REVIEW OF STUDIES OF NATURALLY ACQUIRED IMMUNITY TO MALARIA IN IRIAN JAYA


ABSTRAK


Umur merupakan faktor yang penting untuk menentukan efektivitas vaksin malaria dan hal ini menjadi suatu aspek penting yang perlu diperhatikan dalam strategi pengembangan vaksin. Tingginya gametositemia pada transmigran perlu mendapat perhatian dan pengobatan gametositosidal (mis. dengan primaquine) perlu dipertimbangkan.

Dari sudut kesehatan masyarakat, penelitian ini menunjukkan perlunya pemberantasan malaria untuk transmigran dimulai sejak awal kedatangan mereka.

INTRODUCTION

Naturally acquired immunity to malaria was first described in 1900 by the famous German pathologist, Robert Koch, who conducted his landmark studies of acquired immunity to malaria in Java. Koch conducted microscopic examinations of blood films from people living in Batavia, Tosari, Sukabumi and in the Ambarawa valley near Salatiga. Koch noticed that the prevalence of malaria in areas where malaria transmission was seasonal or rare was evenly distributed among age groups. However, in the Ambarawa valley, where there was heavy malaria transmission, the prevalence of malaria diminished markedly with age. Koch

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made a critical deduction -- prior exposure was related to the distribution of parasites in the community, i.e., there was acquired immunity to malaria parasites. In the next year, Koch confirmed his deduction with studies in New Guinea\textsuperscript{2,3,4}. Adults in Java and New Guinea with life-long exposure to heavy, but not seasonal, malaria transmission were protected from frequent and high grade parasitemia and severe disease. The epidemiology of malaria had never been understood before Koch's immunity hypothesis. Rational analyses of the epidemiology of malaria by Christophers\textsuperscript{5} in India and Schuffner\textsuperscript{6} in Java followed Koch's descriptions of natural immunity. History of exposure defined immunity, and immunity defined the distribution of parasites and sickness in the community, i.e., the epidemiology of the disease.

Naturally acquired immunity to malaria remains a highly relevant research topic today. Good and Miller\textsuperscript{7} described 2 approaches to development of vaccines against malaria parasites; 1) understand the natural immunity to malaria parasites and attempt to reproduce it, or 2) attempt to induce a "supernatural" immunity with the use of select combinations of antigenic peptides, carriers and adjuvant. The greatest advantage of a supernatural vaccine is that it would presumably eliminate or prevent infection, disease or its transmission. The disadvantage of a natural vaccine is the apparent lack of a sterilizing immunity, i.e., even people with the highest degrees of natural immunity occasionally have low-grade asymptomatic parasitemia. On the other hand, naturally acquired immunity to malaria clearly works, whereas supernatural immunity remains to be demonstrated. Regardless of which approach is followed, a fundamental understanding of natural immunity is required. However, naturally acquired immunity remains a poorly understood process. Improving this understanding has been the focus of immunologic studies of malaria conducted in the Arso region.

The migration of nonimmune people from more developed, less malarious provinces to highly malarious, underdeveloped areas presents many challenges to public health workers. A parallel situation exists in the development of relatively remote malarious areas for tourism -- leisure tourists avoid malarious areas. Public health attention is often directed to the immediate concern of the preservation of life and economic viability of communities composed of people that are highly susceptible to sickness and death due to malaria, whether they be farmers or tourists. Scarce public health resources are directed to these new communities of highly susceptible newcomers. The allocation of resources seems proportionate to their relative susceptibility to infection. The situation raises several important questions for the public health officer and policymaker: 1) What kind of malaria control works best in new agrarian or resort communities? 2) How long and to what degree should those measures be applied? and 3) Who is most susceptible to infection, and for how long? The answers to these questions may be addressed by studies of the development of naturally acquired immunity in whole communities that lack prior exposure to endemic malaria.

The term "immunologic studies" is often associated with basic laboratory studies of antibodies, cytokines, immune cells and antigens addressing issues of molecular and cellular biology. In the context of immunologic studies in the Arso region of Irian Jaya, a broader epidemiologic/public health definition
applies as well. The focus of the immunologic studies in Irian Jaya has been the relationship between duration of exposure to infection, age of the host, and susceptibility to frequent high grade parasitemia and severe symptoms8. This is an area of mutual interest to the basic scientist and public health strategist.

