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Malaria Distribution, Prevalence, Drug Resistance and Control in Indonesia

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Abstract

Approximately 230 million people live in Indonesia. The country is also home to over 20 anopheline vectors of malaria which transmit all four of the species of *Plasmodium* that routinely infect humans. A complex mosaic of risk of infection across this 5000-km-long archipelago of thousands of islands and distinctive habitats seriously challenges efforts to control malaria. Social, economic and political dimensions contribute to these complexities. This chapter examines malaria and its control in Indonesia, from the earliest efforts by malariologists of the colonial Netherlands East Indies, through the Global Malaria Eradication Campaign of the 1950s, the tumult following the coup d'état of 1965, the global resurgence of malaria through the 1980s and 1990s and finally through to the decentralization of government authority following the fall of the authoritarian Soeharto regime in 1998. We detail important methods of control and their impact in the context of the political systems that supported them. We examine prospects for malaria control in contemporary decentralized and democratized Indonesia with multidrug-resistant malaria and greatly diminished capacities for integrated malaria control management programs.

2.1. INTRODUCTION

Each year Indonesia's 230 million people collectively suffer at least several million cases of malaria caused by all four known species of human *Plasmodium*. Despite a long history of pioneering work in malaria prevention, treatment and control reaching back to the early 1900s, no systematic review of malaria in Indonesia has yet been undertaken. This chapter attempts to remedy this with a detailed examination of the genesis, nature and outcome of control strategies, along with a comprehensive review of peer-reviewed and published work on malaria. We also examine contemporary malaria in the context of government systems arrayed against it. This article does not include the body of knowledge on the complex array of anopheline vectors of malaria found in Indonesia. That topic is reserved for a separate review.

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2.2. EPIDEMIOLOGY OF MALARIA

2.2.1. Host

2.2.1.1. Human population—The Republic of Indonesia in Southeast Asia makes up most of the Indonesian archipelago that straddles the equator and stretches 5200 km from west Malaysia to Papua New Guinea (Fig. 2.1). The country consists of 17,504 islands (only 6000 of which are inhabited), covering a land area of 1.9 million km^2 (Departemen Dalam Negeri, 2004, 2008). The archipelago comprises seven main islands: Sumatra, Java, Kalimantan, Sulawesi, Maluku, the Lesser Sundas and Papua. Since decentralization of government power in 2000, Indonesia has been considered to consist of 33 provinces, 465 districts/municipalities, 6093 sub-districts and 73,067 villages (Departemen Kesehatan, 2008). Census authorities in 2007 estimated a population of 227 million people, with an average density of 118 people/km^2 (Departemen Kesehatan, 2008). The annual population growth rate was 1.3% (Badan Pusat Statistik, 2007a). The population density on Java and Bali (977 people/km^2) was much higher than on other islands (50 people/km^2). Sixty percent of Indonesians live on Java and Bali, representing only 7% of the land area of Indonesia. More people live in rural (57%) than in urban areas (43%). The ratio of male to female was 1:1. The age distribution of the population was 30% young (0–14 years old), 65% productive age (15–64 years old) and 5% old age (≥65 years old). Life expectancy at birth for Indonesians increased from 52 years in 1980 to 69 years in 2007 (Departemen Kesehatan, 2008). The government's Household Health Survey estimated an illiteracy rate of 7%, with more females (10%) than males being illiterate (4%) and with higher rates in rural (10%) than in urban areas (4%; Badan Pusat Statistik, 2007b). The highest illiteracy rates occurred in Papua (23%; rural 32% and urban 2%) and West Nusa Tenggara provinces (18%; rural 20% and urban 13%; Departemen Kesehatan, 2008). As shall be seen, these are also two of the most malarious provinces in Indonesia.

2.2.1.2. Economics—The East Asian Economic Crisis of 1997 caused the Indonesian Rupiah to lose 85% of its value against the US Dollar within months. This crisis significantly diminished private savings and forced the closure of almost every significant business activity. The crisis also precipitated the fall of the Soeharto regime, and several years of political instability followed. The number of poor increased from 23 million (11%) prior to the crisis to 39 million (18%) in 2006, with a monthly income of less than US$ 17 serving as the measure for the poverty line (Badan Pusat Statistik, 2007a). However, according to a global poverty map, based on night light brightness from satellite imagery, and the criterium of a US$ 2 per day poverty line, Elvidge et al. estimated that 73 million of Indonesia's population (32%) lived in poverty in year 2006 (Elvidge et al., 2009). In 2008, the World Bank reported that 54% of the Indonesian population was living below the poverty line (US$ 2 a day serving as the World Bank's poverty line measure; The World Bank, 2008). The International Monetary Fund estimated that the annual Indonesian gross domestic product (GDP) per capita in 2008 was US$ 2239, a significant increase from US$ 516 in 1998 (International Monetary Fund, 2009). About 88% of the population spent less than US$ 50 per month (rural 96%; urban 76%; Badan Pusat Statistik, 2007a). In 2007, 199 of 465 (43%) districts/municipalities in Indonesia were classified as underdeveloped, with 55% of these situated in the eastern part of Indonesia. In West Sulawesi, Central Sulawesi, Bengkulu and Papua 100%, 90%, 89% and 87%, respectively, of the districts/municipalities were underdeveloped (Departemen Kesehatan, 2008).

The economic crisis also affected government expenditure on health, causing it to fall from US$ 6 (1997) to US$ 1–3 (1997–1998) per person per year (Departemen Keuangan, 1997, 1998, 1999). However, government expenditures on health recovered and even surpassed precrisis figures at US$ 8 per capita per year by 2007 (Departemen Keuangan, 2007). In

2007, the health budget reached Rp. 18.5 trillion (~US$ 19 billion; Departemen Kesehatan, 2008), of which 8.3% was allocated to the Directorate General of Disease Control and Environmental Health and 1.2% was allocated to the National Institute of Health Research and Development (NIHRD). In other words, Indonesia spent US$ 1.8 billion on disease control and research. The health budget in 2007 had increased threefold from that of 1999.

2.2.1.3. Healthcare delivery systems—Healthcare services are made up of primary health centres, public hospitals, private and semi-private pharmaceutical industries and private sector healthcare facilities and personnel. Primary health centres are mainly located in sub-districts and provide maternal and infant care, family planning and in-patient and out-patient services to the community, as well as communicable disease control services. In 2007, there were 8234 primary health centres, with a centre serving, on average, about 27,400 people (Departemen Kesehatan, 2008). The number of primary health centres increases at a rate of about 2.7% per year. The service coverage by province ranged from 8000 to 52,000 people per health centre. Seven provinces failed to meet the standard target of a maximum of 30,000 people per health centre. These were Riau, Banten, West Java, Central Java, East Java, Bali and West Nusa Tenggara. The area coverage per centre was 192 km^2 on average; however, in sparsely populated Papua, Central Kalimantan and East Kalimantan area, coverage was greater than 1000 km^2.

The number of hospitals was 1319 in 2007, which provided a total of 142,707 hospital beds (Departemen Kesehatan, 2008). Ownership of these hospitals was 49% private and 51% public and government operated. The overall ratio of population to each hospital bed was 1581:1. The Indonesian Ministry of Health (MoH) declared the ideal ratio to be 1000 people per bed. The annual increase in hospital beds is typically 1.1%. The total number of people seeking hospital treatment was about 30 million in 2005, with ~7.8% of them being referred from lower levels of healthcare delivery, including primary health centres (Badan Pusat Statistik, 2007b).

In order to increase the coverage of community services, Indonesia implemented community-based health effort programs, such as health posts, with integrated village maternity huts and village drug posts. By 2006, there were 269,202 health posts, called Pos Pelayanan Terpadu or Posyandu, which provided maternity and child health services, family planning, nutritional development, immunization and diarrhoea control (Departemen Kesehatan, 2008). There are four of these Posyandu in each village. In total, there were 25,754 maternity huts, known as Pondok Bersalin Desa or Polindes, which provide midwives with delivery units, as well as providing improved maternity and child health services and family planning services. In addition, there are 9598 village drug posts, known as Pos Obat Desa, which assist in the distribution of some essential drugs directly to the community.

The activities of the pharmaceutical industry ensure the availability, accessibility and distribution of drugs to the community. By 2005, according to the Drug and Food Control Agency, there were 465 standard pharmaceutical companies and 1634 small, traditional drug companies in the production sector (Departemen Kesehatan, 2008). The traditional ‘drug’ companies typically produce herbal elixirs ranging from vitamin supplements and skin ointments, to solutions purported to boost the intellect, energy or sexual stamina. The distribution of pharmaceutical products is managed by 2493 wholesalers, 10,275 dispensaries, and 7056 drugstores (Departemen Kesehatan, 2008). Although many statutes restrict the distribution of prescription drugs, it is generally the case that many anti-infective therapies, including antimalarials, which are officially prescription only drugs, can be purchased over the counter.

According to the Indonesian MoH in 2007 there was about half a million health personnel employed in Indonesia (Departemen Kesehatan, 2008). Nurses and midwives made up 54% and 14%, respectively, of that number. Typically, for every 100,000 people, there were 138 nurses and 35 midwives. Eight percent of these half a million health personnel were licensed physicians, yielding a service ratio of about 19 physicians per 100,000 people. Health personnel specializing in public health made up two percent of this half a million, with a service ratio of approximately four per 100,000 people. The distribution of health personnel was 257,555 (45%) at hospitals and 184,445 (32%) at healthcare centres (Departemen Kesehatan, 2008).

The healthcare situation in Indonesia is relatively poor compared to the situation in neighbouring countries. Table 2.1 shows several indicators of health service quality in Indonesia and in four neighbouring countries, including Cambodia, Thailand, Malaysia and Singapore (International Monetary Fund, 2009; The World Bank, 2008; World Health Organization, 2008b, 2009a). Cambodia has a GDP which is three times lower than that of Indonesia, and a greater proportion of its population live in poverty (68% vs. 54%). Thailand and Malaysia are developing countries with a higher GDP and a poverty rate which is two to four times lower than that of Indonesia. Singapore, meanwhile, is an example of the developed countries of Southeast Asia, with a GDP that is 17 times higher than Indonesia's and with reportedly no proportion of the population living below the poverty line. In terms of healthcare delivery services, the availability ratio of hospital beds in Indonesia is six times higher than the ratio in Cambodia. This ratio is three to five times lower than the ratio in Thailand, Malaysia and Singapore. The ratio of physicians to population in Indonesia is lower (two to 15 times lower) than the ratio in other countries. Similarly, the ratio of nurses and midwives to population in Indonesia is about two to five times lower than the ratio in neighbouring countries. This situation is exacerbated by the sheer size of Indonesia's population; a population 3–45 times the size of the populations in neighbouring countries.

2.2.1.4. Infections research and surveillance systems operated by the government—Most government-affiliated infections research and surveillance systems in Indonesia are managed by three separate government agencies: (1) the NIHRD, (2) the Directorate General of Disease Control and Health Environment and (3) the Directorate General of Medical Care. All of these are under MoH authority. The Ministry of Research and Technology also sponsors infections research, primarily through the research conducted at the Eijkman Institute for Molecular Biology. Moreover, many academic institutions operating under the authority of the Ministry of Education have long histories of vibrant and productive research on infections, especially in schools of medicine and of public health.

The NIHRD commenced operations in 1975. Its main functions were (1) to develop policies, programs and implementation strategies for health systems, health policy, biomedicine, pharmaceutics, ecology, health status, nutrition and food, (2) to evaluate and screen health technologies and (3) to disseminate research results. Most malaria research conducted at the NIHRD is carried out by three main branches: (a) the Research Centre of Biomedicine and Pharmacy, (b) the Research Centre of Ecology and Health Status and (c) the Research and Development Centre of Vectors and Diseases. In 2006, these three NIHRD centres had 88, 50 and 15 researchers, respectively. That year, NIHRD received Rp. 174 billion (~US$ 2 million) and spent 25% on research and development, 72% on human resources and facilities development and 3% on research results dissemination (Departemen Kesehatan, 2006d).

The NIHRD organizes health surveys. The Basic Health Research, called Riskesdas or Riset Kesehatan Dasar project, initiated in 2007, is an example of this. A total of 258,366 households and 987,205 individual household members were sampled, with sampling

reaching every province. The survey collected information about household and individual demographics, mortality, access to health facilities, sanitation, food and drug consumption, history of diseases, perceived responsiveness of health facilities, health behaviour, disabilities, mental health, immunization, growth monitoring and infant health. Riskesdas also collected 36,357 blood samples in order to measure biomedical variables. In the specific instance of malaria, respondents were asked about any history of confirmed malaria, symptoms of malaria and malaria medication usage (National Institute of Health Research and Development, 2008).

As part of the National Health Survey System, the Central Bureau of Statistics (with NIHRD) has conducted a Household Health Survey (SKRT; Survey Kesehatan Rumah Tangga) every five years since 1975. In this survey 10,000 households are selected by stratified multistage random sampling. The survey collects information on household and individual characteristics, environment, morbidity, mortality, pregnancy and delivery (Soemantri et al., 2005). In addition, the National Family Planning Bureau also conducts Indonesian Demography and Health Surveys (SDKI, Survey Demografi dan Kesehatan Indonesia) every 3 years (this began in 1981). The surveys are designed to collect data on fertility, family planning, and maternal and child health. A total of 35,000 households are sampled across all provinces. In order to participate, respondents must be married and aged 15–49 years (females) or 15–54 years (males) (Soemantri et al., 2005).

The Directorate General of Disease Control consists of five directorates: (a) the Directorate of Epidemiology Surveillance (144 personnel), (b) the Directorate of Communicable Diseases (98 personnel), (c) the Directorate of Vector-borne Diseases (104 personnel), (d) the Directorate of Non-Communicable Diseases (80 personnel) and (e) the Directorate of Health Environment (99 personnel). The Directorate of Vector-Borne Diseases is responsible for malaria and vector control activities (Departemen Kesehatan, 2006c).

Malaria surveillance in Indonesia begins with patient registration and data collection at the primary health centres (commonly called by their Indonesian acronym ‘Puskesmas’; Pusat Kesehatan Masyarakat or People’s Health Centre; Departemen Kesehatan, 1997). Primary health centres generate monthly malaria reports from out-patient services and malaria case detection activities. Primary health centres are responsible for analysing data and producing a local area monitoring report on the distribution and trends of the disease. In the specific case of malaria, a puskesmas sends a report to the district malaria control officer who in turn compiles all reports into a district health profile on malaria. The health profile describes monthly and annual malaria cases reported at village level. The district health office then sends aggregated malaria reports three times a year to the provincial health office, as well as to the Sub-Directorate of Malaria Control at the Directorate of Vector-borne Diseases in Jakarta (Departemen Kesehatan, 2006b,f, 2007a). Malaria data also comes from laboratory examination in hospitals. The malaria data is collected through the Hospital Reporting System (known by the Indonesian acronym ‘SPRS’, Sistem Pelaporan Rumah Sakit) which covers all private and government hospitals in Indonesia. The SPRS malaria figures go to the Directorate General of Medical Care (Departemen Kesehatan, 2003a), and they are then passed on to the Sub-Directorate of Malaria.

Finally, primary health centres and the district malaria control office are responsible for the management of vector control activities and for reporting on their progress. The indoor residual spraying (IRS) report, for instance, contains the number of houses sprayed, how many people live in sprayed homes, the insecticide type, the amount of insecticide used and the date of spraying. The number of insecticide-treated mosquito nets (ITN) distributed, the number of people protected, the dates of bed net distribution as well as larviciding activity which includes the coverage area, the amount of larvicide used and the date of the activities

are also reported. Primary health centres and the district malaria control office also document biological control activities such as the introduction of larvivorous fish into areas where mosquito breeding sites have been found. They keep a record of the number of fish introduced and the dates of these activities (Departemen Kesehatan, 2003b).

2.2.2. Parasites

2.2.2.1. The distribution of the *Plasmodium*—The Malaria Atlas Project and its partners in the Sub-Directorate for Malaria Control in the Directorate of Vector-borne Diseases aim to assemble malaria parasite rate surveys across the Indonesian archipelago (Guerra et al., 2007; Hay and Snow, 2006). Table 2.2 summarizes the distribution of human *Plasmodium* throughout the Indonesian archipelago. At the time of writing, we have recorded parasite rate surveys for 2366 locations conducted between 1900 and 2008. The surveys are not equally distributed, with 63% of them conducted in eastern Indonesia (Moluccas, the Lesser Sundas and Papua). From this assembly of data, we were able to report that four species of malaria parasite routinely infect humans in Indonesia: *Plasmodium falciparum*, *P. vivax*, *P. malariae* and *P. ovale*.

Plasmodium falciparum appears to be the most common *Plasmodium* species in Indonesia. One of the earliest published documents concerning the presence of *P. falciparum* in Indonesia was a report by Robert Koch in 1900 revealing its presence in Ambarawa and Ungaran (both in Central Java) and Tanjung Priok (Jakarta; Koch, 1900). Since then, the presence of this parasite has been recorded at 1915 (81%) locations. Most of these locations are located in Papua (33%), the Lesser Sundas (29%) and Sumatra (21%). The median prevalence of *P. falciparum*, from 1900 to 2008, was 5% (ranging from 0.03% to 82%). However, this prevalence was not distributed uniformly across the island groups. Prevalence was higher in eastern Indonesia (median: 6%, range: 0.03–82%) than in the rest of the country (median: 3%, range: 0.1–72%).

After *P. falciparum*, *P. vivax* is the most common of the *Plasmodium* in Indonesia. To the present day, it has been reported at 1786 locations (75% of all surveys). Of these, 32% were located in Papua, 29% in the Lesser Sundas and 23% in Sumatra. The median prevalence of *P. vivax*, between 1900 and 2008, was 3% (range: 0.03–70%). This prevalence was not distributed uniformly across the islands. The prevalence of *P. vivax* in the eastern part of Indonesia (median: 3%, range: 0.04–70%) was higher than the prevalence in the rest of the country (median: 2.5%, range: 0.07–60%).

The assembled data reveal that *P. falciparum* and *P. vivax* infections often occur together (sympatrically) in Indonesia. Of 2366 survey locations, the presence of these two species was confirmed at 1606 locations (68%). *P. falciparum* dominated in more locations than *P. vivax* (62% vs. 33%). The median ratio of *P. falciparum* to *P. vivax* at those areas dominated by *P. falciparum* was 3:1. The median ratio of *P. vivax* to *P. falciparum* at *P. vivax* dominated areas was 2:1. In terms of geographical distribution, 64% of those areas, where the two parasites coexisted, were located in the Lesser Sundas and Papua.

Plasmodium malariae is a relatively uncommon species in Indonesia. The presence of *P. malariae* in Indonesia was first confirmed by Robert Koch in Central Java and Jakarta in 1900 (Koch, 1900). To date, this parasite has been confirmed at 120 survey locations (5%). The parasite was found on all the main islands, however it was mostly recorded in eastern Indonesia, in the Lesser Sundas (38%) and in Papua (29%). The median prevalence of *P. malariae*, from 1900 to 2008, is 2% (range: 0.05% to 53%).

Reports of *P. ovale* come almost entirely from eastern Indonesia. This species has not been reliably documented anywhere else in Indonesia. The first report of *P. ovale* in Indonesia

was from Belu (East Nusa Tenggara) in 1975 (Gundelfinger et al., 1975). Malaria parasite rate surveys carried out since then have recorded *P. ovale* at 16 survey locations (0.6%). Its presence was only recorded in the Lesser Sundas (38%) and Papua (62%) with a median prevalence of 0.2% (range: 0.07–4.9%).

Plasmodium knowlesi, a *Plasmodium* species naturally occurring in macaques in Southeast Asia, appears in no peer-reviewed report describing infections of humans in Indonesia. However, Berens-Riha et al. presented information showing that four of 22 human blood samples taken from Kalimantan were positive for *P. knowlesi* (Berens-Riha et al., 2009). The samples were taken from patients with severe and uncomplicated malaria. Initially, the blood samples were morphologically diagnosed by microscopy as *P. falciparum*. *P. knowlesi* was then determined using a nested polymerase chain reaction (PCR) for all five human-specific primers. Two patients had a mixed infection of *P. knowlesi* and *P. vivax*, one had a mixed infection of *P. knowlesi* and *P. falciparum*, and one showed a very weak band of *P. vivax*, but a strong band of *P. knowlesi*. The natural hosts of *P. knowlesi* are long-tailed macaques (*Macaca fascicularis*), pig-tailed macaques (*Macaca nemestrina*) and banded leaf monkeys (*Presbytis melalophos*; Eyles et al., 1962a,b). The *Anopheles leucosphyrus* group of mosquitoes (about 20 distinct species) transmits *P. knowlesi* very efficiently (Sallum et al., 2005). In Malaysian Borneo, *P. knowlesi* has been found to affect in particular those humans inhabiting the natural habitat of the simian hosts (Cox-Singh and Singh, 2008). *P. knowlesi* has been reported in humans from the Philippines (Luchavez et al., 2008), Thailand (Jongwutiwes et al., 2004), China (Zhu et al., 2006) and Singapore (Ng et al., 2008). The natural simian and anopheline hosts of *P. knowlesi* occur in abundance throughout Indonesia west of the Wallace Line (which runs between Kalimantan and Sulawesi, and between Bali and Lombok; Fooden, 1982). It seems very likely that the absence of reports of *P. knowlesi* in humans represents a failure to conduct sufficiently sensitive surveys (Cox-Singh et al., 2008). An understanding of *P. knowlesi* malaria and preventive measures may be a useful priority for those providing healthcare to communities living in the forest fringe habitats of western and central Indonesia (Cox-Singh and Singh, 2008).

2.2.2.2. Reported versus actual malaria morbidity and mortality—Morbidity and mortality statistics for malaria in Indonesia are routinely under-reported. According to the Household Health Survey conducted by the Central Bureau of Statistics in both 1995 and 2001, an estimated 15–30 million people suffered from at least one attack of malaria in their lifetime, and an estimated 30,000–38,000 deaths occurred in each of those years (Departemen Kesehatan, 1995, 2001). In contrast, the MoH reported only 191 deaths in 1995 and 1774 deaths in 2001 (WHO SEARO, 2008). The World Health Organization South-East Asia Regional Office accepted that there were no reliable records of mortality. The same agency reported that, on average, 45–1774 deaths occurred in Indonesia per year between 1994 and 2003 (WHO SEARO, 2008).

Lederman et al. reported that malaria in Jakarta, the capital city, is not rare and significantly underestimated (Lederman et al., 2006b). Between 2004 and 2005, they recorded 240 imported malaria cases at 28 hospitals, with *P. falciparum* accounting for 67% of cases (mixed infections included). The Jakarta Health Province Office reported 552 malaria cases in 2006 (Dinas Kesehatan DKI Jakarta, 2007). However, in the same period, the MoH reported no malaria data in Jakarta province (Departemen Kesehatan, 2007d). Such discrepancies illustrate the failure to implement reliable and regular case reporting between the provinces and the MoH.

In 2008, the World Health Organization (WHO) released the estimates of malaria cases and malaria deaths for each country (World Health Organization, 2008e). The WHO estimated

that there were 2.5 million cases of malaria in Indonesia in 2006 (World Health Organization, 2008e). This figure was much higher than the 0.3 million cases reported by the MoH. In other words, the figure given by the MoH was only 13.8% of that given by the WHO. One might therefore say that the MoH was under-reporting by as much as 86.2%. In terms of malaria deaths, the WHO estimated that over 3000 deaths had occurred in the year 2006, while the MoH only reported 494 deaths. The number of malaria deaths was therefore also under-reported (85.8%).

The discrepancies in these numbers were also reflected in the World Malaria Report published in 2008 and 2009. Table 2.3 shows the differences of malaria cases and mortality between 2001 and 2006. According to these reports, both reports define reported malaria cases as a combination of probable and confirmed cases. A probable case of malaria is defined as suspected but not laboratory tested, and nonetheless reported as malaria. Such discrepancies illustrate the difficulties in describing the burden of malaria disease in Indonesia.

The contemporary estimates of clinical burden of *P. falciparum* malaria and the number of pregnancies at risk of *P. falciparum* malaria in Indonesia have been published in 2010. Hay et al. presented a new cartographic technique and its application for deriving global clinical burden estimates of *P. falciparum* malaria in 2007 (Hay et al., 2010). The 87 malaria endemic countries were divided into countries with a low risk of transmission (unstable transmission: *Pf* annual parasite incidence (API) < 0.1 cases per 1000 people) and countries with a moderate or high risk of transmission (stable transmission: *Pf*API ≥ 0.1 cases per 1000 people). In countries with unstable transmission, the researchers assumed a uniform annual clinical incidence rate of 0.1 cases per 1000 people and multiplied this by population sizes to get disease burden estimates. In countries with stable transmission, they used a modelled relationship between clinical incidence (number of new cases in a population per year) and prevalence (the proportion of a population infected with malaria parasites) and a global malaria endemicity map (a map that indicates the risk of malaria infection in different countries) to estimate malaria incidences. Combining these estimates for Indonesia resulted in 12.3 million (95% credible interval 6.2–20.9 million) clinical cases of *P. falciparum* malaria in 2007. Almost all this morbidity burden (99%) occurred in areas of stable transmission.

