

20 YEARS OF PROGRESS IN MALARIA RESEARCH

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U.S. Naval Medical Research Unit No. 2 Detachment (NAMRU), in collaboration with National Institute of Health Research and Development (NIHRD) and many other Indonesian government agencies and universities, has conducted studies of malaria throughout Java, Sumatra, Sulawesi, Kalimantan, Flores, Timor, and Irian Jaya. Most studies have characterized the disease epidemiologically by defining the parasitologic distribution of the disease in the population, and by defining the entomologic parameters of local transmission. Studies of patterns of resistance to antimalarials have also been done at many field sites. Several studies on the clinical management of malaria occurred in Rumah Sakit Umum Propinsi in Jayapura. In addition to these studies which impact upon local public health planning policy, immunologic studies routinely occurred in support of the global effort to develop a vaccine against malaria. This report summarizes the progress made in these areas of research during the first 20 years of NAMRU in Indonesia.

EPIDEMIOLOGY

Field surveys of malaria have occurred at sites throughout the Indonesian archipelago. In general, these surveys have shown that the highest rates of malaria occur where transmigrants have settled (Sumatra,

Kalimantan, Irian Jaya). Rates of malaria in settled communities tend to reflect the level of social and economic development. Geographically, the malaria situation tends to improve as one moves westward from Irian Jaya to Java. Irian Jaya has stable hyper to holoendemic malaria, while islands such as Java and Bali have unstable and patchily distributed epidemic malaria. All four species of malaria occur in Indonesia - *Plasmodium falciparum* and *P. vivax* occur on most of the islands, while *P. malariae* and *P. ovale* are more common in the easternmost provinces¹⁻⁵. More detailed epidemiologic and entomologic studies of malaria at specific sites in Timor, Flores and Irian Jaya have led to rational approaches to malaria⁶⁻⁹. At Robek, on Flores, an integrated program of malaria control instituted in 1984 continues to offer greatly diminished rates of transmission in 1990. One study has used the *P. falciparum* ring-infected erythrocyte surface antigen ELISA for the rapid characterization of relative levels of malaria transmission at field sites¹⁰.

PARASITOLOGY/BIOLOGY

These malaria studies provide a view of the relationship between the parasite and its host, whether that relationship is governed through immunologic, physiologic or genetic

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factors. In the latter, for example, studies in Sulawesi and Irian Jaya have documented the prevalence of inborn metabolic defects which may control malaria independently of immune mechanisms¹¹⁻¹². Progress in basic studies of malaria have been promoted greatly by the ability to continuously culture malaria parasites in vitro. Eight strains of *P. falciparum* from Indonesia have been adapted to culture. Once culture-adapted, the parasite is available in a limitless supply. The system provides antigen for immunologic studies and offers a means to study the biology of host-parasite interaction in vitro, as in the merozoite invasion inhibition assay¹³.

Basic studies of malaria also may take place in the field. Studies in Arso PIR, Irian Jaya revealed that mixed infections occurred almost exclusively in hosts with the lowest degrees of antimalarial immunity¹⁴. This was also true for development of gametocytes¹⁵. That finding led to the conclusion that gametocytocidal therapy with primaquine may prove to be an effective transmission-suppressing intervention strategy in populations of new transmigrants inserted into endemic areas⁹.

PREVENTION AND TREATMENT

Studies of drug resistance to malaria have revealed that the easternmost provinces of Indonesia have the most severe problems with multi-drug resistant falciparum malaria¹⁶⁻¹⁸. Other drug studies have defined the most effective chemotherapeutic regimens against chloroquine-resistant falciparum malaria.

For treatment of cerebral malaria, Hoffman *et al.* in 1988 reported results of a double blind placebo controlled trial utilizing

high dose dexamethasone in quinine treated cerebral malaria patients²¹. The study was conducted at the Provincial Hospital in Jayapura and involved 38 cerebral malaria patients. The outcome of this trial showed that high dose dexamethasone is not indicated for treatment of cerebral malaria patients.