DEFINITION OF NATURALLY ACQUIRED IMMUNITY

The term naturally acquired immunity to malaria, hereafter referred to as NAI, may be any phenomenon of immunity which develops after exposure to infection. NAI usually refers to diminished susceptibility to infection in people. However, NAI may be any cellular or molecular process which occurs after the first exposure to the parasite, whether the process is associated with protection or not (which is not yet discernable). The distinction in the application of the term NAI should be made clear -- one is NAI at the organismal and population level and refers to real protection from infection, whereas the other is at the cellular/molecular level and does not necessarily relate to real protection. NAI is a general term, and protective NAI refers specifically to processes associated with demonstrable protection from infection.

Protection from malaria in endemic areas begins in the womb and continues to develop throughout childhood and adulthood. Maternal IgG, and perhaps priming of immune cells with malaria antigen at critical periods of fetal development, prepares the infant born to endemic malaria. Before 1 year of life, this protection wanes and the child begins a period of 1 to 2 years of high susceptibility to illness and death9. Subsequently, the child possesses a so-called "anti-toxic" immunity where frequent and high grade parasitemia is tolerated with relatively little discomfort. For example, a non-immune adult may suffer severe symptoms of malaria and be confined to bed for many days with as few as 20 parasites per microliter of blood. In contrast, a 4-year-old child may have several thousand parasites per microliter of blood and be laughing and playing in his yard (personal observation) -- this is anti-toxic immunity. At about age 5 there may be noticeably fewer and lower-grade parasitemias. This trend continues gradually into adulthood where parasitemias become infrequent and generally asymptomatic. Diminished susceptibility to frequent and severe malaria as a product of heavy exposure to malaria is "protective NAI" as defined in this review.

THE MECHANISM OF PROTECTIVE NAI

Most investigators agree that the mechanism of protective NAI is poorly understood. However, most accept a model for protective NAI which may be described as the cumulative acquisition of protective immunity9. That is, antigenic diversity in the parasite drives host susceptibility for many years, until finally the cumulative effect of heavy exposure and clonal selection provides a repertoire of immune cells which is sufficiently diverse to defeat or suppress the parasite. This model of immunity has been supported by the consistent finding of age-related diminishing susceptibility to infection among people living in hyper and holoendemic areas. Serologic studies have also shown increasing levels of specific antibodies with increasing age. However, recent studies of protective NAI in the Arso region cast doubt on this model10. Whether this model is accurate is a question of significance for non-immune people.
trying to establish new lives in an endemic area. Will adult newcomers require decades of exposure to infection to reach the same level of protective NAI in their native neighbors? In fact, studies of protective NAI in newcomers to the Arso region demonstrated that this expectation is not true. Understanding acquisition of NAI in transmigrants in Arso may hold important clues to understanding immunity to malaria parasites.

**PROTECTIVE NAI IN THE ARSO REGION**

Transmigrants from Java immediately experience very heavy exposure to malaria transmission when entering hyperendemic areas like the Arso region of Irian Jaya (Fig.1). Susceptibility to frequent and high grade parasitemia seems uniform among the age groups during the first few weeks of exposure. However, an age-dependent protective NAI

![Graph showing prevalence of all malaria species over months in Irian Jaya](image)

**Figure 1.** Prevalence of all species of malaria in Arso PIR II in north eastern Irian Jaya among people from Java who arrived free of malaria parasites. After 1 year the prevalence peaked at 70%. The dotted line represents the clearly temporary effect of mass administration of chloroquine sometime between the 12th and 15th month.
develops relatively quickly -- no later than 18 months, and perhaps even sooner (Fig. 2). The diminishing susceptibility to infection with increasing age appeared in measurements of frequency of parasitemia, duration of parasite-free periods (Fig. 3), intensity of asexual parasitemia, and frequency and severity of symptoms (Fig. 4). In all of these measurements, age-dependent protective NAI was nearly parallel to that occurring among the natives of Irian Jaya. Furthermore, humoral immune responsiveness to ring-infected erythrocyte surface antigen (RESA) increased proportionately with age (Fig. 5). Despite a uniform 2 year period of heavy exposure to malaria antigens among the transmigrants, the acquisition of protective NAI was age-dependent. In these studies, care was taken to exclude innate characteristics of immunity to infection by malaria parasites, for example