Dellicour et al. derived the first contemporary estimates of the global distribution of the number of pregnancies at risk of *P. falciparum* and *P. vivax* malaria in 2007 in areas with *P. falciparum* and *P. vivax* transmission (Dellicour et al., 2010). The researchers used data from various sources to calculate the annual number of pregnancies (the sum of live births, induced abortions, miscarriages and still births) in each country. Finally, they calculated the annual number of pregnancies at risk of malaria in each country by multiplying the number of pregnancies in the entire country by the fraction of the population living within the spatial limits of malaria transmission in that country. In 2007, they calculated 6.4 million pregnancies occurred in areas with *P. falciparum* and/or *P. vivax* transmission in Indonesia. These pregnancies resulted in 3.8 million live births. Of 4.4 million pregnancies in areas with *P. falciparum* transmission, 2 million occurred in areas with stable transmission and 2.4 million in areas with unstable transmission. A total of 6.3 million occurred in areas with *P. vivax* transmission and 4.3 million of which occurred in areas in which *P. falciparum* and *P. vivax* coexist. The estimates are an important step towards a spatial map of the burden of malaria in pregnancy and should help policy makers allocate resources for research into and control of this important public-health problem.

2.2.2.3. Occurrence of epidemic malaria—Malaria outbreaks occur in Indonesia every year. For example, in 1998 and 1999 there were outbreaks in eight provinces, covering 10

districts with 19,483 cases and 66 deaths (case fatality rate, CFR 0.3%; Marwoto and Sekartuti, 2003). Between 2000 and 2005, there were outbreaks in 19 provinces, covering 65 districts/municipalities, with 58,152 malaria cases and 536 reported deaths (CFR 0.9%; Departemen Kesehatan, 2006c). In 2006, outbreaks occurred in eight provinces with 3705 cases and 30 reported deaths (CFR 0.8%; Departemen Kesehatan, 2007c). Later, between 2007 and 2008, outbreaks were reported in 11 provinces, covering 20 districts, with 1864 cases and 93 reported deaths (CFR 5%; Departemen Kesehatan, 2009a).

Many factors have contributed to outbreaks of malaria in Indonesia. Some of these outbreaks occur under unique conditions of human migration. For instance, both in 1988 and 1992, the movement of non-immune transmigrants from Java and Bali (hypoendemic areas) to Arso in Papua (hyperendemic area) created local epidemics as early as 2 months after their arrival (Baird et al., 1995d). A strong correlation has also been shown between El Niño Southern Oscillation (ENSO)-related climatic anomalies and the increased risk of malaria exposure and severe disease in highly susceptible highland populations in the Jayawijaya (Papua; Bangs and Subianto, 1999). In 1997, increased malaria coincided with a period of dramatic deficit in precipitation, increased air temperatures and barometric readings, with a 75% overall reduction in normal rainfall. Drought forced people to move to lower elevations because of the grave water and food shortages, thereby increasing exposure to intense malaria transmission.

More typical outbreaks, resurgences in areas where case numbers have been low for a long time, also routinely occur. The relative difficulty of removing the breeding sites of *Anopheles maculatus* and *A. balabacensis* has played an important role in the persistence of hypoendemic malaria on Java (Barcus et al., 2002). Rocky streams that can be found everywhere on steep, forested slopes are ideal breeding sites for these vectors. In addition, hillside residents live in traditional Javanese houses made of wooden planks and bamboo, which do little to deter mosquito access, whilst poor or non-existent roads limit access to health care.

Marwoto et al. found that in Banyumas and Pacitan (East Java) and Pulau Seribu (a group of islands off the shore of Jakarta) in 2000 and 2001, immigrant workers who worked as transmigrant or seasonal workers in endemic malarious areas outside Java Island returned to their home villages which were receptive to malaria due to the presence of malaria vector mosquitoes (Marwoto and Sekartuti, 2003). Marwoto et al. recorded that in Cilacap (Central Java) and Lampung (South Sumatra) in 1998, high mobility was a contributing factor, together with the disused shrimp ponds or fishponds that provided ideal breeding sites for the highly efficient malaria vector *A. sundaicus* (Marwoto and Sekartuti, 2003). In Kulonprogo (Yogyakarta) late case detection, a lack of vector control such as indoor residual insecticide spraying and a lack of knowledge regarding malaria all contributed to an epidemic in the late 1990s and early 2000s (Sudini and Soetanto, 2005). All those who contracted malaria slept without a bed net in homes lacking screening and were thus freely accessible to feeding mosquitoes. Patients lived with cattle in or near their homes, exacerbating rather than mitigating the risk of exposure to those anophelines of the area that readily feed on both cattle and humans. Weak surveillance systems contributed to the worsening of outbreaks, thereby consolidating the epidemic (Dewi, 2002). Microscopic diagnostic services in the epidemic zone were found to be unreliable (Dewi, 2002).

2.2.2.4. Malaria treatment policy and practice

***2.2.2.4.1. Treatment of uncomplicated* P. falciparum:** The evolution of Indonesia's malaria treatment policy is shown in Table 2.4 (Departemen Kesehatan, 2006e, 2007b). The first-line of treatment for uncomplicated *P. falciparum* currently consists of two options. The first option is a combination of artesunate (AS) and amodiaquine(AQ) taken orally for 3 days,

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with a single dose of primaquine (PQ, as a gametocytocide) given on the first day (AS + AQ + PQ). The dosages of AS, AQ and PQ are 4 mg/kg weight/day, 10 mg/kg weight/day and 0.75 mg/kg weight, respectively. The alternative first line of treatment is a combination of dihydroartemisinin (DHA) and piperaquine (PP) taken orally for 3 days, with a single dose of PQ (gametocytocidal) given on the first day (DHA + PP + PQ). The dosages of DHA, PP and PQ are 2–4 mg/kg weight/day, 16–32 mg/kg weight/day and 0.75 mg/kg weight, respectively. However, primaquine is contraindicated in pregnant women, infants less than 1 year old and in people with a glucose-6-phosphate dehydrogenase (G6PD) deficiency. Routine screening for G6PD deficiency very rarely occurs in Indonesia. The laboratory test for this deficiency is available at very few hospitals in Indonesia, and even less so at the periphery of healthcare delivery where most antimalarials are distributed.

The second line of treatment is a combination of quinine(QN), doxycycline(DX) or tetracycline(TC) and primaquine (QN + DX + PQ or QN + TC + PQ). Quinine is given orally three times a day for 7 days at 10 mg/kg weight/medication. Doxycycline is given orally two times a day for 7 days with adults receiving a dosage of 4 mg/kg weight/day and children of 8–14 years receiving a dosage of 2 mg/kg weight/day. If DX is not available, then TC is given orally four times a day for 7 days at 4–5 mg/kg weight/medication. However, doxycycline and tetracycline are not recommended for the treatment of malaria in pregnant women or in children under 8 years of age.

Malaria treatment for *P. falciparum*, where diagnostic facilities are available but AS and AQ are not, is a single dose of sulfadoxine and pyrimethamine at 25 and 1.25 mg/kg weight, respectively. Primaquine is also given once on the first day at 0.75 mg/kg weight. If the treatment fails, the patient is treated following a similar procedure to second line treatment. For malaria endemic areas lacking diagnostic facilities, clinical malaria is treated presumptively with standard chloroquine (CQ) and a single dose of PQ as gametocytocide. Chloroquine is given once daily for 3 days: at 10 mg base/kg weight on the first 2 days and at 5 mg base/kg weight on the third day, whilst the single 0.75 mg/kg weight dose of PQ can be given on any of those days.

The treatment policy for clinical diagnoses of malaria presents a special challenge to Indonesia. In 2006, only 13% (1,246,324/9,319,382) of estimated clinical malaria cases came with a microscopic or rapid diagnostic test (RDT) confirmation (World Health Organization, 2008e). This means that 87% of known malaria cases receive treatments known to be widely ineffective and to actually increase the odds of malaria transmission. To make matters worse, the proportion of cases receiving the appropriate treatment with artemisinin combination therapy (ACT) may be even lower when taking into account the cases not reported to the MoH, which probably represent the vast majority of actual malaria cases in Indonesia. The lack of diagnostic capacity and the policy aimed at conserving relatively costly ACT therapies almost certainly result in most Indonesians being treated with drugs known to be ineffective.

Hasugian et al. conducted a randomized trial that compared the efficacy and safety of treatment by AS + AQ with that of DHA + PP (Hasugian et al., 2007). The study was performed at Timika (Papua) in 2005. Each treatment group enrolled 170 study subjects who were observed over a period of 42 days. A combination of AS and AQ was administered on the basis of weight, with a total artesunate dose of 12 mg/kg weight and a total amodiaquine dose of 30 mg/kg weight. A combination of DHA and PP was administered at a dosage of 6.75 mg/kg weight of dihydroartemisinin and 54 mg/kg weight of piperaquine. The study showed that the cumulative risk of parasitological failure with true recrudescence of *P. falciparum* infection on day 42 was 16% (95% CI 8.5–23%) with AS + AQ treatment and 5% (95% CI 0.7–9.4%) with DHA + PP treatment. Patients treated with AS + AQ showed a

higher risk of failure than those treated with DHA + PP (hazard ratio = 3.4; 95% CI 1.2–9.4). There was no difference in gametocyte carriage between treatments (overall rate, 12.1 cases per 1000-patient weeks). There were significant differences between treatments in terms of tolerability. Patients treated with AS + AQ, as opposed to DHA + PP, were two to three times more likely to report nausea, vomiting and anorexia. However, there were no reported differences between the treatments in symptoms elicited on day 7 and thereafter. In addition, serious adverse events were noted in three patients in the AS + AQ group. Two adults developed recurrent vomiting on day 3 after completion of a course of AS + AQ, requiring hospital admission but followed by a full recovery within a day. An adult with *P. falciparum* infection developed truncal ataxia and intention tremor on day 7 and his symptoms resolved over the subsequent 8 days. He had a recurrence of *P. falciparum* infection on day 21 and was retreated with DHP + PP, without further recurrence of infection, symptoms or cerebellar signs over the subsequent 42 days. Hasugian et al. concluded that, in Papua, DHA + PP was a more effective and better tolerated treatment for the multidrug-resistant *P. falciparum*.

Price et al. assessed the therapeutic efficacy of DHA + PP for uncomplicated *P. falciparum* malaria in children and adults (Price et al., 2007). The study was conducted in Timika (Papua) between 2004 and 2005. A combination of DHA and PP was administered at a dosage of 2.25 and 18 mg/kg weight/day, respectively, in 515 patients with *P. falciparum* infection or mixed infection. All doses were supervised and patients were examined daily for 42 days. At each visit, a blood smear was taken and a symptom questionnaire was completed. The study showed that, by day 42, cumulative risk of recurrence for *P. falciparum* was 7% (95% CI 4.7–9.4%). After PCR correction, the risks were 1.1% (95% CI 0.1–2.1%). The median time to recurrence with *P. falciparum* was 36 days (range: 22–45 days). The authors concluded that DHA + PP was a highly effective treatment of uncomplicated *P. falciparum* malaria in Papua.

Asih et al. evaluated AS + AQ as a treatment for *P. falciparum* malaria in West Sumba in 2006 (Asih et al., 2009). They reported that, of 103 malaria patients treated, 101 had recovered completely by day 7, one had retained parasitemia up to day 14 and the remaining two participants showed the reappearance of parasites on days 21 and 28. The analysis of genotypes indicated that both participants carried different genotypes and were thus classified as reinfections rather than treatment failures. Gametocytes were present in six patients on day 7. In contrast to the findings of Hasugian et al. in Papua, these authors concluded that AS + AQ was a highly effective treatment against *P. falciparum* in the Lesser Sundas.

Syahril et al. evaluated the efficacy of AS + AQ as a treatment for uncomplicated *P. falciparum* malaria in children at Mandailing Natal (North Sumatra) in 2006 (Syahril et al., 2008). One hundred and thirty-five patients were given AS at a dosage of 4 mg/kg weight and AQ at a dosage of 10 mg/kg weight for 3 days. The study resulted in a 100% cure rate on day 28. Syahril et al. reported adverse reactions including headaches ($n = 20$), vomiting ($n = 10$) and tinnitus ($n = 1$). They concluded that AS + AQ was a well-tolerated, safe and highly effective treatment for uncomplicated *P. falciparum* malaria in children in North Sumatra.

The efficacy of QN + DX and QN + TC against uncomplicated *P. falciparum* infections was evaluated in Indonesia. Lubis evaluated the efficacy of QN + DX in children against uncomplicated *P. falciparum* infection in Natal (North Sumatra) in 2006 (Lubis, 2008). The study involved 111 volunteers who were given quinine orally three times a day at 10 mg/kg weight/medication for 4 days and continued at 5 mg/kg weight/medication for 3 days. Doxycycline was given orally at dosage of 2 mg/kg weight/day for 7 days. Malaria smears

were taken on days 0, 2, 7 and 28. The study showed that only 2 of 111 volunteers had malaria on day 2 and a recrudescent on day 28. Common complaints reported were tinnitus (37%), headache (17%) and vomit (14%). The study concluded that QN + DX provided high efficacy against *P. falciparum* in North Sumatra for children. Similar results were also reported by Lubis in Natal (North Sumatra) in 2007 (Lubis, 2009). The study showed that only two of 123 volunteers had malaria on day 2, but they found no parasitemia after day 7 to day 28. The common complaints reported were tinnitus (33%), headache (17%) and vomit (15%). The study also concluded that QN + DX provided high efficacy against *P. falciparum* in North Sumatra for children.

Tarigan investigated the efficacy of QN + TC against uncomplicated *P. falciparum* infection in Natal (North Sumatra) in 2002 (Tarigan, 2003). After randomization, 100 people received QN three times a day for 5 days (Q5) and 93 people received QN three times a day for 7 days (Q7). Quinine was taken orally at dosage of 10 mg/kg weight/medication. Tetracycline was given four times a day at dosage of 250 mg/day to both groups for 7 days. The study showed that 23% (15/64) of Q5 and 2% (1/67) of Q7 were classified as malaria resistant. One individual in Q7 was RI (resistance level 1, asexual parasites disappeared within 7 days but had recurrent parasites between day 8 and 28). Giving QN in 7 days resulted in high efficacy than those of Q5 ($p < 0.001$). The most commonly reported complaints were tinnitus (78%) and balance disorder (62%), but the difference between groups was not significant. The study concluded that giving QN + TC for 7 days was more effective against uncomplicated *P. falciparum* infections in North Sumatra, than giving QN only for 5 days.

***2.2.2.4.2. Treatment of complicated* P. falciparum:** The first line of treatment for complicated *P. falciparum* malaria is the administration of artesunate by intramuscular (IM) or intravenous (IV) route and artemether intramuscular (IM; Departemen Kesehatan, 2007b). Artesunate with a dosage of 2.4 mg/kg weight is given on admission, then at 12 and 24 h, and thereafter once daily until oral medication could be taken reliably. Every 60 mg vial contains anhydrous artesunic acid, which is dissolved in 0.6 ml 5% natrium bicarbonate and then mixed with 3–5 ml of 5% dextrose before injection as a bolus into an indwelling intravenous cannula. When IM artesunate is given, the same dosage is applied. When the patient has recovered sufficiently to take tablets, a combination of AS + AQ + PQ treatment is given as similar dosage at the first-line treatment of uncomplicated *P. falciparum* malaria. Alternatively, IM artemether is given at a dosage of 3.2 mg/kg weight/day, followed by 1.6 mg/kg weight/day until oral medication could be taken reliably. A combination of AS + AQ + PQ treatment is then given at similar dosage for first-line treatment of uncomplicated *P. falciparum* malaria.

The second line of treatment is a quinine IV drip which consists of quinine HCl at a dosage of 20 mg base/kg weight, dissolved in 500 ml dextrose 5% or NaCl 0.9% (Departemen Kesehatan, 2007b). The quinine drip is administered over 8 h and then followed by 10 mg/kg weight injected every 4 h until the patient is able to accept oral medication. When the patient has recovered sufficiently to take tablets, oral quinine at 10 mg/kg weight is administered every 8 h to provide a total quinine course of 7 days (as per guidelines detailed above). If the IV administration of quinine is impossible, then the patient is given quinine antipyrine in IM single doses of 10 mg/kg weight.

The treatment for children is the IV administration of quinine (Departemen Kesehatan, 2007b). Quinine HCl at a dosage of 10 mg/kg weight is dissolved in the amount of 5% dextrose or NaCl 0.9% normally used for a dosage of 75–100 ml/kg weight/24 h. This dosage is administered for every 8 h. This treatment is repeated each day until the patient is conscious and able to accept oral medication. If the child is younger than 2 months, then the dose is reduced from 10 to 6–8 mg/kg weight.

South East Asian Quinine Artesunate Malaria Trial group did an open-label randomized controlled trial in patients admitted to hospital with severe *P. falciparum* malaria in Bangladesh, India, Indonesia and Myanmar between 2003 and 2005 (SEAQUAMAT, 2005). They randomly assigned 730 volunteers with IV artesunate and 731 subjects given IV quinine. The treatment procedure in former group was artesunate 2.4 mg/kg weight given on admission, then at 12, 24 h, and thereafter once daily until oral medication could be taken reliably. Every 60 mg vial contained anhydrous artesunic acid, which was dissolved in 1 ml of 5% sodium bicarbonate and then mixed with 5 ml of 5% dextrose before being injected as a bolus into an indwelling IV cannula. When the patient had recovered sufficiently to take tablets, oral artesunate 2 mg salt/kg weight/day was administered to complete a total course of 7 days (a total cumulative dose of 17–18 mg/kg weight). Alternatively, quinine dihydrochloride was given in a 20 mg/kg loading dose infused over 4 h (in 500 ml 5% dextrose water or 0.9% saline), followed by 10 mg/kg weight infused over 2–8 h three times a day until starting oral therapy. When the patient had recovered sufficiently to take tablets, oral quinine at dosage of 10 mg/kg weight was administered every 8 h to provide a total quinine course of 7 days. The primary endpoint of this study was death from severe malaria (in-hospital mortality). The result showed that mortality was less in artesunate recipients than in quinine recipients (15% vs. 22%; $p < 0.001$). However, no difference in mortality was found in 289 severe *P. falciparum* Indonesian patients in artesunate and quinine (6% vs. 12%; $p = 0.078$). The study suggested that IV artesunate treatment was well tolerated, whereas IV quinine was associated with hypoglycaemia (Risk ratio = 3.2, 95% CI 1.3–7.8; $p = 0.009$).

Tjitra et al. evaluated the efficacy of IM artemether and IV quinine in complicated *P. falciparum* malaria adult patients in Balikpapan (East Kalimantan) in 1993–1995 (Tjitra et al., 1996a). Two groups of 30 patients received either artemether or quinine. Artemether was given at 1.6 mg/kg weight/day on day 0 and followed by a daily dose from the second to fifth day. Quinine dihydrochloride was given intravenously at 20 mg/kg weight/day, dissolved in 10 ml/kg weight 5% dextrose, for first 4 h, then followed by 10 mg/kg weight three times a day until the patient was able to accept oral medication. Oral quinine at dosage of 10 mg/kg weight was administered every 8 h to provide a total quinine course of 7 days. The study showed that mortality rate in the artemether group was less than in the quinine recipients, but not significantly difference (13% vs. 23%; p = 0.32). The most common complications were hyperbilirubinaemia (50%), hyperparasitaemia (28%) and cerebral malaria (25%) in both groups. The authors suggested that IM artemether was as effective as IV quinine for the treatment of complicated *P. falciparum* malaria in East Kalimantan.

***2.2.2.4.3. Treatment of* P. vivax:** The current first line of treatment for *P. vivax* is AS + AQ or DHA + PP (Departemen Kesehatan, 2007b). A combination of AS + AQ or DHA + PP is taken orally for 3 days at same dosage as treatment for uncomplicated *P. falciparum* malaria. In areas where there is resistant to CQ, the MoH proposed that *P. vivax* malaria may be treated additionally with a single dose of PQ given on the first day. However, the dosage of PQ for *P. vivax* was less than the treatment of uncomplicated *P. falciparum* malaria (0.25 vs. 0.75 mg/kg weight). In areas in which ACT is absent, the MoH proposed that *P. vivax* malaria may be treated with CQ + PQ. The CQ was taken orally with a total dosage of 25 mg base/kg weight over 3 days and PQ at dosage of 0.25 mg/kg weight for 14 days.

The second line of treatment is a combination of quinine and primaquine (QN + PQ; Departemen Kesehatan, 2007b). Quinine is given orally three times a day for 7 days at 10 mg/kg weight/medication and PQ at dosage of 0.25 mg/kg weight for 14 days.

Only one study on combined AS + AQ treatment for *P. vivax* malaria has been done in Indonesia. Hasugian et al. reported that the cumulative risk of parasitological failure with *P.*

vivax infection on day 42 was 33% (95% CI 25–42%) with AS + AQ treatment and 9% (95% CI 4–14%) with DHA + PP treatment (Hasugian et al., 2007). Patients treated with AS + AQ showed a higher risk of failure than those treated with DHA + PP (hazard ratio = 4.3; 95% CI 2.2–8.2). In terms of gametocyte carriage, *P. vivax* gametocytemia was significantly less likely to occur with DHA + PP treatment (2.5 cases per 1000-patient weeks) than with AS + AQ treatment (36.5 cases per 1000-patient weeks). The authors concluded that DHA + PP was a more efficient and better tolerated treatment for the multidrug-resistant *P. vivax* in Papua. They also concluded that the pro-longed therapeutic effects of PP decreased the rate of recurrence of *P. vivax* infection and reduced the risk of *P. vivax* gametocytemia. However, these assessments did not apply PQ therapy against relapse and much of what the authors called parasitologic failure may not be accurately described as such. It is more likely that these therapies were 100% effective against asexual blood stages and that the recurrences observed out to day 42 were relapses.

Price et al. assessed the therapeutic efficacy of DHA + PP for *P. vivax* infections in children and adults in Timika (Papua) between 2004 and 2005 (Price et al., 2007). A combination of DHA and PP was administered at a dosage of 2.25 and 18 mg/kg weight/day, respectively, for 256 patients with *P. vivax* or mixed infection. All doses were supervised and patients were examined daily for 42 days. At each visit, a blood smear was taken and a symptom questionnaire was completed. The study showed that by day 42, cumulative risk of recurrence for *P. vivax* was 9% (95% CI 6–12%). In those patients failing with pure *P. vivax*, the median time to recurrence was 43 days (range: 22–45 days). The authors concluded that DHA + PP was an effective treatment of *P. vivax* malaria in Papua.

To date, there are four studies documenting the efficacy of CQ + PQ as a treatment for *P. vivax* malaria in Indonesia. Firstly, in 1994, Ompusunggu et al. reported a low cure rate of 37% (33/90) in Banjarnegara, Wonosobo and Purworejo (Central Java; Ompusunggu et al., 1994). Secondly, in 1995, Baird et al. documented the therapeutic failure of CQ + PQ in Arso (Papua) in 5% and 15% of cases, on days 14 and 28, respectively (Baird et al., 1995a). Then, in 1997, Fryauff et al. evaluated the efficacy of CQ + PQ as a treatment for *P. vivax* in Arso X/XI (Papua; Fryauff et al., 1997a). They reported that out of 27 *P. vivax* malaria patients treated with CQ + PQ, three had recurrent parasitemia by day 28. Finally, in 2005, Tjitra reported that the cumulative incidence failure of treatment with CQ + PQ was 4.7% in Bangka (South Sumatra) and 15.4% in Lampung (Tjitra, 2005). It is important to point out that the standard test for resistance to CQ in *P. vivax* malaria prohibits the application of PQ until day 28. This is because primaquine interferes with the assessment by killing chloroquine-resistant blood and liver stages. At the Arso field site, for example, when PQ was excluded from the *in vivo* assessment, virtually all treatments failed within 28 days (Sumawinata et al., 2003).

***2.2.2.4.4. Treatment of* P. malariae *and* P. ovale:** The treatment for *P. malariae* is CQ once daily for 3 days at a total dosage of 25 mg base/kg weight (Departemen Kesehatan, 2007b). The current first line of treatment for *P. ovale* is CQ + PQ. Chloroquine is given as per *P. malariae* and PQ is given for 14 days at a dosage of 0.25 mg/kg weight/day. The second line of treatment is QN + PQ. Quinine is taken orally three times a day for 7 days at 10 mg/kg weight/medication. Primaquine is taken for 14 days at a dosage of 0.25 mg/kg weight/day. A relapse of *P. ovale* in the next 14–28 days is treated essentially as before, except that the dosage of primaquine is increased to 0.5 mg/kg weight/day. The Indonesian MoH as yet has no guidelines for the treatment of *P. knowlesi* infection.

2.2.2.4.5. Chemoprophylaxis: As a chemoprophylaxis against *P. falciparum* infection, the MoH recommend that non-pregnant adults and older children receive DX at a daily dose of 2 mg/kg weight for 2 days before travelling to endemic areas, and throughout the duration of

stay in an endemic area. Such dose can be taken for periods up to 4–6 weeks (Departemen Kesehatan, 2007b). As a chemoprophylaxis against *P. vivax* infection, the MoH guidelines recommend a weekly dose of 5 mg/kg weight of CQ to be administered a week prior to entering an endemic area, and to take whilst remaining in the area (Departemen Kesehatan, 2006e). Since *P. falciparum* occurs wherever *P. vivax* is found, the rationale for recommending CQ prophylaxis against *P. vivax* malaria only is unclear.

