The limelight has been taken by the artemisinin derivatives which has surpassed all expectations when access is facilitated for its immediate use as first line treatment for uncomplicated malaria. The importance of the artemisinins in malaria control and global health is reflected in their pivotal role in malaria elimination efforts and in the development of funding approaches to reduce their costs and increase access as widely as possible through the Affordable Medicines Facility for malaria (AMFm). Two recent honours reflect their role - the Canada Gairdner Global Health award to Professor Nicholas White for leading the development of artemisinin combination treatments (ACTs) to improve first-line treatment for uncomplicated malaria and prevent resistance and the BMJ Award for Best Research Paper for early treatment of malaria using rectal artesunate in a community based malaria study.

Trials of effective strategies to prevent malaria mortality are few, but influence policy. During the past 20 years there have been three multi-country randomized controlled trials that fall into this category. Impregnated bednet (ITNs) trials undertaken in Africa showed an overall protective efficacy of 17% compared to no nets on child mortality, and a 50% reduction in the incidence of uncomplicated malarial episodes.¹ These results have made ITNs the backbone of malaria prevention efforts. In Bangladesh alone, more than 1.6 million such nets have been distributed in malaria endemic areas in recent years with the financial assistance of Global Fund.

In the new edition of WHO Malaria Treatment Guidelines, malaria control is based upon immediate access to artemisinin based therapy both in uncomplicated and in severe malaria.² The recommendations for severe malaria are based upon two major trials showing the life saving benefit of artesunate - the first demonstrating superiority of parenteral artesunate

to parenteral quinine which, until now, has been the drug of choice for hospital management of severe and complicated malaria. The second trial demonstrated that early treatment with artesunate for patients who might take some hours to get to a hospital (or clinic) prevented death and serious neurological damage.

Until recently we presumed, but had no proof that the broader stage-specific action of the artemisinins - killing young parasites before they sequester as well as killing the pathogenic mature stages - could convert into a survival benefit over quinine in the management of severe malaria. In 2005 the breakthrough SEAQUAMAT study, conducted in four countries of Asia including Bangladesh, proved that when given to adult patients who have severe or cerebral malaria, artesunate treatment prevents 35% more deaths than quinine treatment.³ A similar study involving children in several countries in Africa (AQUAMAT) is likely to be completed this year (personal communication with Professor Nick J White and Dr. Arjen Dondorp).

Study 13 showed that treatment of severe malaria can prevent death and permanent neurological damage when given early enough in the course of the disease to be able to do so. For patients who might take several hours to reach a hospital, long transit times delay parasite control, leading to complications of malaria (cerebral malaria, pulmonary edema, renal failure and severe anaemia) and mortality can be high after treatment because the pathological consequences have advanced even when parasitaemia has been eliminated. Treatment delays of one day are not uncommon after development of severe symptoms.⁴ The randomized, placebo-controlled trial enrolled ~18000 patients, followed principles of best ethical practice and demonstrated that interrupting parasite growth reduced death and permanent neurological damage by about 50% (3.8% vs 1.9%) in patients who had not yet reached hospital within 6 hours of treatment.^{5,6} The Bangladesh component which enrolled ~8000 cases in Chittagong District was led by the Malaria Research Group. The outcomes contributing to this result were all in children as older patients arrived at hospital quickly (within a median of two hours of insertion of suppository). A further study using a case control design is planned to find conclusive answers in older patients.

Effective tools for malaria control are now available. With an increasing number of cheap, practical antigen-based rapid

diagnostic tests, early diagnosis and treatment of malaria in the community and health facilities is now feasible. Combined with preventive measures, significant reductions in malaria are possible if these tools are used widely, effectively and resolutely.

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