![FOUR MONTH SPR (%)](image)

Figure 2. The slide positivity rate for *Plasmodium falciparum* by active case detection during a period of 4 months of surveillance in Arso PIR I in 1988. The transmigrants from Java had arrived in 1986, and already demonstrated a distinct decreases in susceptibility to asexual parasitemia with age.
Figure 3. Each point represents the median number of weeks at which half of the subjects in the indicated age and ethnic groups experienced their first asexual parasitemia by *P. falciparum* during a four month period of biweekly surveillance. This period represents the 19th to 23rd month of residence in Irian Jaya for the transmigrants. The natives of Irian Jaya were far slower to become parasitemic, but the increasing resistance to parasitemia with age was similar in both groups.
Figure 5. The mean optical density (O.D.) values for an enzyme-linked immunosorbent assay (ELISA) for antibody to ring-infected erythrocyte surface antigen (RESA) within indicated age and ethnic groups. The rate of increase in O.D. with age was identical in each ethnic group despite the great disparity in their cumulative exposure to malaria antigen. The transmigrants had been in Irian Jaya for 19 months at the time these serum samples were collected.
Review of studies of naturally...


Glucose-6-phosphate dehydrogenase deficiency and hemoglobinopathies. At the time of these studies in Arso, relatively few such abnormalities were detected\(^1\). Therefore, it appears that transmigrants quickly (within 2 to 5 years) develop a level of protective NAI which is comparable to natives of Irian Jaya of the same age.

Protection is not the cumulative product of many years of exposure. If this is true, then the basis of childhood susceptibility to falciparum malaria is an inherent characteristic of the host rather than the parasite. In other words, antigenic diversity in the parasite does not drive childhood susceptibility to infection. Instead, childhood susceptibility is driven by some characteristic of the acquired immune system which changes with age.

This new model for protective NAI must be borne out by studies in other populations conducted by other investigators before it may be generally accepted. Earlier studies have shown a similar phenomenon\(^5,12\), but were inconclusive. However, a recent study in Sri Lanka showed age-dependent protective NAI in people with only brief exposure to endemic falciparum malaria\(^13\).

PRACTICAL ASPECTS OF NAI STUDIES IN IRIAN JAYA

As Koch’s hypothesis of immunity to malaria led to the practical field of epidemiology of malaria (malariumetry), the studies of protective NAI in Arso provide insight and information of value to the public health officer. Seroepidemiology of malaria, which can be useful in certain settings in Indonesia\(^14\), depends upon an appreciation of the relationship between degree of exposure and humoral immune responsiveness. For example, one should expect the antibody titer in a child to be lower than in an adult, even though they may share an equal degree of exposure within the past few months. This is the basis of the recommendation to select a narrow age range of adults for standardization of seroepidemiologic assays of malaria in Indonesia\(^15\).

Studies of protective NAI in Javanese transmigrants and natives of Irian Jaya demonstrated a rapid onset of protection from frequent and high-grade parasitemia among adults. Children remain susceptible, however, no more susceptible than children native to an endemic area. Asexual parasite counts and the frequency of symptoms among those with parasitemia were comparable among age-matched groups of transmigrants and natives after 18 to 22 months residence. In contrast, the frequency and level of gametocytemia is remarkably greater in transmigrants of all ages than among natives of Irian Jaya (Fig. 6)\(^16\). Thus, transmigrants may be reasonably expected to contribute disproportionately to the transmission of falciparum malaria.

Immunity to malaria parasites plays an important role in the responsiveness of patients to chemotherapy of the infection\(^17\). For example, chemotherapy of chloroquine-sensitive malaria in a non-immune patient requires 25 mg/kg chloroquine, whereas 10 mg/kg chloroquine has been considered sufficient for residents of hyper to holoendemic areas\(^18\). In Irian Jaya, we have seen this principle reinforced by several observations. When Murphy and others screened for P. vivax resistance to standard therapy with chloroquine in Arso, the vast majority of proven cases of
resistance occurred in very young children (unpublished). The cumulative incidence of chloroquine prophylaxis failure against *P. vivax* in among 24 Javanese transmigrants having just 18 months residence in Irian Jaya was 67%\(^\text{19}\) -- among 26 Javanese transmigrants of 45 months residence in a nearby village, the cumulative incidence of chloroquine prophylaxis failure was less than 5% (unpublished). The rate of in vivo resistance of *P. falciparum* to standard therapy with Fansidar differed dramatically among transmigrants of 18 vs. 45 months residence in Irian Jaya (Fig. 7)\(^\text{20}\). Thus, people having less acquired immunity are more likely to demonstrate parasitemias which resist standard curative therapeutic or prophylactic regimens.