In 1994, Ohrt et al. measured the efficacy and tolerability of DX as malaria prophylaxis in areas in Papua with resistance to CQ and SP (Ohrt et al., 1997). After radical cure, 67 Indonesian soldiers were randomly assigned to receive 100 mg of DX per day and 69 soldiers received a placebo for 13 weeks. A health worker visited each post every morning and supervised the medication. Both the health worker and the participants signed the daily drug record form. Malaria smears were obtained weekly and when a patient had symptoms suggesting malaria. The study showed that only one of 67 soldiers in the DX group developed malaria, but 53 of 69 in the placebo group. Doxycycline yielded protective efficacies of 99% against malaria (95% CI 94–100%), 98% for *P. falciparum* (95% CI 88–100%) and 100% for *P. vivax* (95% CI 90–100%). They noted that DX was significantly better tolerated than the placebo (RR 0.64; $p < 0.001$). RR < 1.0 indicated lesser risk in the DX group. They concluded that DX is highly effective and well tolerated in preventing malaria when taken as directed.

Several compelling evidences of PQ as prophylactic regimen were also evaluated in Indonesia. In 1992–1993, Baird et al. investigated the safety and efficacy of PQ relative to CQ for prophylaxis in non-immune people arriving in a hyperendemic area of Arso (Papua; Baird et al., 1995b). Forty-five subjects received PQ at 0.5 mg/kg weight every other day and 54 people in the same village received 5 mg of CQ base/kg weight for 16–19 weeks. A blood film was taken from each subject once a week. The study showed that the risk of malaria among people taking CQ relative to that of subjects taking PQ was 3.9 ($p = 0.014$) for *P. falciparum* and 10.6 ($p = 0.012$) for *P. vivax*. The minimal protective efficacy for PQ prophylaxis was 74% against *P. falciparum* and 90% against *P. vivax*. Primaquine was better tolerated than CQ. Physical complaints in the PQ group were less than the CQ group (Incidence Density Ratio 5.7, 95% CI 3.6–8.9). This study suggested that PQ may offer safe and= effective prophylaxis against hyperendemic malaria among non-immune people.

Soon after, Fryauff et al. evaluated the tolerability and safety of CQ and PQ as prophylactic drugs in Papua in 1993–1994 (Fryauff et al., 1995). After giving informed consent and being curatively treated, 126 adult male Javanese volunteers with normal G6PD activity were randomized to receive PQ daily at 0.5 mg/kg weight ($n = 43$), CQ weekly at 300 mg CQ base ($n = 41$) and placebo ($n = 42$) for 52 weeks. Drug consumption was supervised and each volunteer was visited every day. Malaria smears were made weekly or on any occasion of symptoms compatible with malaria. Physical complaints were recorded weekly. The study showed that prophylactic PQ provided a better protection than the placebo. The protective efficacies of PQ relative to placebo were 95% (95% CI 57–99%) for *P. falciparum* and 90% (95% CI 58–98%) for *P. vivax*. Relative to placebo, chloroquine efficacy against *P. falciparum* was only 33% (95% CI −58% to 72%) and 16.5% (95% CI −77% to 61%) for *P. vivax*. More complaints were recorded in volunteers receiving PQ (Incidence Density = 4.7/100 person-week) and CQ (ID = 6.2/100 person-week) than in those taking the placebo (ID = 3.6/100 person-week; $p < 0.01$). Only the incidence of cough differed significantly in PQ compared to the placebo (IDR 1.7/100 person-week, 95% CI 1.1–1.3). Six of 22 men who took PQ on an empty stomach reported gastrointestinal discomfort. In respect to complete blood count, renal or hepatic function, there was no difference between PQ and the placebo. Only the mean value of urea in the PQ group was significantly higher than the placebo group ($p = 0.03$), but all values were in the normal

range. Therefore, the authors concluded that there was no indication that the use of daily PQ for 1 year had any negative impact on the safety of volunteers. The study provided an evidence that PQ is effective and well tolerated for prevention of malaria.

Fryauff et al. evaluated the response to post-prophylaxis parasitemias after 4 and 28-weeks of daily PQ and weekly CQ prophylaxis (Fryauff et al., 1997c). They found that only one of *P. falciparum* and no *P. vivax* infections occurred during the first month after ending PQ prophylaxis. In contrast, six *P. falciparum* and three *P. vivax* infections occurred within 1 month after ending CQ prophylaxis. After 28 weeks of post-prophylaxis, in the PQ group, nine of the 30 participants (ID = 0.7 infections/person-year) were infected by *P. falciparum* and 13 of 30 people (ID = 1.2 infections/person-year) infected by *P. vivax*. In the CQ group, 10 of 20 participants (ID = 1.5 infections/person-year) were infected by *P. falciparum* and 10 (ID = 1.6 infections/person-year) infected by *P. vivax*. Relative to the placebo, there was no significant difference of attack rates of either infections in PQ and CQ. The geometric mean time to infection of *P. falciparum* parasitemia was longer for PQ (77 days) than for CQ (30 days) or the placebo (45 days), but not significantly ($p = 0.14$). This days also applied for *P. vivax* (PQ = 72 days; CQ = 35 days; placebo = 44 days), but not significantly ($p = 0.09$). The parasitemias of *P. falciparum* and *P. vivax* infections were not different between groups ($p > 0.28$). The mean number of physical complaints registered by subjects receiving PQ, CQ and placebo was uniform. The authors concluded that there was no indication that a daily use of PQ or weekly dose of CQ for 1 year placed subjects at greater risk of malaria infection or to more severe clinical symptoms of malaria than subjects who had taken a placebo. The results suggested that PQ had effectively prevented the establishment of liver-stage parasites.

In 1999, Baird et al. investigated the chemoprophylactic efficacy of PQ for the prevention of malaria in G6PD-normal individuals lacking clinical immunity who were living in Armopa (Papua; Baird et al., 2001). A daily adult regimen of 30 mg PQ for 20 weeks was given to 97 subjects and a placebo was given to 149 subjects. Each health worker was assigned eight to 12 subjects and tasked with visiting their homes each morning to administer the drug with the morning meal. Compliance was verified by signatures of the health worker and subject on a dosing card. At the end of each day, supervisors cross-checked the signatures of dosing cards and affirmed agreement by signing a record sheet. Prophylaxis continued for 20 weeks or until a subject had a blood film positive for *Plasmodium*. The study showed that PQ prevented malaria caused by *P. falciparum* and *P. vivax* for 20 weeks in 95 of 97 subjects. On the contrary, 37 of 149 subjects taking placebo became parasitemic. The protective efficacy of PQ against malaria was 93% (95% CI 71–98%), 88% (95% CI 48–97%) against *P. falciparum* and >92% (95% CI >37–99%) for *P. vivax*. No adverse event prompted withdrawal from the study, and no serious adverse events occurred. The only adverse events with a statistically significant risk ratio (RR) were headache (RR = 0.62), cough (RR = 0.50) and sore throat (RR = 0.34). RR < 1.0 indicated lesser risk in the PQ group. The authors concluded that a 30-mg daily adult regimen of PQ provided well-tolerated, safe, and efficacious prophylaxis against *P. falciparum* and *P. vivax* for 20 weeks among non-immune people living in endemic Papua.

Primaquine offers healthcare providers an excellent option to standard suppressive prophylactics for travellers exposed to malaria. Studies support the view that it is safe, well tolerated and effective in people who are considered good candidates to receive it (Baird et al., 2003b). Many evidences reported the efficacy and safety of PQ in Indonesia; however, PQ is not approved for prophylactic use in Indonesia. The unavailability of G6PD tests across the country suppresses the usage of PQ as a prophylactic measure.

2.2.2.5. Resistance to antimalarials—Effective treatment is an essential element of malaria control (Roll Back Malaria Partnership, 2008). The primary objective of an antimalarial treatment policy is to ensure the rapid and complete cure of infections. In doing so, one reduces morbidity, prevents the progression of uncomplicated malaria into a severe and potentially fatal disease, reduces the impact of malaria infection on the foetus during pregnancy, reduces the reservoir of infection and helps prevent the emergence and spread of drug resistance (World Health Organization, 2008e). Tests for treatment efficacy can be used to help establish whether an antimalarial drug is still effective (World Health Organization, 2005b). Such tests in Indonesia reveal that drug resistance poses a major threat to malaria control efforts (World Health Organization, 2003a). As resistance to one or more antimalarial drugs becomes more prevalent, the malaria control program (MCP) and other concerned institutions need to respond with new therapies. This requires evaluating antimalarial drug efficacy in a timely, relevant and reliable manner. A database for drug monitoring and evaluation that collects baseline drug sensitivity data may serve as the foundation for an appropriate monitoring system for drug efficacy (Tjitra et al., 1997). Such systems have not been assembled in Indonesia. Instead, the characterization of patterns of drug resistance depends upon a patchwork of discreet clinical studies done over the past four decades. The following assembly of these studies provides the highest possible resolution image of drug resistance patterns in Indonesia.

To date, we have assembled records of the antimalarial susceptibility tests carried out in 452 locations across the Indonesian archipelago since 1935. The two antimalarial treatments most often evaluated were CQ and SP. Resistance to antimalarial treatment was found in *P. falciparum*, *P. vivax* and *P. malariae*, but no report of resistance in *P. ovale*.

The distribution of *P. falciparum* resistance to CQ throughout the main islands is shown in Table 2.5. Our analysis of the data, extracted from *in vivo* and *in vitro* tests, shows that 52% (1539/2967) and 59% (1022/1743) of the tests, respectively, revealed resistance to CQ. Table 2.9 shows that *P. falciparum* resistance to CQ in eastern Indonesia was significantly higher than in western Indonesia when only the data from *in vivo* tests was taken into account (56%, 1122/2006 vs. 43%, 417/961; Z-test, $p < 0.001$). The data from *in vitro* tests revealed significant difference in resistance between the two areas (64%, 528/820 vs. 54%, 494/923; Z-test, $p < 0.001$).

The distribution of *P. falciparum* resistance to SP throughout the main islands is shown in Table 2.6. Eighteen percent (184/998) of the *in vivo* tests and 64% (310/487) of the *in vitro* tests revealed resistance to SP. Table 2.9 exhibited that *P. falciparum* resistance to SP in eastern Indonesia was not significantly different from that in western Indonesia when only the data from *in vivo* tests was taken into account (20%, 115/561 vs. 16%, 69/437; Z-test, $p = 0.057$). However, the data from *in vitro* tests revealed significantly lower resistance of *P. falciparum* to SP in eastern than in western Indonesia (43%, 60/141 vs. 72%, 250/346; Z-test, $p < 0.001$).

Table 2.7 summarizes the distribution of *P. falciparum* resistance to QN throughout the main islands. According to our data analysis, one in three of the *in vivo* tests and 7% (15/229) of the *in vitro* tests revealed resistance to QN. Table 2.9 presents that only a small number of *in vivo* tests were carried out. One case of *P. falciparum* resistance to QN was revealed in Papua through the use of *in vivo* test. The *in vitro* tests showed that resistance was present on most of the main islands.

Table 2.8 shows the distribution of *P. vivax* resistance to CQ throughout the main islands. Forty-eight percent (331/687) of the *in vivo* tests revealed resistance to CQ. Table 2.9 shows

that the resistance of *P. vivax* in eastern Indonesia was significantly higher than in western Indonesia (57%, 288/502 vs. 23%, 43/185; Z-test, $p < 0.001$).

2.2.2.5.1. Evaluations prior to 1985

2.2.2.5.1.1. Plasmodium falciparum: *Plasmodium falciparum* resistance to antimalarial treatments has been documented throughout Indonesia prior to 1985. Table 2.10 shows the pre-1985 prevalence of *P. falciparum* resistance to CQ, SP and QN. According to data analysis, 25% (64/252) of the *in vivo* tests and 49% (62/126) of the *in vitro* tests revealed *P. falciparum* resistance to CQ. *P. falciparum* resistance to SP was revealed in 8% (21/272) of the *in vivo* tests and 67% (16/24) of the *in vitro* tests. *P. falciparum* resistance to QN was reported in one of three individuals of the *in vivo* test and all of three isolates of the *in vitro* tests during this period.

The susceptibility of *P. falciparum* to CQ treatment has undergone evaluation since 1973 (Dondero et al., 1974). Dondero et al. carried out two *in vivo* tests in the Seruwai Plantation, Labuan Deli (North Sumatra) in 1973 and 1974. However, they found no resistance to CQ during their 7-day follow-up. The limitation of their study was the low *P. falciparum* prevalence found (<8%), which prevented the detection of late recrudescing resistance in a 28-day study.

Verdrager and Arwati first reported 100% (3/3) *P. falciparum* resistance to CQ in East Kalimantan in 1974 (Verdrager and Arwati, 1974). A year later, Ebisawa and Fukuyama reported two cases of resistance in Manokwari (Papua; Ebisawa and Fukuyama, 1975). In 1980, Simanjuntak et al. carried out *in vivo* and *in vitro* tests and reported 100% resistance (10/10 and 14/14, respectively) in Jepara (Central Java; Simanjuntak et al., 1981). In 1981, Pribadi et al. documented *P. falciparum* resistance to CQ in Southern Sumatra (Pribadi et al., 1981). Treatment with 1500 mg doses of CQ base failed to cure the patients, as did increased doses up to 2250 mg. In vitro tests for three patients showed that *P. falciparum* was resistant to CQ at the RI level. In vivo observations revealed that the parasite was resistant with a delayed recrudescence. In 1983, Smrkovski et al. conducted *in vitro* tests in Flores (Lesser Sundas) and reported that *P. falciparum* was resistant to CQ in 16% (7/45) of the tests (Smrkovski et al., 1983). Tjitra et al. reported that *P. falciparum* was resistant to CQ in 73% (8/11) of the *in vitro* tests conducted in Maluku between 1981 and 1985 (Tjitra et al., 1997).

Rumans et al. first reported *P. falciparum* resistance to SP in 1979 in Jayapura (Papua; Rumans et al., 1979). Since then, Hoffman et al. have conducted tests in Jayapura (Papua), revealing resistance in 5% (2/41) and 11% (2/18) of cases, in 1983 and 1984, respectively (Hoffman et al., 1985, 1987).

2.2.2.5.1.2. P. vivax: Dondero et al. carried out two *in vivo* tests in the Seruwai Plantation, Labuan Deli (North Sumatra) in 1973 and 1974 (Dondero et al., 1974). However, in a total of 16 individuals with *P. vivax* infections, they found no resistance to CQ during their 7-day follow-up. Guldelfinger et al. also reported similar results on 12 individuals in Belu (Lesser Sundas) in 1973 (Gundelfinger et al., 1975).

2.2.2.5.2. Evaluations since 1985

2.2.2.5.2.1. P. falciparum: Table 2.10 shows the distribution of *P. falciparum* resistance to CQ, SP and QN prior to and since the year 1985. Our analysis shows that *P. falciparum* resistance to CQ increased significantly from 25% (64/252) prior to 1985 to 54% (1475/2715) after 1985 (Z-test, $p = 0.001$). When only *in vitro* test results are taken into account, the increase in resistance from 49% (62/126) prior to 1985 to 59% (960/1617) since

1985 is significant (Z-test, $p = 0.026$). The analysis of data concerning *P. falciparum* resistance to SP showed different results. According to *in vivo* test results, the SP resistance increased significantly from 8% (21/272) prior to 1985, to 22% (163/726) after 1985 (Z-test, $p < 0.001$). However, evidence from *in vitro* tests shows that resistance was no different prior to 1985 and after 1985 (67%, 16/24 vs. 63%, 294/463; Z-test, $p = 0.753$). Several studies reported a resistance of *P. falciparum* to quinine; however, we were unable to calculate the difference between levels of resistance over different periods as the sample size was too small. Baird et al. documented the presence of *P. falciparum* resistance to QN in Arso PIR (Papua) in 1991 (Baird et al., 1991b). They reported that 60% (6/10) of isolates required higher doses of QN to achieve 50% inhibition of schizont development.

2.2.2.5.2.2. P. vivax: Table 2.10 shows the prevalence of *P. vivax* resistance to CQ prior to and, since 1985. The resistance of *P. vivax* to CQ increased significantly from 0% (0/28) prior to 1985 to 50% (331/659) since 1985 (Z-test, $p < 0.001$). We also documented high levels of *P. vivax* resistance to CQ after 1985. Baird et al. documented the existence of CQ-resistant *P. vivax* in Papua in 1991 (Baird et al., 1991a). Sixteen of 24 residents in Arso PIR II, taking weekly doses of CQ prophylaxis under supervision, developed *P. vivax* asexual parasitemia at least once during 8 weeks of surveillance. In June 1990, six local residents and one American had serum levels of CQ in excess of the ordinarily suppressive 15 ng/ml at the time of their asexual parasitemias (16–70 ng/ml).

2.2.2.5.2.3. P. malariae: The susceptibility of *P. malariae* to antimalarial drugs in Indonesia has rarely been evaluated. *P. malariae* resistance to CQ in Indonesia was first reported on the island of Legundi (Southern Sumatra) in 2000 (Maguire et al., 2002b). Maguire et al., using active surveillance, found a 17% (127/752) prevalence of parasitemia by *Plasmodium* (31.5% *P. falciparum*, 30% *P. vivax*, 37% *P. malariae*, 1.5% *P. falciparum* and *P. vivax* combined). *P. malariae* was the most common parasite, accounting for a majority of malaria cases (41% in Selesung village and 39% in Keramat village). In a 28-day *in vivo* assessment, Maguire et al. further revealed that among 28 study subjects from Selesung and Keramat villages, one had recurrent parasitemia on day 28 and two had persistent parasitemia up to day 8. The 28-day cumulative incidence of therapeutic failure was 12% by life-table analysis. Whole-blood chloroquine and desethylchloroquine concentrations were at an effective level (larger than 100μg/l) on day 8 in both cases of persistent parasitemia. However, no standard definition of resistance supported that diagnosis, and it remains at least possible (although perhaps unlikely) that CQ-sensitive asexual blood stages may persist to the eighth day post-therapy, by virtue of the longer asexual cycle of development in this parasite, that is, the 36-h cycle of *P. vivax* versus the 48-h cycle of *P. falciparum* malaria. However, Siswantoro et al. made different findings during research conducted in Timika (Papua) in 2005 (Siswantoro et al., 2006). They evaluated the efficacy of CQ in treating 50 patients infected by *P. malariae* and followed their progress over 28 days. The results showed that there was no reappearance of *P. malariae* between day 7 (0/42) and day 28 (0/27).

2.2.2.5.2.4. P. ovale: Siswantoro et al. evaluated the efficacy of CQ as a treatment in 14 subjects with *P. ovale* malaria in Timika (Papua; Siswantoro et al., 2006). They found that there were no recurrences within 28 days following treatment. This single study constitutes the entire body of investigation regarding the therapeutic responsiveness of *P. ovale* in Indonesia.

As shown by the evidence presented thus far, the resistance to antimalarial drugs in Indonesia varies a great deal depending on the drug, the species of parasites, and the geographic location. MoH guidelines remain essentially the same as they were during the Soeharto years where strong central authority created monolithic health policies. A policy to

treat clinically diagnosed cases with CQ and SP may often prove inappropriate. Moreover, 87% of clinical malaria cases appear to receive treatments known to be widely ineffective, as shown by the evidence provided here.

2.3. MALARIA CONTROL IN INDONESIA

2.3.1. Control before independence (pre-1945)

The Dutch made their first voyages to the Indonesian archipelago between 1595 and 1600 (Snapper, 1945). In 1602, the several small navigation companies that had been competing with each other were merged to form the East Indies Company, the Vereenigde Oost-Indische Company (VOC). By the late eighteenth century, the company continually employed 300 surgeons to treat the sick and to take care of the military garrisons. About 200 surgeons were working on the ships sailing between Holland and the Indonesian archipelago or those going between the different islands of the archipelago. Between 1795 and 1800, no ships from Holland reached the Indonesian archipelago because of the strict blockade imposed by England. In 1795, the British took the offices of the Company at the Cape, Near India, Ceylon, Malacca, the east Coast of Sumatra, Ambon and Banda into custody. In 1811, the English conquered Java and the rest of the archipelago. Afterwards, in 1816, the Dutch were solemnly reinstated as rulers of the Indonesian archipelago. Gradually, a new administration was built up.

Malaria has almost certainly been presented throughout the Indonesian archipelago for as long as humans have inhabited it. History recorded by European colonists indicates that malaria was a serious public-health burden during the colonial period, which started around 1600. According to Bontius, in 1630, malaria was prevalent in Batavia (now Jakarta) in the form of tertian or continual fevers (Van der Brug, 1997). Van der Brug claims that malaria explains, to a large extent, the high incidence of morbidity and mortality in 1733 in Batavia (Van der Brug, 1997). Up until 1733, ~500–700 Dutch employees of the Dutch colonial trading company (VOC) died each year as a consequence of typhus, dysentry, malaria and a variety of other causes (accident, injury, murder, etc.). Such losses accounted for ~10% of the new Dutch arrivals in Batavia. After 1733, the already high-mortality rate of 10% jumped to 50–70% of the new arrivals (2000–3000 died per year). Batavia became known as a Dutch graveyard and it seems likely that malaria was the main cause of death. In about 1800, the Dutch began to abandon the old city near the coast and move further inland to the Weltvreeden area (now the area surrounding Merdeka Square). Although high malaria mortality continued to plague the Javanese and Chinese residents of old Batavia, Dutch mortality fell sharply in their new and healthier surroundings. It is most likely that they distanced themselves from the dense populations of *A. sundaicus*, a species which is an efficient and notorious vector of coastal malaria.

Doolan et al. reviewed naturally acquired immunity to malaria (Doolan et al., 2009). In the review, they summarized the findings of Robert Koch who, in 1900, first reported a scientific basis for naturally acquired protection against malaria. Using cross-sectional studies, Koch examined the prevalence and density of parasitemia in areas of low endemicity in Sukabumi (West Java) and areas of high endemicity in Ambarawa (Central Java; Koch, 1900). Koch deduced that protection against malaria was acquired only after heavy and uninterrupted exposure to malaria. He found that, in low-endemicity areas, parasites were uniformly distributed across all ages. In high-endemicity areas, however, the distribution of parasites was age-dependent. A number of malaria studies, conducted in Java since the publication of Koch's work, have largely confirmed his findings. In 1919, Schüffner published his study carried out in Sundatar (West Sumatra; Schuffner, 1919). He found that the prevalence of parasitemia was higher among children than adults. Schüffner was aware of Koch's hypothesis that acquired immunity could only occur as a result of life-

long uninterrupted exposure (Baird, 1998). Schüffner was therefore puzzled by the age-dependent protection from parasitemia that he observed, despite the lack of the high degree of exposure apparently necessary (Baird, 1998).

The Civil Medical Service (CMS) was founded in 1826 (Snapper, 1945), and then reorganized in 1911 (Overbeek and Stoker, 1937). It provided medical services to the community for a wide variety of infections, including malaria. The Public Health Service within the CMS focused on disease prevention, studying, amongst other things, the development of plasmodia in local anophelines and seeking to develop best practices in combating malaria. In 1876, a medical school for Indonesian physicians was opened in Jakarta. In 1913, a similar school was started in Surabaya (East Java). Medical science in Indonesia at the time also greatly profited from the publication of several periodicals, such as Het Natuur en Geneeskundig Archief (1844–1847), Het Geneeskundig Tijdschrift voor Nederlandsch Indie (l851–1942) and Medeelingen van den Dienst der Volksgezondheid van Nederlandsch Indie (1910–1930). In 1924, the Central Malaria Bureau was established as a subdivision of the Public Health Service. This marked the beginning of programmatic malaria control in Indonesia. The Central Malaria Bureau worked with the Division of Sanitary Works and Housing, ensuring that they too concerned themselves with malaria sanitation, that is, building out or away from anopheline breeding sites. The Central Malaria Bureau offered training to over a 100 malaria assistants; the first cadres, or government employees, dedicated to the technical tasks which form part of malaria control operations. In this pre-1945 period, these tasks almost exclusively involved carrying out antilarval measures.

These antilarval measures consisted mainly of environmental modifications. Following the example of Watson in British Malaysia, Swellengrebel pioneered the technique of species sanitation in Indonesia in 1919 (Swellengrebel, 1950). Watson had visited Swellengrebel in Sumatra in 1913 and introduced him to the working concepts of species sanitation (Takken et al., 1990). The technique involved identifying the breeding and feeding sites of the most important vectors, in order to then make a systematic attack on those sites using standard civil engineering techniques. Watson had beaten down a malaria epidemic at Port Swettenham in Malaysia (the newly opened maritime port of the rubber-growing districts) in this manner. He had simply lined the drainage ditches over an area of 24,000 acres with cement and had thus denied the *A. maculatus* species, its much preferred breeding site in rocky pools along streams. As a result, the vector perished and malaria vanished from over 500 square miles. The measures Watson prescribed amount to the essential basis of malaria control today: (1) determine the geographic distribution of malaria; (2) collect, identify and list the species of anophelines present; (3) examine the association of malaria and anopheline distribution and thereby identify the anopheline species involved in transmission; (4) determine the natural rate of infection with each species of malaria parasite and (5) identify the principal breeding places of the incriminated anopheline vector species. This approach concentrates resources for control at the crucial point for their effectiveness: the active breeding sites of the important vectors in those areas where malaria is occurring in humans. In other words, species sanitation was, and is, a useful approach to combating malaria by specifically targeting only the breeding places of those anophelines known to actively transmit malaria (Takken et al., 1990). Swellengrebel embraced this approach (Swellengrebel, 1950), saying in 1931, ‘Malaria is a local disease to be dealt with by local efforts’.