For transmigrants living in Irian Jaya, those who had resided in the province for less than 2 years suffered a much higher failure rate for standard antimalarials than did transmigrants who had been in Irian Jaya for over 3 years⁹. In other words, standard antimalarials may produce acceptable clinical results in long-term residents, while in new residents, the same strains may not respond to standard doses of antimalarials. *Plasmodium vivax*, which routinely resisted weekly prophylaxis with 300 mg chloroquine, was documented in transmigrants living in northeastern Irian Jaya. Those strains failed to respond to therapy with 600 mg chloroquine²².

ENTOMOLOGY

Entomologic work has contributed greatly to our understanding the dynamics of transmission. Patterns of vector abundance, seasonality, vectorial capacity, host preference, feeding behavior, sporozoite rates, and insecticide susceptibilities have been determined in a variety of distinct habitats^{6,7,23}. This information is essential in formulating and evaluating intervention strategies. For example, in Arso PIR it was found that *Anopheles koliensis* was resistant to DDT, both physiologically and behaviorally. Based on the breeding and feeding behavior of this mosquito and the environment in Arso, it was deduced

that larval spraying and application of DDT on the interior walls of homes would be ineffective. Instead, the entomologic data pointed to the use of pyrethroid-impregnated mosquito nets as perhaps most effective. In Robek, Flores, analysis of the bionomics of the anopheline vector revealed that elimination of the breeding sites was practicable, while such strategy in Arso PIR would have been futile. These examples illustrate the importance of careful consideration to entomologic factors in mapping out site-specific intervention strategies.

IMMUNOLOGY

Studies in Irian Jaya have challenged long-held notions about how protective immunity to malaria is acquired in endemic areas. It is well known that continuous, heavy exposure to malaria is required to develop a protective immunity, and since that protection increases slowly with age, it is viewed as the cumulative product of exposure during years of life in an endemic area. But these conclusions were drawn from epidemiologic studies of populations which had spent all their lives in endemic areas - thus, cumulative exposure was synonymous with age and there would be no way to sort out independent effects of these two parameters. With new transmigrants from Java living side-by-side with life-long residents of Irian Jaya, it was possible to evaluate the protective effects of age and exposure separately. It was found that the transmigrants from Java quickly developed age-dependent protection and humoral immune responsiveness to malarial antigens. The age function of these parameters was quantitatively parallel to that in the life-long residents. These findings showed that protective

immunity against falciparum malaria was the product of age and recent exposure instead of being the cumulative product of chronic exposure²⁴. These studies may eventually provide an understanding of effective immunity against malaria as it occurs in nature, which could be exploited as a model for providing artificial immunity, via a vaccine.

The results of another study in Irian Jaya showed that hyperimmune people did not have lymphocytes which recognized the most promising antiparasite vaccine candidate of the time, R32tet32²⁵. Another study showed that protection against malaria did not correlate with levels of antibody to another promising vaccine candidate, Pf-155²⁴. In an attempt to verify the epidemiologic importance of the so-called crisis form factor of falciparum malaria, it was found to be of no apparent consequence in protection against malaria in Irian Jaya²⁶. Another series of experiments in Flores and Irian Jaya implicated antibody-mediated killing of suppressor T-cells as the cause of tropical splenomegaly syndrome²⁷.

DISCUSSION

Monitoring of drug resistance in *P. falciparum* has helped in the delimitation of the areas under the influence of drug resistance and when supported by trials with alternative drugs and drug combinations will constitute the basis for adoption of a rational drug policy in the country. Issues on effectiveness of chloroquine for treatment of *P. vivax* need further studies. Having realized that easternmost provinces of Indonesia have the most severe problems of malaria, more detailed epidemiologic and entomologic studies in this area should be

focused on the development of rational approaches to malaria, e.g., community participation in case detection and drug distribution, use of self-protection devices, and community-based vector control. There is an urgent need in establishment of key parameters to be used by community health workers for identification of breeding places in some areas. Studies on malaria immunology aimed at the development of a malaria vaccine should continue.

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