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DURATION OF RESIDENCE IN IRIAN JAYA

Figure 7. Resistance to Fansidar by *P. falciparum* seems profoundly effected by duration of residence in an endemic area. Fourteen of 24 people with only 18 months routinely failed to clear parasitemia within 7 days of therapy with Fansidar (58%), whereas 26 people of 45 months residence routinely cleared the parasitemia.
CONCLUSIONS

Endemic malaria profoundly effects social and economic development. People are reluctant to invest their futures in areas where a life-threatening disease is common and resistant to most known chemotherapies. This attitude extends to the investment of capital in agriculture, heavy industry, and tourism. Where malaria cannot be eradicated or even effectively controlled, alternative solutions must be offered to address the fears of well-informed, sensible people. In short, living with malaria and minimizing its social and economic impact requires a clear understanding of its distribution in defined populations, and knowing the patterns of susceptibility in these communities.

Immunologic studies of malaria in Irian Jaya have demonstrated that alternative solutions may be possible to diminish both the risk and fear of malaria. The farmer or investor may be assured that non-immune adults exposed to endemic malaria may acquire appreciable degrees of protective immunity within a couple of years. Similarly, resistance to standard antimalarials may be less pronounced after the first couple of years of exposure. Strategies of control for the initial period of susceptibility may be developed by forecasting patterns of immunologic susceptibility and drug resistance in a population. For example, it may be predicted that newcomers will be most susceptible to sickness, gametocytemia, and resistance to therapy with chloroquine. Therefore, one may direct chemotherapeutic control measures in view of these realities, e.g., temporary administration of primaquine for prophylaxis in newcomers may protect against dangerously high initial infection rates by killing the liver stage of the parasite (prophylaxis), and by sterilizing gametocytes in those who were only partially protected. Later, as people become accustomed to malaria and develop improved NAI, chloroquine or other standard antimalarials may suffice for protection from symptomatic malaria. All of these possibilities require careful and certain demonstrations of medical, logistical and economic utility. For example, administration of primaquine on a large scale carries with it a risk of serious side effects in some people, as well as the danger of development of parasite resistance to primaquine. The administration of primaquine for long term prophylaxis has not yet been tried in people native to endemic areas.

Tourists may visit endemic areas with high levels of parasite resistance to antimalarials. They probably know something of the malaria situation and may have access to reliable information about drug efficacies. These well-informed tourists confidently use a regimen of prophylaxis known to be effective in the area. In contrast, the poorly informed tourist may carry chloroquine or nothing at all, and he represents the greatest danger to the local tourist industry by being at high risk of sickness or death due to malaria. The presence of non-immune newcomers to Irian Jaya presents an opportunity to understand resistance to antimalarials in the most susceptible group of people, and to evaluate alternative therapies, i.e., offer solutions to endemic drug resistance.

In summary, the level of acquired immunity among residents of an area is an important consideration in understanding the epidemiology of the parasite, as well as in developing strategies of control, chemoprophylaxis and chemotherapy of the
disease. In addition, the mechanism of protective NAI remains an important issue of basic immunologic science and, ultimately, malaria vaccine development. For NAMRU #2 and collaborating Ministry of Health agencies, Irian Jaya has been the ideal site to address these important issues. Irian Jaya bears the burden of hyperendemic malaria with many non-immune people, and severe resistance to antimalarials. In addition, the punctulatus complex of vector species are notoriously difficult to control in places like the Arso region. So far, Irian Jaya is the only place in the world where resistance to chloroquine by P. vivax appears to be endemic. Finally, Irian Jaya is one of the few areas of the world where all 4 species of malaria occur together. Irian Jaya offers rare medical research opportunities that can be exploited to help deal with the severe malaria problem in Indonesia and other tropical areas.

REFERENCES