Takken et al. reviewed the Dutch literature describing the implementation of sanitation before 1945 (Takken et al., 1990). They described 46 sites, located in Sumatra (13 sites), Java (28 sites), Sulawesi (three sites), the Lesser Sundas (one site) and Papua (one site), at which extensive sanitation measures were implemented. The first systematic antimalarial

measures were undertaken in 1919 at Sibolga (North Sumatra; Takken et al., 1990). Out of all the sites across Indonesia, 41 dealt with a total of eight malaria vectors: *A. sundaicus* (26 sites), *A. aconitus* (nine sites), *A. maculatus* (six sites), *A. sinensis* (three sites), *A. hyrcanus* (two sites), *A. minimus* (one site), *A. bancrofti* (one site) and *A. punctulatus* (one site). Only 15 of the 46 sites documented the effects of sanitation on mortality and spleen index. For these 15 sites, the distribution of sites by species was *A. sundaicus* (13 sites), *A. aconitus* (three sites), *A. maculatus, A. sinensis, A. bancrofti* and *A. punctulatus* (one site each). Spleen index refers to the percentage of people sampled who have a palpable and therefore enlarged spleen, presumably as a consequence of relatively heavy exposure to malaria. This was widely used as a crude measure of transmission intensity before the advent of microscopic blood film examinations. According to this criterium, the sanitation measures against *A. sundaicus* proved extremely successful, with records showing a reduction of the spleen index from more than 80% to less than 20%, and a fall in the mortality rate from 80 deaths to less than 18 deaths per 1000 of the population per year after implementation in Sibolga (North Sumatra).

The sanitation measures implemented in Sibolga are exemplary of antimalaria sanitation measures. In 1912, Sibolga, on the west coast of Sumatra, was an administrative and trade centre. It was situated beside a bay at the mouth of a river and was surrounded by steep foothills. A European residential and administrative area was located on a nearby coastal plain. The community based there suffered epidemic malaria, with a mortality rate of 8% and a spleen index of 15–98%. Investigation showed that the highest larval densities occurred in a nearby swamp area. This area was used to dump waste products from coconut plantations, along with refuse from the town market. The waste blocked the flow of sea water and created breeding sites for *A. sundaicus*. De Vogel recommended eliminating breeding sites by improving drainage. He was unsuccessful in opposing a plan to fill the tidal swamp areas; a plan which was thus implemented by the harbour authorities in 1919 (Takken et al., 1990). This solution cost five times the amount that De Vogel had in mind. Nonetheless, the project roughly halved the spleen index.

Schüffner introduced a new form of species sanitation in 1916–1917 (Swellengrebel, 1950; Takken et al., 1990). In Mandailing (North Sumatra), malaria was endemic, with a spleen index rate exceeding 90% in both children and adults. Rice was grown only in the wet season, as there was no irrigation system. When it was harvested, the rice fields remained fallow. Scattered between these were fishponds harbouring breeding sites for *A. sundaicus* and seven other anophelines. Schüffner taught the people of Mandailing, including school children to recognize the adult mosquitoes of this species. Village leaders from selected villages delivered captured anophelines to the local malaria laboratory, where these were identified and registered by location captured. This represents a superb early example of community participation in malaria control. The detailed and accurate knowledge of local vectors led to successful control. Unfortunately, after only 1 year of such success, the central government declared the practice an illegal forced labour. Schüffner made another contribution when he pointed out that the fish raised in the aforementioned ponds did not contribute to the community's diet. In other words, the elimination of these ponds would not directly affect nutrition in the community. Although they made some contribution to economic activity, on the whole they seemed disposable and they were successfully removed. At the behest of Swellengrebel, the government purchased all fishponds and prohibited the laying out of new ones. After just a few years, the spleen index was down to 10%. The fact that no other species of anopheline besides *A. sundaicus* had been affected by this measure offered a compelling demonstration of the efficacy of properly applied species sanitation.

Another example of successful species sanitation is Mangkuwinoto's work in the plain of Cihea, Cianjur (West Java) in 1917 (Overbeek and Stoker, 1937; Swellengrebel, 1950). Cihea plain was a rice-growing region dependent on rain cycles for cultivation. Rice fields were cultivated once a year during the wet season. Planting and harvesting occurred at about the same time as the cultivation and fields lay fallow in the dry season. An irrigation project, begun in 1854 and continuing until 1904, eventually covered over 5000 ha of rice fields. This meant that rice could be grown all year round. Each farmer planted and harvested at the time he thought best. This new practice led to severe malaria epidemics. In 1911, Van Gorkom surveyed the affected villages and found a spleen index of 42% among native workers and their families living on the rice estate, and a spleen index exceeding 50% in the surrounding villages (Takken et al., 1990). In 1913, Van Gorkom showed that malaria led to a reduction in the number of labourers who were able to cultivate water-covered rice fields. More uncultivated rice fields in turn led to the creation of more breeding sites for anophelines. He recommended regulating the water supply by diverting irrigation from uncultivated rice fields, and by improving the drainage system from all fields. These recommendations failed owing to objections from farmers. There were insufficient labourers available to prepare the rice fields in the short time frame imposed by his plan. Farmers kept their fields submerged because the dry soil needed inundation before the next cycle of cultivation. In 1917, Van Lonkhuysen and Darling incriminated *A. aconitus* as the vector in Cihea (Darling, 1926). Later in the same year, Mangkuwinoto, as health officer for the region, confirmed *A. aconitus* as the dominant local vector of malaria. He described uncultivated and weed-covered rice fields as the preferred breeding site for this mosquito. The largest quantities of larvae occurred in fields where rice had been harvested and the remaining stalks simply trampled down (Swellengrebel, 1950). These rice fields were still being deliberately flooded in preparation for the next planting. Mangkuwinoto's recommendations resembled those of Van Gorkom (Takken et al., 1990). This time, however, the scheme proved exceptionally successful in Cihea. He collaborated with agricultural experts and set up a revised planting schedule. The regulation of the water supply was introduced by dividing the agricultural area into two separate irrigation schemes. The irrigation supply to the area covered by the first scheme was conducted on 15 September 1919 and to the second on 1 December. At the end of December, 70% of the fields had been prepared or planted. On February 1, and every 2 weeks thereafter, the irrigation supply to the area of the first scheme was reduced by one-sixth before being completely stopped on April 15 (Takken et al., 1990). The gradual reduction of the irrigation supply to the area of the second scheme was staggered in the same way from the beginning of April. Following the end date for irrigation, water was supplied only for bathing, drinking, washing and the watering of non-rice crops. Fish cultivation was prohibited. Swellengrebel noted that enforcing this planting schedule stopped the exhaustion of the soil and thus improved its growing qualities (Swellengrebel, 1950). There was no need to keep a harvested field flooded in order to provide a neighbouring field with water. Although this measure did not completely remove all breeding sites of *A. aconitus*, the number of malaria cases sunk to a very low level. Overbeek and Stoker documented that the spleen index for the entire Cihea plain, which had been 88% in 1919, fell to 72% in 1922, 20% in 1931 and 13% in 1935 (Overbeek and Stoker, 1937). The annual all-cause death rate fell significantly from 34 per 1000 population (1919) to 15 per 1000 population (1935). The collaboration with local farmers was necessary to keep the regulation functional. The solution, of course, had to allow for effective agriculture. Mangkuwinoto, local administration officials and irrigation superintendents delivered malaria education to village leaders and landowners (Takken et al., 1990). They showed them anopheline larvae, anopheline adults and dissected mosquito stomachs, and also taught the preparation and reading of blood slides, described anopheline-borne malaria transmission and explained the importance of measures against the mosquitoes. Today, one can visit this district and see a stone landmark praising the historic effort that so improved the health of the residents. Unfortunately, the landmark

makes no mention of the malariologist responsible for this effort. Instead, it is dedicated to Wiranata Koesoma, who served as Regent of Cianjur between 1912 and 1920.

Swellengrebel documented the situation in the plain of Cihea from 1942 to 1945, during the Japanese occupation of Java (Swellengrebel, 1950). The Japanese occupiers identified *A. maculatus* as the main vector and discouraged the maintaining of the planting schedule. Remarkably, residents defied this and continued to follow the schedule. In 1946, malaria nonetheless remained a problem in Cihea with a spleen index of ~30%. At some later date, probably during the Global Eradication campaign of the 1950s and 1960s, malaria finally vanished from the region. Bowolaksono concluded in 2000 that the old irrigation system implemented by Dutch colonial authorities was still being used, albeit without irrigation scheduling (Bowolaksono, 2000). Between 1989 and 1999, not a single case of malaria was reported by the two primary health centres (Bojongpicung and Ciranjang). *A. aconitus* mosquitoes are still present, but the parasite seems to be entirely absent.

Species sanitation measures were also implemented to combat coastal malaria at Batavia (Jakarta) and Pasuruan (in East Java). In 1908, De Jonge found a higher mortality rate and a higher spleen index in coastal areas of Batavia than in other parts of the city (Takken et al., 1990). His investigations led him to identify rice fields and marine fishponds as the main breeding sites of malaria vectors. He concluded that environmental management was not feasible and suggested instead that quinine be distributed to malaria patients for free. Van Breemen and Sunier investigated the association between malaria and the presence of marine fishponds in the coastal areas of Jakarta in 1917 and 1918 (Van Breemen and Sunier, 1919). They noted that the mortality rates and spleen indices among communities surrounding marine fishponds were higher than in other communities. *A. sundaicus* were found breeding in vast numbers in these ponds. They recommended that all fishponds be filled in, and that the land be reclaimed for agriculture across a broad swath of what is now north Jakarta. However, the authorities considered these recommendations to be impractical and expensive. Moreover, the community would lose a vital source of both food and income. The difficulty was that water plants floating near the surface of the fishponds, whilst on the one hand providing food for the fish, were on the other hand providing shelter for anopheles larvae (the thick mats of algae or vegetation protect the larvae from predation by fish). Van Breemen tried to make use of tidal movements and free access between fishponds and sea water as Mangkuwinoto had done in Probolinggo (East Java) in 1921 (Takken et al., 1990). It was hoped that this would make the fishponds unsuitable breeding places. However, this approach failed because the height of the tide in Probolinggo (over 2.5 m) had been much greater than it was here (1 m).

In Pasuruan (East Java), in 1922, Reijntjes disproved the notion that cultivated fish depended on the water plants at the surface of the fishpond for food (Takken et al., 1990). He showed that the blue-green algae at the bottom of the pond were their primary food source. He drained experimental ponds for a few days each month to expose the bottom of the ponds to sunlight. A shallow layer of water was maintained for several days to stimulate the growth of these algae. During this time, the fish were kept in a narrow ring channel. Once the algae had thrived, the ponds were refilled with seawater. The floating water plants were killed off by this process. The cultivation of fish thrived and the anophelines vanished. In 1928, fishpond management, as outlined by Reijntjes, was adopted in Jakarta. Between 1928 and 1932, 291 ha of fishponds were sanitized against *A. sundaicus* using this method. In 1931, the Central Malaria Bureau evaluated the efficacy of this sanitation measure and found that the number of malaria cases (calculated according to the spleen index) had fallen from 39 per 1000 population (1925–1929) to 27 per 1000 population (1931).

As far as the use of quinine as a malaria treatment and a method of control were concerned, Indonesia was well known as being the most productive producer of cinchona in the world before 1945. In 1987, Gramiccia reviewed the historical endeavour of smuggling cinchona seedlings from South America to Europe and Asia (Java and India; Gramiccia, 1987). Sydenham in 1666 and Torti in 1712 recorded how the cinchona bark's effectiveness against malaria fever increased the demand of the plant. By 1820, Pelletier and Caventou had established how to isolate quinine from the bark, thus creating a huge demand for bark that yielded the highest quantities of quinine. In 1852–1854, the Dutch Government sent Hasskarl, an employee at the botanical gardens in Bogor (West Java), to South America. He soon requested that Schukraft, the Dutch Consul in La Paz, bought good Cinchona seeds from the South American Indians and have them sent to Java. About 75 of the 500 seedlings sent were still alive on arrival in Bogor. In 1857, Junghuhn was appointed, after Hasskarl, as the inspector of the cinchona-cultivation in Java and he instructed to plan the cinchona at higher altitude (de Knecht-van Eekelen, 2000). The cultivation of these seeds was a success on the plateau of Pangalengan (West Java). At this early stage, however, none of the four varieties of *Cinchona calisaya* yielded more than very low quantities of quinine (0.3–1.5%). Commercial success was not yet within grasp. In 1865, Charles Ledger, a British trader, sent cinchona seeds of high-yield varieties to London. He had only managed to find these among a pure population of cinchona trees in Eastern Bolivia in 1851, with the help of his local companion, Manuel Incra Mamani. Charles Ledger asked his brother George Ledger to sell the seeds to the British Government. The British Government refused and George then sold 1 pound of these seeds to the Dutch Consul in London. The seeds were sent to Java and received in December 1865 by the Dutch Cinchona Plantation headed by Van Gorkom (Kerbosch, 1931). Of 20,000 germinated seeds, 12,000 were planted alive. In 1872, Moens first analysed the bark of Ledger's cinchonas and found an astonishingly high yield of quinine in the bark (13.25% weight to weight). Such a yield effectively gave the Dutch on Java a monopoly on the trade in quinine. In Java, there were 127 cinchona estates and 85 of them were located in Preanger (West Java). These plantations constituted 75% of total production in Java. Extremely fertile volcanic soils and suitable elevation contributed to the huge success of cinchona cultivation. In 1875, Indonesia was responsible for 97% of the world's production of cinchona bark. Indonesia maintained this monopoly right up to the invasion of Java by the Imperial Japanese Army in early 1942. Dutch merchants at seaports in Cilacap, Batavia and Surabaya refused the requests of Allied naval commanders to load the many tons of quinine stored in maritime warehouses onto their warships evacuating to Australia as the Japanese advanced. The loss of Java and its cinchona plantations, along with this huge stock of quinine, helped to spark the urgent wartime effort by the American government to develop new therapies for malaria. This effort would ultimately result in chloroquine and primaquine, the former rendering quinine no longer valuable as a trading commodity.

Leimena noted that there was no possibility of controlling malaria during the Japanese invasion of 1942–1945 (Leimena, 1956). All activities were directed at supporting Japan's war machine. Many malaria sanitation measures were neglected. Although the training of malaria assistants was continued by the Japanese, it was a superficial effort without yield (Azir, 1957). Many health personnel were captured and died in internment camps. The medical school in Surabaya (East Java) was closed down and the newly graduated physicians were forced into military service. Indonesian scientists at the famous medical research institute of Nobel laureate Christiaan Eijkman in Jakarta were accused by the Japanese of creating biological weapons. They were all imprisoned and only a forced confession by the director (Achmad Mochtar) led to their release. He was beheaded by his captors on 3 July 1945. The long war brought starvation, deprivation, slave labour and a surge in endemic malaria where it had existed previously, and epidemic malaria where it had

previously been brought under control. The period between 1942 and 1945 is therefore an anomaly and by no means representative of the progress made between 1915 and 1941.

During the period before 1945, 98 cross-sectional malaria surveys were conducted across the archipelago. The distribution of these surveys was as follows: 60% in Sumatra, 23% in Papua and 16% in Java. The prevalence of *P. falciparum* in Papua (12%; 926/7677) was higher than it was in either Sumatra (8.9%; 3142/35,115) or Java (5.1%; 87/1696). The prevalence of *P. vivax* was also higher in Papua (6.1%; 469/7677) than it was in Sumatra (3.4%; 1196/35,115) or Java (3.3%; 56/1696). However, the prevalence of *P. malariae* was much higher in Java (13%; 221/1696) than in either Sumatra (1.2%; 421/35,115) or Papua (0.5%; 38/7677).

Nonetheless, malaria control measures available in Indonesia in the period before independence were, in retrospect, extremely limited. Not only were tools such as routine microscopic diagnosis, chloroquine, primaquine and DDT not yet available, the few tools that were available tended to be found only where the Dutch had a commercial interest. Vast swathes of the archipelago lived with malaria much as they had done in the millenia before. There was no healthcare delivery system. There was no government to take responsibility for the health of all residents rather than only those in areas near Dutch interests. Indonesian nationalists would fight and win a bloody war of independence from the Dutch from 1945 to 1949.

2.3.2. Malaria Control Program (1945–1958)

During the early period of independence, Indonesia faced multidimensional problems. After the declaration of independence on 17 August 1945, important military clashes occurred against the British forces. They were present primarily to disarm and repatriate Japanese forces, but they had been forced into the position of supporting the reintroduction of Dutch military rule and authority. In 1947 and 1948, the nationalists fought against the reintroduced Netherlands Indies Civil Administration (NICA). Nevertheless, as the war for independence raged, the MoH of the Republic of Indonesia was established between 1945 and 1947. The ministry oversaw the successful manufacture of quinine at Leles, Lawang and Madiun (Leimena, 1956). At this time, there were only 830 physicians in Indonesia for about 60 million people. Essential drugs were obtained from Red Cross organizations in countries such as India, Australia, Egypt and Malaya. After an initial peace agreement in 1948, the territory of Indonesia was reduced and the MoH now served only 30 million people. In Magelang (Central Java), the MoH established a malaria research centre and a centre for rural hygiene. At this time, 472 physicians and 167 nurses specially trained to treat malaria. After the transfer of sovereignty was formally signed on the 27 December 1949, a period of health reconstruction was established under the United States of Indonesia. The national MoH was established as a collaboration of the health ministries of seven member states. The number of physicians increased to about 1200 for 75 million people. On 17 August 1950, the United States of Indonesia changed its name to the Republic of Indonesia and the national body of health services was reorganized once again. Leimena, who was Health Minister at the time, identified malaria as public enemy number one, owing to its role in the huge loss of manpower and economic activity. It has been estimated that malaria affected 30 million of the 77 million people who populated the Indonesian archipelago in the late 1940s and early 1950s (Azir, 1957; Ketterer, 1953).

By 1945, the discovery of DDT (in 1939) and its wartime exploitation by the Allied Forces had led to it being used for IRS for public-health purposes. Many studies examined its effectiveness against anopheline mosquitoes. In 1949, Swellengrebel and Lodens found that a single application of 5% DDT solution in kerosene reduced the density of *A. aconitus* and *A. subpictus* for 6 months in Cianjur (West Java; Swellengrebel and Lodens, 1949). In 1950

Bonne-Wepster and Swellengrebel reported that the residual effect of DDT on *A. sundaicus* lasted for 5 months in Tanjung Priok (north Jakarta; Bonne-Wepster and Swellengrebel, 1950). In 1951, van Thiel and Winoto reported that with two cycles of DDT spraying, the infant parasite rate was reduced from 36% to 0% in Marunda (north Jakarta; Van Thiel and Winoto, 1951). The results of these studies showed the way towards an era of attacking endemic malaria.

The MCP of the fledgling Republic of Indonesia received generous support from their counterparts abroad. Suparmo detailed the difficulty in acquiring DDT and sprayers (Soeparmo, 1958). Mainly, the MCP was operated by the MoH with assistance from the Technical Cooperation Administration Mission (formerly the Economic Cooperation Administration Special Technical and Economic Mission, currently the United States Agency for International Development, USAID). USAID assistance began in October 1950, providing US$ 1,449,000 for DDT, technical assistance, educational activities, sprayers and other commodities. The population goal of the spraying program was about 5 million people by the end of 1953. In 1950, the WHO provided US$ 74,000 for a malaria control demonstration area on the south coast of Java. In 1951, the Malaria Institute, USAID and the WHO launched an MCP focusing on routine DDT spraying in Java, South Sumatra, Northern Central Sulawesi and Maluku in areas with spleen indices of 50% or higher. The acceleration of the MCP (1952–1959) was launched by routine implementation of DDT house spraying and mass chloroquine treatment (Soeparmo and Laird, 1954).

In 1954, however, DDT resistance in mosquitoes was reported. Crendell discovered DDT-resistant *A. sundaicus* at Cirebon (West Java; Crendell, 1954). In 1956, Chow and Soeparno reported that, in Semarang (Central Java) and Surabaya (East Java), *A. sundaicus* had become 23–27 times more resistant to DDT than when the insecticide had first been implemented (Chow and Soeparmo, 1956). Dieldrin was introduced to combat this DDT resistance. *A. sundaicus* gradually disappeared from the northern coastal area of Java (Soemarlan and Gandahusada, 1990). Despite the decrease in malaria on the northern coast of Java, it persisted (and still does) on the southern coast. This may have been a consequence of the presence of another important vector, *A. maculatus*, a dominant species found along the copious hillsides along the southern coast (the northern coast is a plain almost completely without hills).

The success of DDT spraying was reported from what continued to be (until 1963) the Dutch colonial possession of western New Guinea (currently Indonesian Papua). In 1954, Metselaar carried out spraying in houses along Lake Sentani with a 2 g/m^2 dosage of 5% DDT wettable powder (WP; Metselaar, 1956b). The parasite rate fell from 47% (736/1566) to 20% (260/1301) in hyperendemic areas and from 16% (346/2162) to 6% (81/1350) in mesoendemic areas. Meanwhile, in control areas (in Nimboran), the parasite rate dropped from 87% (871/1001) to 64% (495/773). In experiment areas, the sporozoite rate fell from 1.2% (9/744) to 0.2% (4/1657) in the punctulatus group of mosquitoes. Metselaar found that the spraying did not completely prevent transmission as a few sporozoite-positive mosquitoes and new infections in infants were found. He concluded that the eradication of local vectors and malaria parasites in New Guinea could not be achieved through residual spraying, but that it was reasonable to expect a much lower degree of endemicity as a result of spraying.

Spraying alone did not interrupt malaria transmission in Papua. Van Dijk performed mass chloroquine treatment in Demta where DDT spraying had been going on twice a year since 1954 (Van Dijk, 1958). He achieved almost complete population coverage and distributed chloroquine once a week for 8 successive weeks. A year later, the parasite prevalence had dropped from 41% to 2%. The use of chloroquine in table salt distributed to the population

in these highly endemic areas may have been the starting point of the resistance to chloroquine developed by the *Plasmodium* on the island of New Guinea.

Malaria control produced beneficial economic effects in Indonesia. Ketterer and Suparmo provided evidence of economic benefits to rice production, export products and transmigration projects (Ketterer, 1953; Soeparmo and Stoker, 1952). In September 1951, DDT spraying was conducted along the bay of Banten (Northwest Java) with the total cost of initial spraying reaching US$ 12,000. This was an area of more than 10,000 acres of highly productive land, which had been abandoned after the Japanese occupation had destroyed the pre-war drainage system. A malaria epidemic in 1944 affected 80% of the people living there and had forced them to abandon the land. As soon as the DDT spraying was successful, all idle land was cultivated and produced rice again. As a result, the total value of rice production was US$ 740,000. In other words, with an investment of just US $12,000 in malaria control, the direct yield in rice production alone paid for the intervention more than 500-fold. In palm oil estates, DDT spraying in 1950 reduced the rate of malaria admissions to hospitals from 30% (700/2363) to 7% (90/1346). This resulted in a dramatic decrease in absenteeism and an increase of working days and productivity. DDT spraying was conducted in the transmigrant areas of Metro (Lampung) and Dumoga (North Sulawesi) in 1951 and 1952. In Metro, the prevalence of malaria in infants (0–12 months) fell from 21% (392/1849) before spraying to 2% (27/1506) after spraying (Soeparmo and Stoker, 1955).

In conclusion, in the period between 1945 and 1958, malaria control activities relied heavily upon DDT spraying. The success of DDT in various places in reducing malaria transmission motivated a broader application. Healthcare systems were just beginning to be established at the district level at a time of growth for the government and for military hospitals. Passive case detection (PCD) started and clinical examination became a dominant instrument for malaria diagnosis. In urban areas, malaria examination was by microscopy. Whatever the method of identification, malaria was treated using chloroquine and quinine.

2.3.3. Malaria Eradication Program (1959–1968)

Successful malaria elimination campaigns in Greece, Italy, Japan, Taiwan, Australia and almost all the Caribbean islands, to name a few, gave hope that malaria could be eradicated. The Global Malaria Eradication Program (GMEP) was launched at the 8th World Health Assembly in 1955. This strategy relied heavily on DDT spraying to interrupt malaria transmission. In response, the Indonesian Government altered its policy from an MCP to a Malaria Eradication Program. In January 1959, the Indonesian Government together with the WHO and USAID established The National Malaria Eradication Services (NMES) or KOPEM (Komando Operasi Pembasmian Malaria) which aimed to eradicate malaria by 1970. The program was launched by President Soekarno in Yogyakarta on 12 November 1959. This date is still celebrated in Indonesia today as National Health Day.

The NMES divided the nation into 66 zones, each with an average population of 1.4 million people. Each zone was further divided into 20–40 sectors. The program consisted of three phases: (1) 1 year of pre-eradication, (2) 3 years of attack and (3) 3 years of surveillance prior to maintenance. After the first year of spraying, the transmission index or infant parasite rate was expected to be zero, indicating that malaria transmission had been stopped (Soemarlan and Gandahusada, 1990). With reinfection no longer an issue, all remaining malaria cases were to be treated and cured. Only a few cases would then remain after 3 years. Any relapses or imported cases were to be detected and cured. DDT spraying operations were conducted twice a year. Over 9000 tons of DDT were used to protect about 65 million people in 42 zones of Java and Bali during the period 1959–1963.

However, insecticide resistance developed among mosquitoes. *A. sundaicus* and *A. aconitus* were found to be resistant to the DDT replacement, dieldrin. The first record of dieldrin resistance in *A. sundaicus* was on the coast near Yogyakarta in 1959. *A. aconitus* was found to be resistant to dieldrin in Subah (Central Java) in the same year (Soerono et al., 1965). Reports of dieldrin-resistance came from South Sumatra and all of Java. It became apparent that dieldrin resistance was spreading in *A. sundaicus* and *A. aconitus*. This hampered the eradication plan.

Moreover, the criterium which had to be met in order to switch from attack phase to consolidation phase was not fulfilled. An API below 0.1 per 1000 of the population was designed as the cut-off between the attack and the consolidation phase. Data cited by Atmosoedjono in Takken et al. showed that the API in Java and Bali was still higher than 0.1 per 1000 of the population between 1963 and 1968 (Takken et al., 1990). Unfortunately, no malaria data was reported between 1959 and 1962. PCD never reached the minimal 10% of annual blood examination rate (ABER) as recommended by the WHO (Ray and Beljaev, 1991). In 1966, the number of malaria cases increased and within 2 years the number was four times as high. The resurgence of malaria cast doubts upon the feasibility of malaria eradication. Technical problems, government policy and financial constraints all imposed limits on the plan for eradication (Soemarlan and Gandahusada, 1990). In the period of violence that followed the attempted coup d'état in 1965, the NMES discontinued all its activities (Takken et al., 1990) and, in 1968, it was integrated into the Directorate General of Communicable Disease Control in Jakarta. This situation weakened the eradication program and, by 1969, the national program switched back to malaria control.

2.3.4. Malaria Control Phase (1969–1999)

The Indonesian MCP followed the guidelines of the global malaria control strategy set forth by the WHO. The strategy included early diagnosis and prompt treatment, selective and sustainable preventive measures, early epidemic detection, containment or prevention of epidemics and the strengthening of local capacities for basic and applied research. For the purposes of applying distinct malaria control strategies, Indonesia was stratified into two broad areas: (1) Java and Bali and (2) the outside islands, representing all those islands which were not Java or Bali. The strategy for case detection in Java and Bali differed from the strategy in the outside islands. In Java and Bali, malaria case detection was carried out by active and PCD, mass fever surveys, contact surveys and migration surveillance. In contrast, in the outside islands, only PCD and malariometric surveys were undertaken.

Malaria control activities in Java and Bali differed from those of the outside islands. In Java and Bali, all provinces were prioritized for malaria control, while in the outer islands, emphasis was placed on provinces in which transmigration projects and economic development projects were taking place, as well as on areas bordering neighbouring countries. Chemoprophylaxis was only recommended for use among visitors or, temporarily, among migrants to the outside islands. Presumptive treatment, radical treatment, mass drug administration and treatment for transmigrants differed between the two areas. For example, during this era of control, primaquine for use as a hypnozoitocide against relapse in *P. vivax* malaria, or as a gametocytocide against transmission was only recommended for Java and Bali and not for the outer islands. In both areas, an outbreak investigation was called for, owing to suspicions that an outbreak was in progress. IRS with DDT continued as the main strategy for vector control. Other interventions such as bed nets, larviciding, biological control and source reduction were applied only in limited areas.

Java and Bali continued DDT spraying but on a much smaller scale. By the mid- to late 1980s, less than 2.3% of houses were covered. From 1986 to 1988, less than 6% of the houses on those islands other than Java and Bali were covered by IRS. The government

stopped using DDT in 1989 and, in 1994, it was banned altogether, largely as a consequence of the US refusing shrimp imports from Indonesia as a result of DDT contamination. From 1979, several alternative insecticides were used for either fogging against adult mosquitoes or for IRS activities. These insecticides included fenitrothion, deltamethrin, bendiocarb, lambda-cyhalothrin and malathion.

Another vector control tool used in Indonesia was larviciding. Larviciding was first conducted in Bali in 1974 using kerosene (Smalt, 1937). It was estimated that, as a result of these operations, 0.7 million people were protected and 70 ha of larval habitat across Bali were treated. During this period, larviciding was conducted in areas where *A. sundaicus* was found; fenitrothion was used at a dosage of 1 cc/50 m^2. Recommended larvicides during this period were Paris green, kerosene, diflubenzuron and temephos.

In terms of source reduction by environmental management, several recommendations were made during this period. In 1981, Kirnowardoyo recommended a number of ways in which affected communities could control *A. aconitus* (Kirnowardoyo, 1981). He suggested that farmers should maintain a flow of water in irrigation ditches, rotate planting cycles in order to prevent large areas from being flooded at the same time, flood paddies every 10 days, alternate between using paddies for rice in the wet season and for other crops in the dry season, release larvivorous fish in flooded rice fields and place domesticated animals near human dwellings in order to discourage mosquitoes from entering dwellings (zooprophylaxis). He made similar recommendations for the protection of communities against exposure to *A. sundaicus*. His suggestions were that the community should always clean fishponds and remove floating vegetation; the community should cover ponds with soil; the cutting away of mangrove forests should be discouraged; if a mangrove forest had been removed, fishponds should be created; the public should release larvivorous fish into ponds; and zooprophylaxis should be deployed (as described above).

Mangrove forests play an important role in Indonesia's malaria control. The Indonesia Ministry of Environment estimated that mangrove forests in Indonesia covered an area of 9.2 million ha in 2000 (Kementerian Lingkungan Hidup, 2007). Only 2.6 million ha of mangrove forest are currently in good condition. These areas are of economic value. Badly managed fishponds in coastal areas provide ideal breeding sites for *A. sundaicus*. This is not merely conjecture; in the past, the loss of mangrove forests has brought on malaria epidemics at Teluk Betung Port (1915; Sudomo, 1994), Batavia (1919; Van Breemen, 1919), Pariaman (1921; Sudomo, 1994), Belawan Port (1922; Schuffner and Hylkema, 1922), Nias (1929; Soesilo, 1929), Tanjung Priok (1939; Sudomo, 1994), Cilacap (1984; Sudomo, 1994) and South Lampung (1992; Sudomo, 1994). Sudomo found that the recultivation of mangrove forests in Flores (East Lesser Sundas) reduced the malaria prevalence from 16% to 4% over a period of 5 years, as well as reducing the density of the vector population (Sudomo, 1987).

The migration of people into heavily endemic areas presents particular challenges for malaria control. Important lessons were learnt and passed on by Baird et al., following several years of work in transmigration villages in northeastern Papua (Baird et al., 1995d). They suggested 10 measures to reduce the risk of epidemic malaria among transmigrants in Papua who originated from non-endemic areas, namely (1) screening all candidate transmigrants for G6PD deficiency and providing supervised primaquine prophylaxis for 3 months; (2) increasing financial and administrative support for public-health officers, in order to allow them access to the resources needed to prevent epidemic malaria, specifically among newcomers; (3) establishing on-site microscopic diagnosis; (4) before the arrival of the newcomers, screening and treating construction teams and indigenous people who will live with them, providing them with G6PD testing and primaquine prophylaxis if needed;

(5) providing effective treatment for slide-proven malaria with careful microscopic follow-up and alternative treatment in resistant cases; (6) providing ITN, curtains and shams; (7) conducting on-site education programs to inform people about mosquito vector bionomics (allowing them to identify breeding sites and feeding behaviour) and to alert them to the importance of early diagnosis and treatment; (8) appointing a local voluntary cadre trained to carry out a number of tasks including encouraging neighbours to seek treatment if they recognize symptoms, spotting and eliminating mosquito breeding sites, understanding mosquito feeding activities and personal protective measures, collecting blood films, and reimpregnating netting and curtains as appropriate; (9) providing reliable motorized transport to evacuate severely sick or injured patients to hospital; and (10) offering an incentive to motivate community participation in malaria control efforts.

Malaria control in Indonesia during the period 1969–1999 faced many constraints. In the highly endemic area of Papua, Gunawan described that the constraints included the lack of coordination between control activities and development projects (especially transmigration and resettlements projects), the difficulties of attracting and retaining experienced and qualified personnel, the lack of supervision, the spontaneous movements of transmigrants from elsewhere in Indonesia and the increase in drug resistance brought on by negative treatment seeking and treatment adherence behaviour (Gunawan and Marwoto, 1991).

In summary, control activities during the period 1969–1999 were centred mainly on Java and Bali, where 60% of Indonesians lived and most economic activity occurred. The burden of malaria on these islands had been substantially reduced since 1945. Malaria control strategies were therefore managed differently for Java and Bali than for all other islands. Eastern Indonesia, in this period, as it still does today, faced many challenges to do with malaria and its control; challenges linked to the sparse population, underdeveloped social and economic systems, fewer educational opportunities and the difficulties that vast distances and poor transportation impose. The aim of malaria control in the next period was to close the gap between western and eastern Indonesia.

2.3.5. Indonesian Roll Back Malaria campaign (RBM; 2000—present)

During this period, two global events affected malaria control policy in Indonesia. The first was the RBM initiative launched by the WHO in 1998. This initiative aimed to spark efforts that would lead to halving the number of malaria deaths by 2010. In Indonesia, on 8 April 2000, the MoH, following the WHO's global RBM campaign, launched an Indonesian version called 'Gebrak Malaria' or, in English, 'Crush Malaria'. This program consists largely of seven steps recommended for control in malaria endemic districts. These steps are (1) producing a map of endemicity and identifying foci of malaria, (2) identifying the feasibility of collaboration between communities and related government sectors, (3) developing strategic plans for malaria control, (4) obtaining support from the District Health Office and Legislative Council, (5) developing an integrated working plan for malaria control, (6) implementing the working plan and (7) monitoring and evaluating the strategy and the progress made. The 'Crush Malaria' program is supported by the following activities: (1) active and passive case finding coupled with periodic mass surveys, including a mass fever survey, a mass blood survey (MBS) and a malariometric survey (all of which require community participation at the designated village malaria post), (2) case management with effective drugs, (3) vector control and (4) surveillance. However, the new era of widespread drug resistance, the broad decline of vector control activities, the severe economic and political upheavals and the fledgling democratic government now seeking to decentralize its authority have all been a serious challenge to malaria control.

The second event which took place was that Indonesia's MoH launched a malaria elimination call on the 28 April 2009 (Departemen Kesehatan, 2009b). Malaria elimination

activities are to be conducted in four stages. These stages include: (Stage 1) The thousand Islands (Jakarta) and Bali and Batam Islands in 2010; (Stage 2) Java, Aceh and Riau Islands in 2015; (Stage 3) Sumatra, West Nusa Tenggara, Kalimantan and Sulawesi in 2020 and (Stage 4) Papua, West Papua, East Nusa Tenggara and Maluku Islands in 2030. To achieve the goal of elimination, the MoH has set targets. The first target is that in 2010 all health service facilities must have the capacity for malaria examination. In other words, all people diagnosed with clinical malaria must be confirmed as malaria cases by microscopy or reliable RDT. The second target is for Indonesia to enter the pre-elimination stage in the year 2020. The third target is for the whole of Indonesia to be free of malaria transmission in 2030.

Following this call for elimination, Indonesia must now start to improve the surveillance system, the malaria outbreak management system and the tools for communication, information and education. The improvement of the capacity for early detection and outbreak management is essential. A robust malaria information system must be established to store, analyse and present information as needed. Indonesia has to establish reliable migration and surveillance systems. The improvement of malaria mapping skills is very important as risk maps can be used to inform operations, to identify ongoing transmission foci or hot spots and to focus elimination efforts (Feachem and Sabot, 2008; Feachem and The Malaria Elimination Group, 2009; Feachem et al., 2009).

2.4. OBSTACLES AND OPPORTUNITIES IN MALARIA CONTROL IN INDONESIA

2.4.1. Malaria case detection

Malaria case detection is a special challenge for an archipelago nation like Indonesia. According to Indonesia's National Malaria Control guidelines (Departemen Kesehatan, 2007a), case detection activities cover active case detection (ACD) and PCD, mass fever surveys, MBSs, malariometric surveys, migration surveillance and contact surveys. ACD is conducted by village malaria workers, health personnel or village malaria cadres. Such teams take blood slides from symptomatic patients visited at home. They give presumptive treatment and send the slide for microscopic examination at a primary health centre. If proven positive, they return to the home and deliver radical treatment. The frequency of such visits depends on endemicity class. In regions with a high (API > five cases per 1000 per annum) or medium case incidence (API ≥ one case per 1000 per annum), biweekly and monthly home visits, respectively, are prescribed by the MoH. In contrast, PCD consists entirely of patients seeking treatment (at hospitals, primary health centres or sub-primary health centres). In some cases, teams may enter communities and aim to collect a blood film from every resident with a fever or complaint of fever: this is called a mass fever survey (MFS). The MoH prescribes MFS in areas where a monthly parasite incidence exceeding three per 1000 people (or an annual rate of 36/1000) has doubled from one month to the next, or in low risk areas following a case in an infant (indicating high likelihood of local transmission). An MBS aims to collect blood films from all residents regardless of symptoms. This provides the most accurate estimate of true prevalence of active malaria in a community. The MoH prescribes MBS in areas of high endemicity or in areas where a malaria outbreak may be in progress. The MoH classifies an MBS aimed at children below 10 years of age as a 'malariometric survey'. The MoH also prescribes migration surveillance for residents of non- or low-endemic areas returning from highly malarious areas of Indonesia. Finally, the MoH prescribes contact surveys in which blood films are taken from at least five households neighbouring a confirmed malaria case. Below, we examine the available literature on these case detection practices in Indonesia.

2.4.1.1. Active case detection—Utarini et al. studied the role and performance of ACD by village malaria workers and PCD by health facilities in Jepara (Central Java) during the years 1994–1998 (Utarini et al., 2007). They found that ACD detected more cases than PCD (ratio 1.4:1), covered a broader geographical area (4.7 vs. 4.1 km; $p < 0.05$) and detected more malaria cases among children (33% vs. 22%; $p < 0.001$). However, they also documented a major problem with ACD: a significant delay between the taking of blood films and diagnosis compared to PCD (2.3 vs. 1.1 days; $p < 0.001$). Village malaria workers typically only transport slides to the health centre twice a week. Moreover, microscopic examination services are usually not available at health centres 7 days a week. Patients with positive slide results were almost always given treatment the next day (mean 1.2 days). In view of these findings, and the diminishing number of village workers available owing to budget difficulties, Utarini et al. recommended that ACD be continued only in highly endemic settings. In other words, PCD worked reasonably well in areas of low to moderate risk, but an investment in village malaria workers would be likely to pay health dividends in areas of high endemicity. Ompusunggu et al. noted that a failure to provide compensation to village malaria workers diminished case detection coverage (Ompusunggu et al., 2005). During their study in Purworejo (Central Java), village malaria workers were given Rp. 150,000/month (US$ 16/month) from the government as well as additional incentives for each malaria survey. This incentive scheme significantly increased the amount of slide taken from 37% (47/128) in the previous year to 84% (212/254) in the study period ($p < 0.001$). In other words, the ratio of malaria slides collected by ACD and PCD increased from 1:2 to 5:1. However, the proportion of slides collected by ACD dropped significantly to 54% (37/68) in the second year ($p < 0.001$). The reason for this reduction was that neither were malaria surveys conducted during this period nor was any additional fee provided.

In an attempt to cope with a chronic shortage of village malaria workers, community participation schemes have been explored in Indonesia. Ompusunggu et al. evaluated a scheme called Ten Houses Grouping (Dasa Wisma) in Purworejo (Central Java; Ompusunggu et al., 2005). Each group of 10 houses elected a leader to report suspected malaria cases to the community malaria cadre (who each represented four groups of 10 households). The community malaria cadres were elected by group leaders. The malaria cadre was usually a local housewife who received video training from investigators aimed at increasing their knowledge of malaria. Topics of training included the clinical diagnosis of malaria, malaria blood slide creation, slide transfer, presumptive treatment and reporting flow. Cadres in the Purworejo study usually dispatched blood films within 24 h of collection. They got paid Rp. 1000 (US$ 0.1) per malaria positive slide submitted by malaria patients. The government paid the transportation cost. After 1 year, it was found that the Dasa Wisma scheme resulted in the collection of significantly more slides (24%; 538/2225) than the village malaria worker scheme (19%; 212/1124; $p < 0.001$). They also found that more cases were detected using Dasa Wisma (33%; 177/538) than the number of cases detected by village workers (9%; 19/212; $p < 0.001$). Assessment after 2 years showed that Dasa Wisma continued to perform better (13%; 297/2225) than the village malaria worker scheme (3%; 37/1124; $p < 0.001$). However, the number of cases detected by each scheme did not differ to a great extent (23%; 67/297 vs. 16%; 6/37, respectively, $p = 0.379$). Moreover, a significant reduction in slide collection in both schemes after 2 years ($p < 0.001$) was observed. The number of slides collected by village malaria workers was substantially lower than the number collected as part of Dasa Wisma once the incentives were stopped. Ompusunggu et al. suggested that health personnel should provide continuous support to malaria cadres.

Some studies emphasize the importance of community participation in bringing about successful malaria case detection. A scheme involving such community participation was evaluated by Pribadi et al. in the hyperendemic province of Riau in Sumatra (Pribadi et al.,

1986). A program of weekly chemoprophylaxis was instigated, with chloroquine being administered to about 700 residents by nine cadres. Assessment after 1 year showed that almost every household member (94%) had taken the drug regularly. A small percentage (6%) refused the drug or agreed on an irregular basis. The parasite rate dropped from 54% to 13% and spleen index reduced from 22% to 5%. Also at Riau (Sumatra), Santoso et al. evaluated a 'malaria task force' scheme established to help with malaria case detection and control (Santoso et al., 1991). The malaria task force consisted of volunteer school teachers and community leaders. They received training in the use of malaria medications and were, at least ostensibly, supervised by the physician at the nearest primary health centre. Each member of the task force monitored 20 households.

Some studies point to the importance of promoting such schemes for case detection. Sekartuti studied the work of and the attitude towards 22 village malaria workers (Petugas Penemu Penderita Malaria) selected from their local community in South Lampung in 2003 (Sekartuti, 2003). Before training, their understanding of malaria was evaluated and found to be poor. For example, most of them did not realize that malaria parasites occur in human blood. Practically none of them (1/22) had door or window screens at home and most (15/22) did not use mosquito netting. Among those patients who had heard of village malaria workers, most (86/103) consented to the worker taking a blood film. Those who refused often cited a lack of confidence in the skill and knowledge of the worker as the reason. Nonetheless, 96% (202/210) of respondents supported the idea of using these village workers and most (193/210) hoped the program would continue. In East Kalimantan, the acceptance of cadres also seemed to hinge upon the perception of their skill by the community (Sukowati et al., 2000).

2.4.1.2. Passive case detection—Primary health centres outside Java and Bali rely almost entirely upon PCD as the primary means of case finding (Departemen Kesehatan, 2007a). Therefore, improving PCD represents an important goal in supporting malaria control in those relatively high endemic settings. Sekartuti et al. reported the efforts aimed at improving PCD, that is, improving treatment seeking behaviour among residents, in Banjarnegara (Central Java). They used slide shows for school children and patients (Sekartuti et al., 2004b). Shinta et al., in turn, noted the important role played by community leaders in Purworejo (Central Java; Shinta and Sukowati, 2005). Improving the effectiveness of PCD provides additional benefits such as improving microscopy, competency, and community awareness (Sekartuti, 2000).

Hunt et al. evaluated the use of 24 school health units (Usaha Kesehatan Sekolah, UKS) for malaria case detection in three districts (Banjarnegara, Purworejo and Jepara) in Central Java in 1991 (Hunt et al., 1991). All UKS teachers received training from the Ministry of Education and Culture in collaboration with the local primary health centre at the district level. The training materials included malaria knowledge, detection, treatment and prevention. UKS teachers had the responsibility to make malaria slides and give presumptive treatment among students with malaria symptoms, to send slides to primary health centre, and if positive, the health centre staff would give radical treatment. Hunt et al. noted the advantages and constraints involving UKS in PCD. The advantages were (1) an intensive detection of high-risk fever cases among the school students and (2) the teachers as malaria health educators. In contrast, the constraints were the availability of logistic, limited time to send slides to primary health centre, slide taking supervision and teacher turnover. However, Hunt et al. observed that less than 10% of UKS were taking malaria slide smears. Schools had no more supply of blood slides and the lancets. They referred students with malaria symptoms to primary health centre or inform malaria cadre to take malaria smear at schools. In order to intensify the role of schools, training, supplies and supervision are encouraged.

Accurate clinical diagnoses are necessary to determine the local specific malaria symptoms. Health officers may then design a health message for the community that stresses how clinical malaria typically occurs in that community. Resource limitations, as in most human endeavours, may restrict the practicality of applied research activities like these (Sekartuti et al., 2004c). Health officers must convince funding agencies of the practical importance of such work in the face of their continuing reliance upon the clinical diagnosis of malaria as a consequence of the shortages in both competent malaria microscopists and supplies of RDTs.

2.4.1.3. Migration surveillance—The mobility of people among Indonesia's thousands of islands seriously challenges malaria control. This may become particularly important as Indonesia strives to eliminate endemic malaria from Java and Bali by 2015. Transmigration in Indonesia, that is, the movement of people within Indonesia's borders, typically sees people move from densely populated Java and Bali to the sparsely populated and usually highly endemic outer Islands. These migrants routinely return to Java and Bali, either permanently or, more often, for family reunions and holidays. In addition, the armed forces of Indonesia (Tentara Negara Indonesia, or TNI) and the national police force (Polisi Republic of Indonesia, or POLRI) must supplement local forces with those from Java and Bali when conducting routine security operations in the islands outside of Java and Bali. These civilian and military migrations, reaching tens of thousands each year, represent a significant threat of renewed or scaled up malaria transmission on Java and Bali.

Transmigration as a government-operated enterprise in Indonesia was launched under Dutch administration in 1905 (Hardjono, 1982). The Republic of Indonesia continued the practice after gaining independence in 1945. However, the practice was abruptly halted after the fall of the Suharto regime in 1998 (Hardjono, 1982). Officially, transmigration policies and practices pursued economic development in remote areas, and strove to offer economic opportunities to a landless peasant class. A more cynical view, however, classified the program as a forced migration that expanded and cemented Java's social and political sphere of influence across a highly diverse and sometime divisive republic. In either case, transmigration helped shape the malaria problem in Indonesia in important ways. Moreover, these migrations continue in earnest up to the current day, only now without formal government ownership of the movement. People elect to migrate to the outside islands, either to set up their own enterprises or to go directly to a large development project. Regardless of the reasons for the movement, the impact of transmigration on malaria and vice versa is an important consideration in the context of control.

Simanjuntak, in 1999, stated that all transmigrant locations in 21 provinces had malaria and that the average number of clinical malaria cases per year ranged from 33 to 69 per 1000 of the population (Simanjuntak, 1999). In 1998, the highest numbers were reported from Papua (274/1000), East Nusa Tenggara (120/1000) and West Nusa Tenggara (95/1000). Simanjuntak claimed that two outbreaks of malaria typically occurred each year in such locations, with usual CFR of 6%. He documented the delay in insecticide spraying in the homes of newly arrived migrants, the lack of antimalarial drugs and the delayed arrival of medical personnel. Simanjuntak also implicated apparently poor site selection criteria for the establishment of such settlements, and the apparent ease with which mosquitoes gained access to people, owing to poor construction. Abisudjak et al. criticized the responsible government institutions, citing essentially similar problems (Abisudjak and Kotanegara, 1989). These authors described land usually occupied by transmigrants as having been primary forests (52%), secondary forests (13%), bushes (21%), swampy forests (5%) and plantations (7%).

Baird et al. evaluated records of emergency evacuation (1997–2000) to hospital with a diagnosis of severe malaria from a transmigration village in northeastern Papua (Arso XIV; Baird et al., 2003a). Residents of Arso XIV came predominantly from Java (83% of residents), where the risk of malaria has been less than 1 infection/10,000 person-years for most areas since the mid-1960s. Exposure to biting anophelines occurred in and around homes between dusk and dawn. Attack rates for malaria in the Arso region have typically ranged between 0.5 and 4 infections/person-year. They found that the overall incidence of evacuation was 7.5/100 person-years. In all, 142 adults and 53 children were evacuated over the 30-month period. The 30-month risk of evacuation in adults relative to children was 2.8 (95% CI = 2.0–3.9; $p < 0.001$). RR for adults was greatest during the first 6 months (RR > 16; 95% CI 2.0–129; $p < 0.001$), and diminished during the second 6 months (RR = 9.4; 95% CI 2.7–32.8; $p < 0.001$) and the third 6 months (RR = 3.7; 95% CI 1.7–7.9; $p < 0.001$). During the next two 6-month intervals, the RR for adults was 1.6 and 1.5 (95% CI range: 0.8–2.6; $p < 0.18$). The authors considered that age-related differences in the immune systems of children and adults are the most likely explanation for the apparent susceptibility of adults to onset of severe disease caused by primary exposure to *P. falciparum*.

At a former primary forest site which had become a palm oil plantation at Arso (Papua), Baird et al. documented what amounted to epidemics of malaria within 3 months of arrival of new migrants (Baird et al., 1995d). Malaria blood survey of those sites showed 30–70% prevalence of parasitemia with virtually universal symptomatic malaria. Even several years after settlement, the incidence of malaria at Arso ranged from two to five infections per person per year (Jones et al., 1994), but symptomatic malaria had sharply waned, especially among adults. Entomological surveys at Arso showed that, on average, 15 anophelines would feed on each person every night, and that 1% of these mosquitoes carried sporozoites (Baird et al., 1995d). The average migrant at Arso in the late 1980s was exposed to sporozoites once a week, which developed into full-blown malaria five times a year, assuming a 10% efficiency of infection with sporozoite inoculation (Pull and Grab, 1974). This estimate agreed with the measurements of force of infection (Jones et al., 1994).

Baird et al. observed that nurses in transmigration villages at that time relied almost entirely upon a clinical diagnosis of malaria (Baird et al., 1995d). Therefore, asymptomatic carriers went undetected and fuelled the conditions for an epidemic. Baird et al. concluded that new transmigrants brought to highly malarious areas merited additional resources not usually prescribed for all new settlements. Such targeting, they reasoned, would improve the likelihood of social and economic success of settlement. In terms of case detection, the authors suggested that on-site microscopic diagnostic capabilities (RDTs did not exist at that time) should be established to permit monthly MBS among residents, as should the aggressive elimination of asymptomatic gametocytemia for a period of at least 6 months following the arrival of newcomers.

Krisin et al. documented the patterns of disease experienced by groups of Javanese transmigrants at Armopa (Papua) from the time of first settlement in September 1996 until 1999 (Krisin et al., 2002). During the 34 months of their continuous observation, the health clinic they had established received over 22,000 visits (an average of 700 visits per month) from both indigenous Papuan people and the Javanese transmigrants. They found 3631 new cases of malaria in the Javanese transmigrants. In other words, ~20% of visits included a microscopically confirmed diagnosis of malaria. In the same area, Barcus et al. documented an incidence of malaria ranging from 1.1 to 1.5 infections/person-year (Barcus et al., 2003). The mean time to first parasitemia was 185 days (range: 11–856 days) for *P. falciparum* and 190 days (range: 14–901 days) for *P. vivax*. Unlike other new transmigration villages in that region, however, the presence of the research team and the clinic and services it offered

resulted in the almost complete lack of attacks of severe and life-threatening malaria (Krisin et al., 2003).

Migrations within Indonesia certainly bring cases of malaria from high to low endemic areas. Several studies have reported high rates of those malaria cases classified as imported. Baird et al. reported that 3–72% of malaria cases were imported into West Java, Central Java and East Java between 1985 and 1987 (Baird et al., 1993). Dakung et al. evaluated 3506 fever patients in Jakarta who were seen between 1964 and 1980, and found that 357 (10%) had malaria (Dakung and Pribadi, 1980). The ratio of *P. vivax* to *P. falciparum* to mixed infection was 2:1:0.1. Most cases (82%) were known to be imported into Jakarta from Sumatra, West Java, East Timor and Papua. More recently, Lederman et al. evaluated 240 civilian and military patients diagnosed with malaria in Jakarta hospitals (Lederman et al., 2006b). The majority of civilians contracted malaria during recent travel to Papua and South Sumatra (Bangka Island and Lampung), whereas military patients contracted malaria in Aceh (north Sumatra). Less than 1 week of travel is much more common in civilian travellers (5/26) than in military travellers (1/58), who almost always stay for longer periods of duty. The number of people coming from sites in the outer islands to Java or Bali, whatever the reason or duration, reaches millions annually and the risk of malaria associated with these human migrations (or travel) must be considered an obstacle to control.

The economic importance of tourist destinations in endemic settings merits special attention as far as control is concerned. Ompusunggu et al. evaluated the magnitude of malaria endemicity at 11 tourism beaches in three districts in West Java (Ompusunggu et al., 2002). They found a slide positivity rate (SPR) of 0.4% (11/3106). They considered this to be evidence of local transmission and believed it was necessary to call for stepped-up control measures. Kurniawan interviewed 22 tourists who were diagnosed with malaria after returning from work or vacation visits to Ujung Kulon (West Java), Purworejo (Central Java) or Papua (Kurniawan, 2003). Although the majority of respondents (61%) knew of the risk of malaria, none had used malaria prophylaxis. Approximately 25% used mosquito repellent as a precaution against malaria. Those patients suggested that communications media such as brochures and posters displayed in tourist areas would help elevate awareness of the risk. Such measures, however, rarely prove practical or acceptable in the tourism industry. Travellers in Indonesia, or the health professionals advising them, should be aware of the high-risk areas and prescribe appropriate awareness, personal protection measures or chemoprophylaxis to those venturing to such sites.

2.4.2. Malaria diagnostics

A reliable diagnosis of malaria lies at the core of successful control. This is true whether the patient is resident in an endemic setting, or has returned to a non-endemic area as a tourist, businessman or soldier. The National MCP of Indonesia lists three diagnostic tools for routine use: clinical diagnosis, microscopic diagnosis and RDTs (Departemen Kesehatan, 2007a).

2.4.2.1. Clinical diagnostic—The clinical diagnosis of malaria depends almost entirely upon the instincts of the provider. Tjitra et al. studied 560 symptomatic adults and children attending the primary health centre in West Sumba (Lesser Sundas) in 1998 (Tjitra et al., 1999). A diagnosis of clinical malaria was based on fever or history of fever in the last 48 h and no other evident cause of fever. It was revealed that 294 (53%) of the patients had parasitemia (with or without sexual forms) when diagnosed by microscopy. The typical symptoms of malaria (fever, chills, headache, nausea, vomiting, muscle aches, malaise, etc.) are notoriously non-specific, and may easily be confused with a number of endemic viral or bacterial infections in Indonesia. Even if the provider happens to be extraordinarily good at

identifying malaria, the clinical diagnosis comes with a very important pitfall: guidelines call for treating clinically diagnosed patients with chloroquine or sulfadoxine/pyrimethamine rather than artemisinin combined therapy (ACT). The MoH apparently wishes to conserve ACTs for patients confirmed to actually have malaria. The problem for the patient who actually does have malaria is a high probability of failed therapy.

The problem linked to clinical diagnosis has been acknowledged and in their plans for malaria elimination, Indonesian health authorities call for all primary health centres to confirm malaria using microscopy (Departemen Kesehatan, 2009b). The Indonesian NIHRD (Sekartuti et al., 2004c), funded by the Global Fund, investigated the malaria baseline data at six highly malarious districts in Eastern Indonesia, namely Biak Numfor (Papua), Sorong (Papua), Ambon (Maluku), Ternate (Maluku Utara), Kupang (East Lesser Sundas) and West Sumba (East Lesser Sundas) in 2004. They revealed that primary health centres rarely recorded the many clinical diagnoses of malaria that were made. Diagnoses supported by microscopy or RDT were infrequently available. The studies showed that only 16% (43,054/267,747) of malaria patients were examined by microscopy between 2001 and 2003 (Sekartuti et al., 2004c). In other words, 84% of malaria patients were diagnosed clinically. Another estimate shows similar results. In 2006, the WHO estimated that there were 9.3 million fever cases in Indonesia (World Health Organization, 2008e). The World Malaria Report of 2008 reported that 1,246,324 microscopic or RDT diagnoses had been made in Indonesia throughout 2006 (World Health Organization, 2008e). In other words, only 13% of fever cases were diagnosed with a microscopic or RDT confirmation, and 87% of malaria patients were diagnosed clinically and presumably treated with CQ or SP. Until the availability of diagnostic services is substantially expanded, the standard treatment for malaria in Indonesia will continue to be CQ or SP.

2.4.2.2. Microscopic diagnostic—Many workers consider the microscopic examination of Giemsa-stained thick and thin blood films (Wongsrichanalai et al., 2007) to be the most suitable diagnostic instrument for malaria control. Not only can it differentiate between species (as many RDTs can do), but it can also provide detailed information about stages present and their counts per unit volume of blood (which no RDT can do). However, malaria microscopy requires highly specialized equipment and persistently applied technical training and certification of competency. Poor malaria microscopy is probably more harmful to the patient and malaria control than are good clinical diagnoses. In Indonesia, no peer-reviewed publication has yet revealed the number of health centres that have the diagnostic capacity for malaria microscopy, or the required level of proficiency among the microscopists performing the tests. A research report from the NHIRD showed that 65% of the health centres in six districts in eastern Indonesia had microscopes (Sekartuti et al., 2004c).

Other studies have evaluated the performance of malaria diagnostic services at primary health centres and at district level hospitals and clinics. In Donggala (Central Sulawesi), Chadijah et al. evaluated the performance of microscopic diagnosis in 2005 (Chadijah et al., 2006). They used 566 malaria test slides. They found that the mean sensitivity in primary health centres was lower than it was in district level hospitals (42% vs. 86%). In other words, false negatives were more frequent in primary health centres than they were in district level hospitals (58% vs. 14%). Moreover, the mean specificity in primary health centres was lower than it was in district level hospitals (84% vs. 96%). Conversely, false positives were more frequent in primary health centres than in district level hospitals (16% vs. 4%). Tjokrosonto et al. evaluated the accuracy of malaria diagnoses in Banjarnegara (Central Java) in 1990 (Tjokrosonto, 1994). They reported the lack of agreement between diagnoses made at primary health centre level, district level and national level. Using 335 test slides, the proportion of false positives was 37% at primary health centres and 29% at district level hospitals. The proportion of false negatives was 14% and 9% at primary health

centres and at district level hospitals, respectively. For *P. falciparum* identification, the mean false positive and false negative rates at primary level and district level were about 37% and 20%, respectively. For *P. vivax* identification, the mean false positive and false negative rates at those levels were about 54% and 9%, respectively. The high rates of error both at the health centres and district health offices should be investigated and remedied.

Multiple factors contribute to the poor performance of microscopy diagnosis in Indonesia. Foremost among the many likely factors will be the low compliance to minimal laboratory standards, poor quality of slide preparation, inadequate or obsolete microscopes, lack of supply stocks, heavy workload and inadequate quality assurance. At Lampung (southern Sumatra), Sekartuti put the low quality of microscopic diagnosis at primary health centres down to the multiple use of slides, the low volume of blood taken for examination and the inability to count parasite density (Sekartuti, 2003). Ompusunggu et al. reported similar problems in West Sumba (Lesser Sundas; Ompusunggu et al., 2006). They also observed the repeated use of glass slides (due to the scarcity of this resource) and the poor quality of slide preparation. Kismed conducted a qualitative study in 10 healthcare centres in Sambas (West Kalimantan) involving 41 laboratory workers, paramedics and heads of clinics (Kismed, 2001). They concluded that a lack of human resources resulted in the poor preparation of blood slides by the health officers. Reporting also suffered. The absence of a system for cross-checking, together with minimal or even no feedback from supervisors, also contributed to the poor performance of microscopic examination as a diagnostic tool (World Health Organization, 2009b).

2.4.2.3. Rapid diagnostic test—The past decade has seen the emergence of immunochromatographic technology which allows for a simple, one-step device for the diagnosis of malaria. Several dozen commercial brands are now available, collectively referred to as RDTs (Wongsrichanalai et al., 2007; World Health Organization, 2006d), and all employing antigen capture by monoclonal antibodies. Like the extremely simple take-home pregnancy test kits, the malaria RDT produces a coloured line within 5–20 min. Some, but not all, RDT products offer great promise in extending reliable diagnosis to areas where traditional microscopy may be difficult to establish or maintain (World Health Organization, 2003e). The WHO has recently published a systematic evaluation of the performance of 41 commercially available RDTs from 21 manufacturers (World Health Organization, 2008c). Of the 41 products, 16 detect *P. falciparum* alone, 22 detect and differentiate *P. falciparum* from *non-P. falciparum* malaria, and three detect both *non-falciparum* and *P. falciparum* malaria without distinguishing between them. RDTs were evaluated against (1) a panel of parasite-positive, parasite-negative cryo-preserved blood samples and a panel of parasite-negative samples, (2) thermal stability and (3) ease-of-use descriptions. This evaluation provided a standardized laboratory-based evaluation of RDT performance. The study showed that several RDTs are available which consistently detect malaria at low parasite densities (200 parasites/μl), have low false positive rates, are stable at tropical temperatures, are relatively easy to use and can detect *P. falciparum* or *P. vivax* infections, or both. Performance between products varied widely at low parasite densities (200 parasites/μl), however, most products showed a high level of detection at 2000 or 5000 parasites/μl.

In Indonesia, in 1995, several studies were carried out evaluating the performance of RDTs. Fryauff et al. tested the sensitivity of the ParaSight *F* test (*F* test) in detecting *P. falciparum* infections among malaria-immune (410 native Papuan) and non-immune (369 new transmigrants) populations in Arso PIR V, Armopa SP-1, Oksibil and Tarontha, all hyperendemic areas in Papua (Fryauff et al., 1997d). They found highly significant differences between populations in terms of the sensitivity of the test (Papuan, 60% vs. transmigrants, 84%; $p < 0.001$), and in terms of its specificity (Papuan, 97% vs. transmigrants, 84%; $p < 0.001$). For the Papuan, levels of sensitivity of the test were higher

in the ≤10 year age group than in the >10 year age group (70% vs. 40%). For transmigrants, the test had high levels of sensitivity in both age groups (81–85%). The test had high levels of specificity for both age groups in the Papuan population (96–98%). For the transmigrants, the specificity levels of the test were higher in the ≤10 year age group than in the >10 year age group (94% vs. 79%). Fryauff et al. suggested that the significant difference in the sensitivity and specificity of the *F* test was related to the age-dependent immune status of the populations being tested. Sensitivity was lower in the older generations of the Papuan population who had had life-long exposure to *P. falciparum* malaria and had therefore developed clinical immunity.

Fryauff et al. evaluated the performance of OptiMAL in Armopa (Papua) in 1997 (Fryauff et al., 2000). Measures of sensitivity were derived by applying the OptiMAL test for the detection and differentiation of light, asymptomatic *P. falciparum* and *P. vivax* infections. They found that concordance between OptiMAL and microscopy was 81% and 78% by two independent readings. The sensitivity of the tests to any malaria species was 60% and 70% in two separate readings and its specificity was 97% and 89% in two readings. Most cases identified by microscopy as *P. falciparum* were graded as negative or non-*falciparum* by both OptiMAL readings. OptiMAL false negatives and misidentifications were seen to be related to low parasitemias (<500/μl). The OptiMAL assay demonstrated 88–92% sensitivity to infections of 500–1000 parasites/μl. Fryauff et al. concluded that this device should not be approved for diagnostic use but could be made commercially available for research purposes only. It was markedly less sensitive than expert microscopy in terms of discriminating between different malaria species.

Tjitra et al. evaluated the new, combined *P. falciparum* and *P. vivax* immunochromatographic test (ICT Malaria *P.f/P.v.*) in Sumba (Lesser Sundas) in 1998 (Tjitra et al., 1999). With 560 symptomatic adults and children, they found that the ICT Malaria *P.f./P.v.* was sensitive (96%) and specific (89%) in the diagnosis of *P. falciparum* malaria. The specificity for the diagnosis of *P. vivax* malaria was 95%. However, the sensitivity levels (75%) were relatively low. The sensitivity to *P. vivax* malaria was 96% with parasitemias of >500/microlitre but only 29% with parasitemias of <500/microlitre. Nevertheless, compared with the test using HRP2 alone, use of the combined antigen detection test would reduce the rate of undertreatment from 15% to 4% for microscopy-positive patients. This would be at the expense of only a modest increase in the rate of overtreatment of microscopy-negative patients from 7% to 15%. Tjitra et al. concluded, however, that the cost remained a major obstacle to the widespread use of ICT Malaria *P.f./P.v.* in areas of endemicity.

Arum et al. compared the performance of the ICT method with that of microscopic diagnoses in East Lombok (Lesser Sundas) in 2005 (Arum et al., 2006). From 604 samples, they showed that the ICT revealed 100% sensitivity, 97% specificity, 83.2% positive predictive value and 100% negative predictive value. Therefore, Arum et al. concluded that the malaria ICT was reliable enough to be used as a malaria test.

Ginting et al. conducted the performance of the Parascreen Pan/*Pf* test with that of microscopic diagnoses in Mandailing Natal (North Sumatra) in 2006 (Ginting et al., 2008). The Parascreen test was considered positive *P. falciparum* malaria when the specific histidine-rich protein-2 (HRP-2) line was visible. Testing 104 symptomatic adults and children, they found that the Parascreen was moderately sensitive (76%) and highly specific (100%) in diagnosing *P. falciparum* malaria. The sensitivity increased in higher parasitemia. The sensitivity test was 81% for parasitemia of 100–200/μl, 87% for 200–400 parasites/μl and 100% for more than 400 parasites/μl). However, the test had a very low sensitivity for parasitemia less than 100/μl (0%).

Several studies have evaluated RDTs in the context of malaria control strategies. Utami et al. investigated the application of RDT by village malaria cadres in Purworejo (Central Java) in 2005–2006 (Utami, 2004; Utami et al., 2008). The cadres involved, each one responsible for 40 households, had been trained to identify clinical malaria signs and symptoms and make blood films. The cadres were then also trained to use RDTs. Case finding was reported to the primary health centre where parasitological confirmation of a positive test outcome would be performed. Over 12 months, the cadres identified 119 RDT-positive cases of malaria. High specificity levels were found for *P. falciparum* (98%) and *P. vivax* (100%). However, they found that the sensitivity of immunochromatographic tests (60% for *P. falciparum* and 57% for *P. vivax*) was low when compared to microscopic diagnosis.

2.4.2.4. Improving malaria diagnostic accuracy—Improving diagnostic accuracy is a technical, financial and human investment. Chadijah et al. suggested several technical solutions, such as repeated microscopy diagnostic training, standardized examinations, the introduction of a microscopist certification, regular supervision and cross-checking and the updating of equipment (Chadijah et al., 2006). Sekartuti suggested further ways of improving the quality of microscopic examinations: the glass slides must be clean, with proper staining, and sufficient time must be allocated for slide reading (Sekartuti, 2003). Correct microscopy requires persistence, experience and dedication by the microscopists and the systems supporting them (Chadijah et al., 2006).

The establishment of a quality assurance system requires standardized operating procedures, along with materials and training modules for improving or demonstrating the competence of microscopists. Maguire et al. developed a standardized method for producing large numbers of consistently high-quality malaria slides (Maguire et al., 2006b). They built up a repository of stained blood films to use as support for training and competency assessments. Whole blood was collected by venipuncture from *Plasmodium*-positive donors in Indonesia and Cambodia, and, importantly, individuals with no history of risk of exposure to malaria (newly arrived expatriates in those countries). Technicians systematically prepared hundreds of Giemsa-stained thick and thin smears from each donor. After obtaining a provisional microscopic diagnosis, one slide from each of the first 35 donors was distributed to 28 individuals acknowledged by reputation as experts in the microscopic diagnosis of malaria. These reference readers recorded the presence or absence of *Plasmodium* species, the life-cycle stages and the parasite density. The results given by the reference readers were compiled, in order to (1) identify unqualified microscopists with consistently incompatible results relative to other readers and (2) derive a composite diagnosis based on the combined analyses of all the reference readers and on the PCR analysis. The composite diagnosis was then accepted as the true diagnosis. Three tiers of diagnostic proficiency were established and the level of proficiency of each microscopist was established by assigning demerit points based on the types of errors made. A false positive was considered a more serious error (10 demerits) than a false negative (five demerits). The accuracy of diagnosis by species was taken into account (mixed infections, three demerits). The accuracy of the parasite count was also considered, individual accuracy being ascertained by accepting the median count among qualified readers as the best estimate of the true count (one demerit given when parasite density was outside the 99% confidence interval). When all results had been analysed, Maguire et al. excluded four readers with demerit points greater than one standard deviation above the mean. A composite diagnosis and parasite density were then derived based on the remaining 24 readers. In comparison to the composite diagnoses, reference readers correctly identified the presence of parasites 85% of the time when parasite densities were <100 parasites/μl. The percentage of correct primary diagnoses improved at higher densities: 99% for densities between 100 and 350/μl and 100% for densities >350/μl. Reference readers correctly identified 96% of true negative slides. They

correctly identified *P. falciparum*, *P. vivax* and *P. malariae* mono-infections 99%, 86% and 50% of the time, respectively.

2.4.3. Malaria treatment

2.4.3.1. Access to treatment centres—Most Indonesians have difficulty accessing adequate health services and this problem comes to bear directly upon the treatment of malaria. The Basic Health Survey (BHS) in 2007 involved 258,366 households sampled from over 90% of all districts/cities in the archipelago (National Institute of Health Research and Development, 2008). This survey evaluated access to health service facilities and community-based health efforts (Upaya Kesehatan Berbasis Masyarakat, UKBM). Health service facilities consisted of hospitals, primary health centres, practiced physicians and nurses. UKBMs consisted of integrated service facilities (Pos Pelayanan Terpadu), village health services (Pos Kesehatan Desa), village medicine shops (Pos Obat Desa) and village midwifery services (Pos Bersalin Desa).

Accessibility to health facilities was measured by the BHS in terms of distance from the facility (National Institute of Health Research and Development, 2008). Table 2.11 shows the accessibility to health facilities by region throughout the Indonesian archipelago. Forty-eight percent of those households sampled were located within 1 km of health services (western: 49% vs. eastern: 46%). Another 46% were located between 1 and 5 km from the services (western: 47% vs. eastern: 46%). Accessibility varied widely among provinces, for example, the percentage of households within 1 km from a health facility ranged from 27% to 73% (National Institute of Health Research and Development, 2008). About two-thirds of households were within 15 min of a health facility (western: 71% vs. eastern: 56%) and most of the remainder were between 15 and 30 min (western: 22% vs. eastern: 27%). Only 9% of households reported needing over 30 min to reach the closest health facility (western: 7% vs. eastern: 13%).

UKBM, as would be expected of community-based health efforts, showed patterns of easier access when compared to health facilities. Table 2.11 shows the accessibility to community-based health efforts by region throughout the Indonesian archipelago. Seventy-nine percent of those households sampled were located within a kilometre of UKBM (western: 80% vs. eastern: 76%). Eighty-five percent of households were within 15 min of a UKBM (western: 88% vs. eastern: 81%). Seventy-nine percent of households were within a kilometre of a UKBM, compared to just 48% which were within a kilometre of a health centre. This is an important distinction with respect to the access to antimalarials and information about malaria. Focusing malaria education and treatment resources through UKBMs may thus be appropriate.

The village drug post, a source of common anti-infectives including those used to treat malaria, is manned by a volunteer with limited training. About 90% of respondents in the BHS reported not using this service, overwhelmingly (95%) as a consequence of there being no such post in their village (National Institute of Health Research and Development, 2008). The effectiveness of the village drug post in providing easier access to antimalarials cannot be adequately assessed until more such posts are established.

2.4.3.2. Treatment seeking behaviours—People exhibit distinct behaviour in seeking treatment for malaria or a malaria-like illness. Such behaviour is certainly influenced by the accessibility to care, but many other factors such as risk, experience, economics and culture also come into play. Actions taken by the community were classified as follows: no action, self-treatment (using both modern and traditional medicines) and consultation (going to a traditional healer, malaria worker, midwife, paramedic, doctor, health centre or hospital; Utarini et al., 2003).

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Sanjana et al. assessed malaria knowledge, attitudes and practices in communities experiencing epidemic malaria in Purworejo (Central Java) in 2001 (Sanjana et al., 2006). They surveyed 1000 randomly selected households in 50 villages. The sample was restricted to the nine sub-districts in Purworejo which presented the greatest transmission risk according to the malaria surveillance statistics of the reporting year 2000. All were in the Menoreh Hills or the foothills of the Dieng Plateau. Four local residents received training on how to collect answers using the survey consisting of 93 questions. Training focussed on interview conduct and highlighted the necessity of strict adherence to the sampling protocol and of obtaining informed consent. They requested an interview with the head of the household, but any resident over the age of 15 could serve as an interview subject. A specific protocol provided the interviewers with a guide to the random sampling of households within villages. Trained interviewers began by visiting the household of the head of the village. They then walked ~100 m from that house in opposite directions along set compass headings. The house closest to that point was then sampled. They repeated this sampling protocol, moving along their respective assigned compass headings until completing 10 households each per village. Of the 409 households reporting malaria illness in the year prior to the survey, 211 (52%) respondents had treated the last malaria illness in the family with medicine without going to a health facility. These patients obtained medication primarily from local drug vendors (64%) and community health workers (25%). Three hundred and fifty-eight (88%) of the 409 households also sought advice or treatment outside the home (multiple responses possible). The main sources consulted were health centres (28%) and private healthcare providers (22%). The median time required to reach the place of consultation was 15 min (range: 0–240 min). The modes of transport employed to reach the source of treatment were as follows: on foot (51%), by motorcycle (23%), by local village transport van (16%) and by bicycle (7%). The median cost of treatment reported by those who self-treated and by those who sought treatment outside the home was Rp. 6000 (US$ 0.6) and Rp. 7250 (US$ 0.7), respectively.

Karyana et al. also conducted a cluster randomized survey of malaria treatment seeking practices in Timika in 2007 (Karyana et al., 2007). They reported that 26% (302/1177) of the people surveyed did not seek treatment when they had febrile illness as they did not feel unwell enough (62%, 198/302). Of those people with febrile illness who did seek treatment, 10% treated themselves at home. Forty percent went to a public or malaria control clinic, 27% went to a pharmacy or drug store and 23% went to a private clinic. As far as seeking treatment outside the home is concerned, there was a significant difference between Papuans and non-Papuans (57% vs. 78%; $p < 0.05$). In other words, indigenous Papuans were less likely than immigrants to use health facilities as their source of malaria treatment.

The Indonesian Health Household Survey (HHS) was implemented in 2004, by the Indonesian NIHRD and the Indonesian Centre of Statistics (Soemantri et al., 2005). The survey selected 9082 households and 41,764 respondents were interviewed across all provinces (Pradono et al., 2005a). Of these, 3947 respondents were under 5 years of age. Mothers were questioned about treatment seeking behaviour when their children had malaria. The study revealed that 4% of respondents had experienced malaria fever in the last year. Among them, 21% took no action, 31% self-treated and 48% obtained medication from health facilities. The main reasons for not seeking treatment at health facilities were that respondents did not consider malaria to be a threatening illness (67%), did not have sufficient funds for care (37%), did not have sufficient funds for transportation (23%) or had no transportation available at all (16%; Pradono et al., 2005b).

In contrast, Kasnodihardjo et al. found a high rate of consultation of health professionals among respondents with malaria in Sumatra (Kasnodihardjo and Manalu, 2008). They surveyed 495 people from two districts in South Tapanuli (North Sumatra) in 2008. They

found that 16% of respondents self-treated whilst 84% sought out malaria medication from health personnel. Tana employed longitudinal surveys of 429 subjects in Kulonprogo (Yogyakarta, Java) both in 2001 and in 2003 (Tana, 2003). Three percent of the subjects self-treated and 97% sought a consultation. Similar findings were also reported among 156 respondents surveyed by Yoda et al. in Lombok and Sumbawa (both in the Lesser Sundas archipelago) in 2004 (Yoda et al., 2007). About 1% of respondents either self-treated or took no action. A clear majority (81%) sought out malaria treatment at health facilities.

A delay in receiving medication is well known to create the risk of a poor treatment outcome with malaria. Indonesians often tend to put off visiting health facilities until pressed to do so by worsening symptoms. Hunt et al. reported that among 525 respondents seeking treatment in health primary centres in three districts in Central Jawa in 1991, the mean number of days between onset and seeking treatment was 3–4 days (Hunt et al., 1991). Most of them (77%) did not go to school or work when they had malaria-like symptoms. As a result, on average, they missed 5 days of work or school. Mardiana et al. reported that, in Jepara (Central Java), in 2000, 24% of 100 people interviewed waited 1 or 2 days after they had fever before visiting a health facility (Mardiana and Santoso, 2004). However, most of them visited health facilities after the third day of fever (66%). Shinta et al. found a similar pattern in Purworejo (Central Java) in 2003 (Shinta et al., 2005). About 25% of the 100 respondents would visit a health facility within the first 3 days of being ill. Three percent of respondents waited for 10 days before seeking malaria medication at a health facility.

Health education improves people's understanding of malaria treatments and, in turn, improves adherence to prescribed therapy. Saikhu and Gilarsi reported that of 6484 respondents in four districts in Central Java in 2001, 75% could not describe treatments for malaria (Saikhu and Gilarsi, 2003). However, of those respondents who had already had malaria, only 2% did not know what malaria treatments were available. A study was conducted in six districts in Eastern Indonesia between 2001 and 2003 revealing that only 14% of 1577 health personnel in pregnancy clinics had received training on malaria treatment and prevention (Sekartuti et al., 2004c). This proportion was even lower in hospitals (0.4%, 6/1245) and primary health centres (6%, 13/233).

2.4.4. Vector control

Vector control involves strategies that reduce larval vector density, human-vector contact or the duration of vector survival (Najera and Zaim, 2003). The reduction of larval vector density may be achieved through either larviciding, the use of larvivorous fish or source reduction by environmental management. Reducing human-vector contact may be achieved by using mosquito bed nets, screening windows and doors of homes or by employing measures of personal protection (e.g. behavioural avoidance, appropriate clothing, repellents and fumigant insecticides) or zooprophylaxis. The survival of adult vectors may be reduced by indoor spraying with residual insecticides (IRS) and by the community wide use of ITN.

2.4.4.1. Control of larvae

2.4.4.1.1. Larviciding: The earliest efforts to systematically control malaria in Indonesia involved larviciding (Najera and Zaim, 2003). The effectiveness of larviciding depends upon the permanence of breeding sites and on their location in terms of the access provided to humans. A variety of larvicides have been used for malaria control, including oils, chemical insecticides, insect growth regulators and microbial insecticides. Indonesia's MCP recommends insect growth regulators (methoprene, pyriproxyfen) and microbial insecticides (the bacterium *Bacillus thuringensis israelensis* or BTI) as the preferred larvacidal measures. Methoprene (World Health Organization, 2006h) and pyriproxyfen (World Health Organization, 2005a) prevent larvae from maturing. The effectiveness of these agents is

measured in terms of the emergence of adult mosquitoes from treated water within laboratory cages. Another larvicide, BTI (World Health Organization, 2006f), produces toxins that effectively kill mosquito larvae. The microbe poses no threat to humans, animals or other aquatic organisms. The effectiveness of BTI is determined in a field setting by counting the density of larvae in treated bodies of water.

Larviciding presents operational challenges that limit its utility to specific settings. For example, unless breeding sites have been identified and mapped to permit sufficient coverage, little impact upon malaria transmission would be achieved. Also, effective dosing may vary widely according to specific habitats. Success may hinge upon the tedious and exacting task of determining that dose.

Many studies have evaluated BTI efficacy in Indonesia, specifically against *A. aconitus* (Blondine, 2000, 2004; Blondine and Boewono, 2004; Blondine et al., 2000a,b), *A. barbirostris* (Blondine et al., 1994; Widyastuti et al., 1995, 1997.), *A. maculatus* (Blondine and Widiarti, 2008; Munif and Pranoto, 1994) and *A. sundaicus* (Blondine et al., 2004, 2005; Hakim et al., 2005; Kirnowardoyo et al., 1989; Schaeffer and Kirnowardoyo, 1983). However, BTI application is a challenge to apply for large-scale malaria control. Geographical reconnaissance of the breeding places of local vectors needs to be carried out first, along with the more detailed definition of vector bionomics and human habitat mapping (Najera and Zaim, 2003). Once this has been done, the task would be to determine the sufficient dosage of larvacidal component (Kirnowardoyo et al., 1989). The susceptibility of each vector species should be monitored after the application of BTI.

Blondine et al. reported the efficacy of the liquid formulation of BTI cultured in coconut water against *A. aconitus* larvae in Semarang (Central Java) in 2000 (Blondine, 2000). They administered dosages of 0.15 ml/100 ml water and 0.2 ml/100 ml water. Their experiment used 15 treatment pools and five control pools. Treatment pools were filled with the locally cultured BTI from coconuts and the control pool was not treated. The evaluation of this formulation was done by collecting larvae for 3 days before application, then conducting daily observations until day 6 after application. The study showed, at the formulation of 0.15 ml/100 ml water, the reduction of larvae relative to control was 94–99% on the first 3 days. The reduction of larvae density decreased from 76% on day 4 to 25% on day 6. At the formulation of 0.2 ml/100 ml water, the reduction of larvae relative to control was 81% on day 1. The reduction of larvae decreased from 73% on day 2 to 34% on day 6. Blondine et al. concluded that the liquid formulation of a locally cultured strain of BTI from coconuts, administered at a dosage of 0.15 ml/100 ml water or 0.2 ml/100 ml water was effective against *A. aconitus* larvae until 3 days.

In 1994, Blondine et al. executed a trial of BTI against *A. barbirostris* in East Flores (Lesser Sundas archipelago; Blondine et al., 1994). A dosage of 0.06 ml of BTI per m^2 in three types of pond (clear, grassy and mossy) was evaluated. Intervention and control ponds were assigned to each pond type. Spraying was done on a weekly basis for 4 weeks. It was revealed that, within 24 h, the mean reduction in larval densities during four applications in intervention ponds relative to control ponds was 98% in clear ponds, 90% in grassy ponds and 54% in mossy ponds. They concluded that BTI may be effective in clear and grassy ponds but less so in mossy ponds. Widyastuti et al. also evaluated BTI at field-scale in East Flores (Lesser Sundas) in 1992 (Widyastuti et al., 1995). The study used three intervention ponds and one control pond. The tested dosages were 0.06, 0.075, 0.1 and 0.12 ml/m^2. They found that mean larval densities within 24 h in intervention ponds fell from 55 to 7 larvae per 20 dips at dosages ranging from 0.06 to 0.12 ml/m^2. No village-scale study of BTI against *A. barbirostris* has been reported from Indonesia.

Munif and Pranoto conducted a trial of BTI against *A. maculatus* at Kulonprogo (Jogyakarta, Java) in 1994 (Munif and Pranoto, 1994). They evaluated three distinct means of application: sprayers, plastic bags and direct pouring into streams. The sprayer application used a dosage of 1.5 l/ha. Spraying was done evenly on river pool surfaces. The plastic bag application was done by placing a 1.5 l/ha dosage of larvicide in 40 plastic bags at 40 mosquito breeding sites. The plastic bags were filled with pebbles to hold them in place underwater. The direct pouring application was done by dissolving larvicide at a dosage of 1.5 ml/ha in 20 l of water. The water was then allowed to flow into the river at an upstream location. Each method was repeated four times over 21 days, with a weekly interval between each run. Larvae were collected at 1 h prior to treatment, 24 h post treatment and then again after weeks 1, 2 and 3. They found that the spraying application reduced larval density from 95 to 3 larvae on day 1, a figure which increased to eight larvae (week 1), dropped again to one larvae (week 2) and finally increased to 21 larvae (week 3). In other words, the mean reduction of larval density relative to pre-treatment was above 96% up until week 2, but only 34% in week 3. The plastic bag application reduced larval density from 95 larvae to none on day 1, but this increased to 7 larvae (week 1), 23 larvae (week 2) and finally 61 larvae (week 3). The plastic bag application therefore reduced larval density relative to pre-treatment by about 90% up until week 2, but only by 36% in week 3. The direct pouring technique prompted larval density to fall from 79 to 1 larva (day 1), which dropped further to none (week 1) and then increased to four (week 2) and seven (week 3). This technique took longer to take effect, that is, the reduction of larvae was only 7% on day 1 and 58% after week 1. However, a reduction rate of 98% was reached after weeks 2 and 3. It was therefore concluded that spraying and plastic bag application reduced larvae at a faster rate than direct pouring. However, direct pouring was effective until the third week.

Blondine et al. reported the efficacy of the liquid formulation of BTI cultured in coconuts against *A. maculatus* larvae in Kulonprogo (Yogyakarta) in 2008 (Blondine and Widiarti, 2008). BTI was cultured in soybean infusion medium. In laboratorium scale, it was revealed that the liquid local strain of BTI recovered from soybean medium and administered at dosages of 0.59 ml/100 ml water killed 90% of larvae within 24 h (lethal concentration 90% or LC90). They tested three liquid formulation of locally strain BTI at dosages of 0.59 ml/100 ml water (LC90), 2.95 ml/100 ml water (5 × LC90) and 5.9 ml/100 ml water (10 × LC90). Their experiment used nine treatment pools for each formulation and nine control pools. Treatment pools were filled with locally cultured BTI from soybean and the control pool was not treated. The density of larvae was observed a day before application, then on days 1, 2, 4 and weeks 1, 2, 3 after application. They showed that, at formulation of 0.59 ml/100 ml water, the reduction of larvae density relative to control was 95–99% on first 2 days, then decreased from 78% on day 4 to 37% on week 3 after application. At dosage of 2.95 ml/100 ml water, the reduction of larvae density relative to control was 99–100% on first 2 days, then decreased from 87% on day 4 to 41% on week 3 after application. At a dosage of 5.9 ml/100 ml water, the reduction of larvae density relative to control was 100% on first 2 days, then decreased from 87% on day 4 to 61% on week 3 after application. Blondine et al. concluded that the liquid formulations of the locally cultured strain of BTI from soybean infusion medium, administered at a dosage of equal or higher than 0.59 ml/100 ml water, were effective against *A. maculatus* larvae.

Various studies consistently show that BTI effectively reduces densities of *A. sundaicus* larvae in Indonesia. Kirnowardoyo et al. evaluated the efficacy of three distinct BTI H-14 formulations (liquid, granule and briquette) against *A. sundaicus* larvae in Banyuwangi (East Java) and Jembrana (Bali) in 1984 (Kirnowardoyo et al., 1989). Active BTI 100 ml was diluted into 8 l of water, then sprayed on a 200 m^2 water surface. The liquid formulation was applied on a weekly basis for 12 months. The evaluation of this formulation was done by collecting larvae every week, 6 h prior to treatment and then again 24 h after treatment.

They found that the larval density had fallen from 27.3 to 3.5 larvae/10 dips (reduction = 87%) 24 h after the first application. The mean reduction of larval density for each application ranged from 76% to 100%. The second (granule) formulation containing 500 g of BTI was dispersed over a 10,000 m^2 water surface. The evaluation of this formulation was done by collecting larvae every 3 days for a month. The granule formulation of BTI H-14 effected a reduction from 38 to 0.2 larva/10 dips (reduction 99%) on the first day after treatment. After 3 days, however, the larval density increased to 54 larva/10 dips. Between day 6 and day 25, larval density ranged from 29 to 59 larvae/10 dips. The final (briquette) formulation was applied by using bamboo sticks to bind briquettes to an improvised floating device. The distance between the bamboo sticks was 3 m. It was shown that BTI H-14 briquettes could reduce larval densities from 9.9 larvae to 2.1 larva/10 dips (reduction: 79%) within 24 h after the treatment. The effect of the briquettes remained satisfactory (~90% reduction in larval density) for at least 24 days. Kirnowardoyo et al. concluded that the liquid and briquette formulations provided good larval control for *A. sundaicus*, whilst the granule formulation was less successful.

Blondine et al. examined the efficacy of the liquid formulation of BTI cultured in coconuts against *A. sundaicus* larvae in Cilacap (Central Java) in 2003 (Blondine et al., 2004). BTI was cultured in coconuts because these contain the amino acids and carbohydrates capable of supporting the expansion of BTI numbers. Old coconuts (weight 400–700 g) were used as culture media. A hole with a 1.5-cm diameter was made in each coconut. The BTI dosage used was 5 ml in 100 ml of water. BTI was injected into 12 coconuts and the hole was then covered and coated with candle wax. Coconuts were stored at room temperature for 4–7 days. It was found that the liquid local strain of BTI recovered from coconuts and administered at dosages of 0.1 ml/100 ml water and 0.0751 ml/100 ml water killed 90% of larvae within 24 and 48 h. Their experiment used 12 treatment pools and four control pools. Each pool had sentinel traps containing 15 larvae. All larvae (dead and alive) were replaced with 15 new larvae on each observation day. Treatment pools were filled with locally cultured BTI from coconuts and the control pool was treated with uninfected coconut water. The mortality and density of larvae were observed a day before application, then on days 1, 2 and 4, and weeks 1 and 2 after application. The reduction of larvae relative to control was 100% on day 1, 91% after week 1, and 84% after week 2. Blondine et al. concluded that the liquid formulation of a locally cultured strain of BTI from coconuts, administered at a dosage of 5 ml/100 ml water was effective against *A. sundaicus* larvae.

Hakim et al. studied the residual effect of granule and liquid BTI formulations in Ciamis (West Java) in 2005 (Hakim et al., 2005). Fifteen *A. sundaicus* larvae were caught in shrimp ponds and put into the plastic containers. The larval mortality was observed after 24 h. Probit analysis showed LD90 at dosage of 0.869 kg/ha for granule and 1795 ml/ha for liquid formulation. Then authors tested the LD90 and two other doses: 0.5 g/ha (granule) and 1000 ml/ha (liquid). For granule formulation, they found 100% mortality at dosage of LD90 and the recommended dosage on day 1 and after 2 weeks, 41% mortality rate at LD90 and 50% at recommended dosage ($p = 0.229$). For liquid formulation, they also found 100% mortality at dosage of LD90 and 99% at the recommended dosage on day 1. After 2 weeks, 45% of larvae were killed at dosage of LD90 and 37% of larvae at recommended dosage ($p = 0.565$). These authors thus recommended that lower dosages than those recommended could be applied for field purposes. They found that granule formulation could kill more than 90% of larvae for up to a week, whilst liquid formulation could last only 4 days. They concluded that granule formulation was more effective than liquid formulation at recommended dosages.

The effectiveness of other larvicidal measures has been examined in Indonesia. Barodi et al. conducted a small-scale field study at Kulonprogo (Yogyakarta) in 1993 (Barodji et al.,

1995). The study focussed on nine temporary shallow ponds located near three rivers. They assessed the emergence of adult mosquitoes before and after the application of pyriproxyfen. One to two months before application, they collected larvae from puddles and reared them in the laboratory until adults emerged. They found that the proportion of adult mosquitoes emerging without larvicide was 83% (795/953). Pyriproxyfen was applied at dosages of 0.01 and 0.05 ppm against *A. maculatus*, *A. flavirostris* and *A. balabacensis*. Larvae and water samples were collected for each puddle on days 1, 3, 5, 7, 35 and 49 post-application. Larvae obtained from each puddle were reared using water samples from each. The first week collection showed a significant reduction of adult mosquitoes emerging at a dosage of 0.01 ppm (intervention: 2.8%, 35/1257 vs. control: 86%, 472/552, $p < 0.001$) and 0.05 ppm (intervention: 1.3%, 13/1033 vs. control: 86%, 472/552, $p < 0.001$). On day 35, a dosage of 0.01 ppm still achieved significant reductions (intervention: 17%, 17/103 vs. control: 73%, 63/86, $p < 0.001$), as did 0.05 ppm (intervention: 20%, 31/158 vs. control: 73%, 63/86, $p < 0.001$). However, by day 49, the reduction of emergent adult mosquitoes was no longer significant at a dose of 0.01 ppm (intervention: 60%, 36/60 vs. control: 63%, 38/60, $p = 0.707$). This was also true at the higher dosage of 0.05 ppm (intervention: 58%, 35/60 vs. control: 63%, 38/60, $p = 0.575$). The investigators concluded that 0.01 ppm remained effective for 35 days and that increasing this dose fivefold presented no apparent advantage.

Mardiana reported the efficacy of methoprene against *A. farauti* larvae at laboratory-scale in 1996 (Mardiana, 1996). Briquette formulation was used to retain four concentrations (i.e., 0.0029 g/50 l water, 0.0058 g/50 litre water, 0.0116 g/50 l water, and 0,0232 g/50 lwater). A total of 400 larvae (100 larvae per each concentration) and 100 larvae were exposed to treatments and control, respectively. The study showed that the higher concentration was associated with higher mosquito mortality. The mosquito mortality rate was 73% at concentration of 0.0029 g/50 l water, 92% at 0.0058 g/50 l water, 97% at 0.0116 g/50 l water and 99% at 0.0232 g/50 l water. The effective dose of methoprene was then estimated using probit analysis for 50% lethal or 95% lethal. The analysis resulted 0.0014 g/50 l water (50% lethal) and 0.0085 g/50 l water (95% lethal). The author concluded that briquette methoprene was effective to control *A. farauti* larvae at least in laboratory-scale.

Waris evaluated the efficacy of pyriproxyfen as larvicidal control of *Anopheles subpictus* in South Kalimantan in 2003 (Waris, 2003). A total of 1,200 *A. subpictus* larvae were kept in groups of 150 in 25 × 20 × 3.5 cm containers for each concentration plus a control group. A dosage of 2 grams pyriproxygen per 1 liter water was dissolved into seven concentrations: < 0.001 ppm, 0.001–0.005 ppm, 0.01 ppm, 0.02 ppm, 0.04 ppm, 0.08 ppm, 0.16 ppm. After the larvae were treated with the various concentrations of pyriproxyfen, the number of dead larvae and number of pupae were recorded for ten days. The surviving pupae were then observed for a further ten days and the number of dead pupae and adult mosquitoes were recorded. The study showed that in the treatment groups, 88% (927/1,050) of the larvae were prevented from becoming pupae in ten days. The larvae mortality rates varied among the concentrations from 66% and 100%. Of the 123 pupae to survive, 100% died before maturing into adults. In comparison, the control group showed 168 out of 350 (48%) larvae failed to become pupae and of the remaining 182 pupae, 52% (95/182) died before maturing to the adult stage. In other words, 48% of the surviving pupae emerged as adult *An. subpictus* mosquitoes. The authors concluded that pyriproxyfen was effective as a larvicide against *A. subpictus* larvae in South Kalimantan.

The use of the entomopathogenic fungus *Metarhizium anisopliae* for vector control has been evaluated in Indonesia. Munif et al. carried out a study of this fungus when used in the control of *A. aconitus* in Banjarnegara (Central Java) in 1994 (Munif et al., 1994). They evaluated a 900 m paddy treated with a dosage of 300 mg conidiospora/m^2. They found a 90% reduction in larval density. More importantly, there was a 10-fold reduction in the

measured biting rate of anophelines. This relatively small experiment suggests that *M. anisopliae* is an effective control agent. However, the further documentation of the entomopathogenic fungus in community-based larvaciding studies is still lacking.

In terms of community support for the application of larvicides, Blondine et al. interviewed 60 people in Cilacap (Central Java) in 2003 (Blondine et al., 2004). They assessed the community's knowledge about, attitude towards and practice of BTI larvicide application. Before the community received malaria education, none of them had known that BTI could kill mosquito larvae. Once they had received this education, 47% (14/30) understood that substances like BTI could be used to kill mosquito larvae. Despite half the community not having a full understanding of the use of this larvicide, 83% (25/30) agreed to apply BTI to their fishponds in support of this control activity. They found that fish farmers at Cilacap (Central Java), once they had been made aware of the intent and nature of BTI application, were much more likely to accept it.

Taken together, the studies of larvicides in Indonesia demonstrate good results against the major anopheline vectors. The use of larvicides with slow-release technologies appears to represent the most effective approach. However, as with any larvicide, the strategy may only work well when an effective coverage of breeding sites is achieved, and when the area in which it is implemented is well mapped and characterized. However, no studies in Indonesia have yet evaluated the impact of larvicides on the actual risk of malaria transmission and disease burdens. The presumption of effective control with diminished densities of larvae may not be borne out by more careful study. Efficacy against malaria transmission will almost certainly hinge upon the percentage of breeding sites actually covered, much in the same way that ITN impact hinges upon the percentage of people actually using the nets. Achieving high levels of coverage with larvicides requires entomological and mapping expertise that is generally not available at the district level where the responsibility for such interventions lies. Moreover, even when such expertise is available, larviciding may not be suitable because the breeding sites of the vectors may be simply too widespread and temporary to accomplish any significant coverage. For example, the *Punctulatus* group of mosquitoes in New Guinea breeds in temporary pools such as those in tire ruts and even footprints—larviciding such sites would be futile. The utility of larvicides against some of the most important anophelines of Indonesia has been proven in concept, but no demonstration of utility in practice has been made and the settings in which this could be realized are probably quite limited.

2.4.4.1.2. Larvivorous fish: Another means of biological control of malaria vectors is the introduction of larvivorous fish to breeding sites (Fletcher et al., 1992; Howard et al., 2007; Kusumawathie et al., 2008; Roll Back Malaria, 2005; Sabatinelli et al., 1991; World Health Organization, 2006c). This approach has been most effectively applied in man-made mosquito breeding sites. It has a long history and constituted the core of MCP strategies before the introduction of DDT (Roll Back Malaria, 2005; Roll Back Malaria Partnership, 2008). In 1946, Gerberich reviewed the available literature dealing with larvivorous fish and counted 216 species of fish, used in the control of 35 species of mosquitoes, in 41 countries (Gerberich, 1946). In 1984, Sharma identified 315 species of larvivorous fish (Sharma, 1984). The most suitable species of fish all meet the following criteria: carnivorous, surface feeder, rapid breeding in confined spaces, quick swimmer, tolerant of thick vegetation and broad fluctuations in temperature and acidity (WHO Study Group on Vector Control for Malaria and other Mosquito-Borne Diseases, 1995; Wickramasinghe and Costa, 1986). Many authors suggest the same steps in fielding fish aimed at reducing the risk of malaria (Dua et al., 2007; Ghosh and Dash, 2007; Kusumawathie et al., 2006; Mohamed, 2003; Rasool and Suleman, 1999; Wickramasinghe and Costa, 1986). The first steps are mapping the fish breeding sites and collecting species of fish with larvivorous potential from those

sites. The most suitable species should be identified by testing and evaluating its feeding behaviour and then the optimum manner of rearing the species must be found. Making the fish strategy popular amongst the people who own or manage the sites is equally vital. The evaluation of the impact of these fish upon larval densities should be followed by an assessment of malaria risk in those communities covered.

The MCP in Indonesia provides guidelines for the introduction of larvivorous fishes (Departemen Kesehatan, 2006a). The recommended larvivorous fish in Indonesia are *Poecilia reticulata* (Indonesians call these ikan guppy), *Aplocheilus panchax* (ikan kepala timah) and *Gambusia affinis* (Departemen Kesehatan, 2006a). In Central Java, Nalim et al. investigated the potential of *P. reticulata*, first introduced into Indonesia in 1961, as a method of control against the *A. aconitus* mosquito, which is found in rice fields (Nalim and Boewono, 1987; Nalim et al., 1985, 1988). The study involved 92 farmers cultivating 24 ha of rice fields. The farmers were given training about health and agricultural practices twice a month along with regular farmer union meetings. The first distribution of 60,000 1-month-old fish fry was a failure as a consequence of improper handling by the farmers. Later, 478,000 fish were successfully distributed with the assistance of local fishery personnel. The scheme initially aimed for a density of 2 fish fry/m^2. The daily consumption of larvae averaged 119 per fish. To determine the direct impact of these fish, an emergence trap was designed to trap mosquitoes emerging from ricefields. The study showed that *P. reticulata* reduced *A. aconitus* emergence from over 3 to 0.01 mosquitoes/m^2/day. More importantly, the SPR for malaria among residents dropped from 17% to 0.2% in the 5 years of implementation. The study noted that proper training in fish handling is the key element in larvivorous fish introduction.

In North Sumatra, Sudomo et al. evaluated the larva-eating activity of *Oreochromis niloticus*, first introduced into Indonesia in 1969 (Nurisa, 1994), to control the fishpond mosquito *A. Sundaicus* (Sudomo et al., 1998). Fishponds were found in many locations in the study area. Each of three ponds (6 × 7 m) was allocated as treatment and control ponds. The ponds were filled with water to a height of 30–50 cm. After 4 weeks, all ponds had grown water plants and *A. sundaicus* larvae were found in all the ponds. *O. niloticus* fish were distributed at 3 fish/m^2 or 126 fish/pond. The size of these fish ranged from 6 to 8 cm in length and their weight ranged from 10 to 12 g. The number of anopheline larvae found in ponds with larvivorous fish after 11 weeks was 50% less than the number found in ponds without larvivorous fish (5.5 vs. 10.1 larva/pond), but not significantly different ($p = 0.128$). It is somewhat doubtful whether such modest reductions would translate into a reduced risk of malaria among inhabitants. It may also be that the initial density of fish per pond was not adequate.

Effectiveness may also hinge upon community awareness. Hunt et al. reported that only 1% of 636 respondents interviewed in three sub-districts in Central Java recognized the role of fish in paddy field for the control of mosquito larvae (Hunt et al., 1991). Sekartuti et al. reported that none of the 420 respondents living along a coastline in South Sumatra knew of the existence of fish that eat mosquito larvae (Sekartuti, 2003). Similar findings were reported from Eastern Indonesia (Sekartuti et al., 2004c). The effective application of larvivorous fish requires studies demonstrating coverage requirements, community acceptance and the real impact such a strategy could have upon malaria risk in those communities.

2.4.4.1.3. Source reduction by environmental management: Environmental management aims to create habitats not suitable for breeding by anopheline vector species. The history of this approach, also called species sanitation, is detailed in Section 2.3.1. This approach is particularly important in Indonesia due to the abundance of vectors that, if permitted, may

thrive in agricultural settings. Agricultural practices, like irrigation, crop selection and rotation, impact on the risk of malaria transmission.

Nalim carried out a study using agricultural practice against malaria vectors in Salatiga (Central Java) in 1980 (Nalim, 1980). She evaluated the impact of draining two rice paddies; one selected as an intervention plot and the other as a control plot (3 km^2 each). The two sites were 6 km apart but both had a similar ecological setting. Larval densities were measured twice a week from the beginning of planting until the harvest 5 months later. The measurements were taken at 30 randomly selected sites in each of the two plots. Adult mosquito densities were also measured using six emergence traps (42 cm in diameter) at each study plot. Flooded paddy fields were drained for 3 days after 2 months of rice growth, and were then flooded again for 10 days. A month after the paddy had been flooded, all species (*A. aconitus*, *A. annularis*, *A. vagus*, *A. indefinitus*), except *A. barbirostris* (larvae density: 0.04 larvae/dip; adult density: 0.61 mosquitoes/day/m^2) were absent. The author concluded that 3 days of paddy drainage could reduce the density of larvae and the emergence of adult mosquitoes. The basic requirements for good results, as expressed by the author, were sloped paddy for good drainage, irrigation mechanics for ease of draining and filling and the cooperation of local authorities and farmers.

Takagi et al. monitored larval densities of *A. sundaicus* in shaded and unshaded fish farming ponds in North Sumatra in 1986 (Takagi et al., 1995). Four fishponds were shaded for the experiment. The size of these ponds was 2.5 m in width and 7–10.5 m in length. They removed all fish from the ponds to exclude the effects of predation. Ponds were shaded using the fresh leaves of the locally abundant Nipa palm. The density of larvae in shaded ponds fell from 38 to 1.2 larvae/10 dips after 17 days of shading ($p < 0.001$). In contrast, this difference in larva density was not detected in the unshaded ponds (before: 11.5 vs. 11.7 larvae/10 dips; $p > 0.05$). The authors argued that this shading for larval control would be relatively easy and inexpensive. However, shading would not be practical for the larger fishponds, as nipa palm fronds are typically about 2 m in length. This measure also requires the monthly replacement of the Nipa leaves.

In Bintan (Riau), in 1993, Pribadi et al. studied the community's knowledge about, and attitude towards malaria, as well as the malaria prevention practices employed (Pribadi et al., 1997). Of 204 residents interviewed, half understood that mosquitoes breed in ditches. The other half had no concept of where mosquitoes may breed. Sampling only 55 people, the question of eliminating breeding sites was posed. Most identified the filling in and drying out of ditches as possible methods. Few respondents were aware that oiling water, applying insecticides or planting mangrove trees were related to malaria control.

Historically at least, species sanitation in Indonesia has a very good record of positive results against malaria. Moreover, a very limited number of more recent studies show data suggesting that such measures may be superbly effective in limiting the risk of transmission. The effective interventions carried out under Dutch colonial administration focused on economically important zones and broader practicality was not assessed. Contemporary studies assess this broader applicability but with a limited scope of findings. No work in contemporary Indonesia has demonstrated the impact of a village- or district-wide implementation of specific species sanitation measures upon the risk of malaria.

2.4.4.2. Control of man-vector contact

2.4.4.2.1. Mosquito nets and insecticide-treated mosquito nets: Sleeping under bed nets treated with insecticides has been proven to have a positive impact on all-cause mortality in communities with hyper- to holoendemic malaria. As shall be seen, however, similar studies in the hypo- to mesoendemic setting, which is typical of most endemic zones in Indonesia,

are lacking. It remains unclear what benefits, if any, are gained by distributing ITNs. Nonetheless, Indonesia aggressively distributes ITNs, aiming for 80% coverage in high-risk areas, in particular, amongst young children and pregnant women. However, several problems have arisen in regards to this prevention method in Indonesia.

In 2007, the Indonesian Demographic and Health Survey (IDHS) was implemented by the Indonesian Centre of Statistics, supported by the United Nations Population Fund (UNFPA), Macro International Inc., the US Agency for International Development (USAID) and the Ford Foundation and UNICEF (BPS and Macro International, 2008). Using a stratified two-stage design, the survey selected 40,701 households and interviewed 41,653 respondents in all provinces. The IDHS collected information on the impact of malaria interventions at the community level and included questions on the ownership of bed nets and the use of bed nets by pregnant women and young children. The survey revealed that the ownership of ITN in Indonesia is still low (2.8%). Fewer households in eastern Indonesia own ITNs than in western Indonesia (9% vs. 3%). Protection against malaria for children under 5 years by ITN was low (3.3%). Fewer children under 5 years slept under ITNs in eastern Indonesia than in western Indonesia (9.7% vs. 2.7%). The proportion of pregnant women aged 15–49 who protected themselves against malaria by sleeping under an ITN was also low (2.3%). Fewer pregnant women slept under ITNs in eastern Indonesia than in western Indonesia (6.1% vs. 1.9%).

Another study confirmed low rates of ITN usage in Indonesia. In 2004, the Indonesian HHS was implemented by the Indonesian National Institute for Health Research and Development and the Indonesian Centre of Statistics (Soemantri et al., 2005). A stratified two-stage design was used to select 9012 households. A total of 38,276 respondents were interviewed across all provinces (Pradono et al., 2005a). The HHS collected information on health household status, health systems, medical check ups, healthcare facility responsiveness, treatment costs, mortality and blood examination and included questions on the use of ITNs. Similarly to the IDHS, this survey found low ITN usage rates in Indonesia (2.5%). The low rates of coverage may be related to the lack of data demonstrating the efficacy of this intervention.

An exhaustive review of the available sociological studies involving mosquito netting since 1990 revealed none describing malariometric or broader all-cause morbidity and mortality effects linked to ITN interventions. In 2001, Sanjana et al. conducted a cross-sectional KAP study in 50 villages in nine sub-districts of Purworejo, Central Java, in the midst of a malaria epidemic (Sanjana et al., 2006). Of 1000 randomly surveyed households, 36% owned at least one bed net. Of the households with bed nets, 92% had made the purchase themselves, 51% reported that all household members slept under the nets, 9% claimed no bed net usage, and 40% reported that only some household members slept under the nets. An average of three people per household had slept under a bed net the previous night. Fifty-three percent of the households had paid less than Rp. 20,000 (US$ 2) for their bednets, 33% had paid between Rp. 20,000 (US$ 2) and Rp. 50,000 (US$ 5) and 0.6% had paid more than Rp. 50,000 (>US$ 5). There was no correlation between the households which owned bed nets and the households in which a member had suffered from malaria in the past year (OR = 1.0, $p = 0.89$). This was not the type of randomized, longitudinal study required to draw real conclusions about the protective effects of ITNs. Nonetheless, these may be the best available data on this question and they certainly point in the direction of there being no discernable benefits, even in the epidemic setting of this study.

Saikhu and Gilarsi used secondary data from the Benefit Evaluation Study (BES) conducted by the Indonesian National Health Institute for Research and Development and the Indonesian Centre of Statistics in 2001 (Saikhu and Gilarsi, 2003). The study was conducted in four districts in Central Java: Banjarnegara, Pekalongan, Kebumen and Jepara. There

were 15,901 respondents of all ages from 4032 households. The authors aimed to show the association between knowledge about malaria and the number of malaria cases. Remarkably, only 6485 respondents had heard of malaria and, perhaps more remarkable still, these were the respondents who then went on to constitute the evaluated population. The analysis showed that most respondents (68%) understood that malaria was transmitted by biting mosquitoes. Only a quarter (26%) knew that bed nets were a way to prevent malaria. The study found that there was no significant correlation between the knowledge that bed nets can be used as a prevention method and the number of malaria cases in a household (p = 0.884). Like the KAP study in Purworejo (Sanjana et al., 2006), this survey does not serve as a demonstration of the efficacy of ITNs against malaria. However, the results at least suggest that bed nets may have some limited impact upon the risk of malaria in some areas of Indonesia. In the instance of this particular survey, not knowing about bed nets as a means of malaria prevention had no bearing upon the reported risk of malaria (OR = 0.97, 95% CI 0.7–1.4).

Yoda et al. evaluated the effect of a cooperative malaria control project carried out between 2001 and 2004 by the Indonesian MoH and Nagasaki University, Japan in Lombok and the Sumbawa Islands (Lesser Sundas; Yoda et al., 2007). The three control activities conducted as part of this project were malaria case detection and treatment, the systematic distribution of ITNs and health education for health workers and villagers. Eighteen months after termination of the project, its effectiveness was evaluated by interviewing the heads of the 600 families who had been involved. Before the project began, only 14% of households surveyed were in possession of ITNs. During the project, 98% of the participating households used bed nets every night. Once the project ended, 88% of the participants continued to use the bed nets. Of those who received bed nets, 91% did not treat them with insecticide owing to a lack of insecticide, because they disliked insecticide, or because they felt no need to treat the nets. People who did not use nets tended to sleep outside the house, lack the necessary funds to purchase a net, or simply not understand that nets protected against malaria (presuming they actually do). Unfortunately, this study did not report the impact of the intervention upon malaria risk or upon the burden of the disease in communities.

High levels of awareness somehow failed to translate into presumably effective measures of self-protection, that is, obtaining and using mosquito netting. Sekartuti et al. conducted a health education intervention study at high-risk sub-districts in epidemic Purworejo in 2000 (Sekartuti et al., 2004b). Using a structured questionnaire, they surveyed the heads of 219 randomly selected households. The percentage of respondents sleeping under bed nets was 14%. Respondents not using nets cited inconveniences such as comfort, cost and lack of mosquitoes. Suharjo et al. conducted a KAP study in Banjarnegara involving 100 households in 2002 (Suharjo et al., 2004). The study showed that the proportion of bed net usage was 11%, even though 86% of households were easily accessible to mosquitoes. A majority of respondents agreed with the statement that malaria was a serious problem (64%), that it could have a serious impact on their life (89%), and that it was a threat to health (63%). It remains unclear just where the gap in understanding occurred that permitted people who were perfectly aware of the risks of malaria not to take this simple precaution against it. In Jepara, Mardiana et al. revealed that 19% of the 100 families surveyed slept under bed nets in 2000 (Mardiana and Santoso, 2004). The low income respondents prioritized spending money on food as opposed to buying a net. Ompusunggu et al. observed the behaviour of 46 patients with a *P. falciparum* infection in Mbilur Pangadu, West Sumba (Lesser Sundas) in 2002 (Ompusunggu et al., 2006). The study found that no patient had used a bed net or any other form of protection against mosquito bites. Most of the respondents treated the traditional houses shared between as many as four families as their permanent residence. The wooden slat structures offered few barriers to access by

mosquitoes. This study did not compare the behaviour of these malaria patients with that of people in the same region without malaria. It is therefore difficult to draw conclusions on the absence of net use among patients with malaria.

Arsunan et al. conducted a KAP study in Kapoposang Island, Pangkajene (South Sulawesi) in 2003 (Arsunan et al., 2003). The study involved 264 respondents selected using a random sampling procedure. The authors found that more than half the respondents (58%) slept under bed nets. About 81% of respondents agreed that the use of bed nets was a good idea. Those who lacked nets cited cost as the primary reason. There was a significant correlation between the lack of knowledge of methods of protection against malaria and risk of being infected ($p < 0.001$; OR = 5.2, 95% CI 1.7–18.4). There was also a significant correlation between lack of willingness to protect oneself against malaria and risk of malaria ($p < 0.001$; OR = 6.3, 95% CI 1.9–26.1). A very significant association appeared between the extent to which people practiced malaria protection and the risk of contracting the disease ($p < 0.001$; OR = 11, 95% CI 3.5–47). The authors also explored the relationship between knowledge, attitude and practice. It was found that a lack of knowledge about malaria could significantly increase negative practice in respect to malaria prevention (OR = 2.4; 95% CI 1.4–4.1; $p < 0.001$).

Roosihermiatie et al. implemented a case–control study to examine the correlation between bed net usage and malaria risk in Bacan Island, Maluku in 1998 (Roosihermiatie et al., 2000). Most subjects tended to burn mosquito coils at night, starting at 8 p.m. Only 15% of the 112 respondents surveyed owned mosquito nets and none were ITNs. Just 10% of those who owned nets said that they slept under them. The malaria risk for those above the age of 15 who never used mosquito nets was insufficiently assessed to draw any conclusions.

Between 1993 and 1994, Suharjo et al. conducted a study examining insecticide-impregnated bed net usage in malarial endemic areas in East Mimika (Papua; Suhardjo et al., 2003). The study took place in three villages with 1790 residents and involved the distribution of 766 ITNs (one ITN for two to three people). In two of the three villages people were given ITNs. The households were observed by investigators two nights per week (19–21) for 2 years. Three months and six months after distribution, all residents from the three villages received health education on malaria. In the two villages supplied with ITNs, residents were taught how to use and maintain the nets. The average use of ITNs increased from 41% at the time of the first health education lesson, to 63% at the time of the second. Average ITN usage also increased from 21 days per month to 24 days per month. This study showed that health education by local cadres slightly improved community practice in using ITNs. This study did not evaluate the relationship between ITN use and the risk of malaria. Another study in Eastern Indonesia (Sekartuti et al., 2004c) reported that a very low rate of health personnel ever received training in the use of impregnated nets (0.7%; 14/2104) and that none of the villages had the minimal one cadre who was supposed to have received training on ITN maintenance.

Sutanto et al. evaluated the efficacy of ITN intervention against malaria in hypo-to holoendemic areas in Mimika (Papua) between 1993 and 1995 (Sutanto et al., 1999). Two comparable-endemicity villages were chosen as a treatment site and a control site. The distance between the two villages was about 2 kilometres. 158 households were located in the treatment site and 201 households in the control site. Most of inhabitants (90%) were indigenous population and worked as fishermen and hunters. Before intervention, villagers usually slept on the floor or mattress without bed nets. Adults normally sat outside of the houses in the early evening until 10pm. Nylon-net was impregnated with permethrin at dosage of 0.5 gr/m2, while control nest were impregnated with milk solution. 277 ITNs were distributed to the treatment village (1.7 nets/household) and 261 non-ITNs to the control

village (1.3 nets/household). Malaria surveys were conducted once before and 8 times during intervention. The study showed that before intervention, the risk of malaria in the treated village was higher than that of the control village (RR = 2.5, 95% CI 1.6-3.6). Since then, the risk of malaria in the treated village was gradually declined. The intervention of ITN protected inhabitants in the treated village against malaria compared to those in the control village (RR = 0.24, 95% CI 0.1-0.4) over a year of intervention and (RR = 0.25, 95% CI 0.2-0.4) after two years. They concluded that the ITN application was effective to reduce the level of malaria endemicity from high endemicity to low endemicty in the treated village in Papua.

Sutanto et al. evaluated the influence of permethrin ITNs on natural immunity in a hyperendemic area in East Mimika (Papua) between 1993 and 1995 (Sutanto et al., 2003). One hundred and thirty-eight Papuan inhabitants were recruited from an ITN-treated village for serological investigation. Their sera were analysed for total IgG before intervention and 2 years after intervention using synthetic peptides, that is, $NANP_5$ and $EENV_4$-BSA. Analysis was then carried out only on individuals who were IgG positive before and after 2 years of intervention to investigate the change of antibody. Twenty-five and 68 individuals were positive IgG for $NANP_5$ and $EENV_4$-BSA, respectively. Their results showed a significant decrease in the levels of geometric mean of antibody level IgG to NANP5 (before 279 vs. after 132, $p < 0.01$) and to $EENV_4$-BSA (before 745 vs. after 543, $p = 0.046$). Additionally, the *P. falciparum* infection rates tested with CS reduced from 18% (14/77) to 12% (9/77), but not significant ($p = 0.258$). However, the *P. falciparum* infection rates tested with RESA reduced significantly (before: 17%, 18/108 vs. after: 1%, 1/108; $p < 0.001$). In other words, the application of ITNs reduced the risk of malaria infection, leading to a lower parasite burden and reducing the host immune suppression. The result showed in hyperendemic malaria people's immune response diminished during ITN intervention.

Barodji et al. evaluated the efficacy of ITN in East Flores (Lesser Sundas) in 1993–1994 (Barodji et al., 2004a). Twenty-four houses in three villages were recruited as treatment sites and eight houses in Ebak village, 10 km away, as control sites. Nylon bed nets of ~2 × 2 × 2 m were treated with a dosage of etofenprox at 0.2 g/m^2. Treatment was conducted by trained health workers every 6 months for 18 months. Nets were returned to participants after each treatment. The residual mortality against 90 *A. barbirostris* was evaluated for 24 h after a 30-min exposure to the nets. The tests were repeated on weeks 1 and 2, and each month for 5 months. Night mosquito landing density was evaluated every night (18–24 p.m.) and morning resting densities at 6–7 a.m. A malaria survey was conducted 3 months before intervention began and 1 month after each treatment cycle only at one treatment village and control village. It is unclear why the authors only measured in one of three treatment villages or how they selected the survey village. A direct contact test showed that 5 months after treated the mosquito mortality rate was 100%. In the treated village, the indoor mosquito landing densities reduced from 0.29 (before intervention) to 0.22 mosquitoes/man-hour (after 6 months) and below 0.04 mosquitoes/man-hour in the next 12 months. Relative to control, there was a 76% of reduction in indoor mosquito landing density. The morning resting density decreased from 0.38 mosquitoes/man-hour (before intervention) to less than 0.08 mosquitoes/man-hour (reduction 93%) after the first 6 months, but have since increased. In terms of malaria morbidity, the authors noted that *P. falciparum* prevalence in one treated village decreased from 10% (13/128) before the intervention to 6% (15/244) and 4% (6/142) at the second and the third cycle, respectively. However, after 6 months, the prevalence was 13% (10/78). In the control village, the prevalence of *P. falciparum* was relatively high at 8.6% (14/163) at before intervention and, on average, 18.2% (52/286) after first cycle. The authors noted no reported side effects by inhabitants and health workers to the insecticide. The small sample sizes used in this study limit what conclusion can be drawn.

Barodji et al. evaluated the efficacy of the insecticide permethrin at a dosage of 0.5 g/m^2 on nylon and cotton nets against *A. maculatus* and *A. barbirostris* (Barodji et al., 1999). Three treatments were applied. For the first treatment, the nets were impregnated with insecticide suspension, and left to dry naturally. For the second treatment, the nets were inserted into plastic bags filled with the insecticide suspension where they were crumpled, removed and left to dry naturally for 1 day. Finally, the nets were sprayed using IRS sprayer and also dried naturally for 1 day. A direct contact test against *A. maculatus* and *A. barbirostris* was conducted by exposing 30 mosquitoes of each species for 3 min to each of the treated nets. The mosquitoes were then transferred into clean cups (no insecticide). The mosquito mortality rate was observed for 24 h. Against *A. maculatus*, mosquito mortality rate on nylon nets was higher compared to the cotton nets for all three of treatments: impregnating (99% vs. 60%), crumpling (48% vs. 16%) and spraying (87% vs. 34%). *A. maculatus* mortality rate in impregnated nylon nets (99%) was higher than sprayed nylon nets (87%) or crumpled nylon nets (48%). Against *A. barbirostris*, a direct contact test showed that the mosquito mortality rate on nylon nets was higher than the cotton nets for all treatment types: impregnating (97% vs. 46%), crumpling (31% vs. 14%) and spraying (76% vs. 29%). *A. barbirostris* mortality rate on impregnated nylon nets (97%) was higher than on sprayed nylon nets (76%) or crumpled nylon nets (31%). Therefore, the authors concluded that nylon was superior than cotton as net material. They also summarized that the practice of spraying mosquito nets during IRS was also possible method against *A. maculatus* and *A. barbirostris*.

Barodji et al. evaluated the efficacy of ITN against *A. barbirostris*, *A. subpictus* and *A. sundaicus* in East Flores, Lesser Sundas in 1996 (Barodji et al., 2004b). Eight houses in Waiwadan village were recruited as treatment sites. They had no houses for control. Nylon bed nets were exposed to a dosage of cyfluthrin at 0.05 g/m^2. The sets were treated by trained health workers. Night mosquito landing density was evaluated every night (18–24 p.m.). A malaria survey was conducted 3 months before the intervention and every 3 months after the ITN application. The study showed that the cyfluthrin treated nets provided impact in *A. sundaicus* and *A. subpictus*, but not *A. barbirostris*. Against *A. barbirostris*, indoor mosquito landing densities only reduced from 0.74 (before intervention) to 0.68 mosquitoes/man-hour (after 3 and 6 months). However, its landing densities increased from 0.4 (before) to 0.8 mosquitoes/man-hour (after 3 and 6 months) outdoors. Against *A. subpictus*, indoor mosquito landing densities reduced from 7.7 (before) to 2.5 mosquitoes/man-hour (after 3 and 6 months). Outdoor mosquito landing densities decreased from 10.1 (before) to 4 mosquitoes/man-hour (after 3 and 6 months). Indoor and outdoor landing densities of *A. sundaicus* before intervention were 2.4 and 1.3 mosquitoes/man-hour. Less than 0.03 indoor or outdoor mosquitoes/man-hour landing both 3 or 6 months after intervention. In terms of malaria prevalence, the authors reported that SPR reduced from 17% (48/275) before the ITN intervention to 13% (17/128) 3 months after application and 4% (11/250) 6 months after. However, the malaria prevalence increased to 7.5% (39/518) 9–12 months after intervention. The authors noted no reported side effects by inhabitants and health workers to this insecticide. They concluded that ITN application by cyfluthrin could reduce mosquito landing density of *A. sundaicus* and *A. subpictus* in East Flores, and decreased malaria prevalence for 3–6 months after application.

Hakim et al. compared the mosquito mortality rate among permethrin, deltamethrin and lambda-cyhalothrin ITNs at dosage of 0.5 g/m^2 against *A. sundaicus* in Ciamis (West Java) in 2006 (Hakim et al., 2008). Each 4-m^2 net was treated by those insecticides and mixed with adhesive glue contained 86% acrylic and 14% arthathrin. This acrylic bonded the insecticide to the fibre net allowing it to remain effective after multiple washes and arthathrin helps the acrylic particles dissolve into insecticides. As control, they used permethrin ITN without the additional glue. Each net was exposed to 50 *A. sundaicus*. At 5-

min intervals, the number of dead mosquitoes was recorded and after 40 min all remaining mosquitoes were moved to clean cup and observed for 24 h. After the observations were completed, nets were washed with water and detergent for 5 min, dried and re-tested. Nets were washed 30 times. The study showed that mosquito mortality rate with adhesive permethrin and deltamethrin ITNs was 100% up to 20 washes, then decreased to 80% on 30 washes. Mosquito mortality rate with lambda-cyhalothrin ITNs was 100% after 30 washes and with the non-adhesive permethrin ITNs reduced from 100% before washing to 92% after one wash and diminished gradually to 2% after 30 washes. The study concluded that in the laboratory at least, the presence of acrylic and arthathrin was effective to maintain ITN's efficacy against *A. sundaicus*.

Despite the distribution of 2.4 million ITNs from 2004 to 2007 (World Health Organization, 2008e, 2009c), no study has yet demonstrated that this intervention actually reduces the risk of malaria or the burden of morbidity and mortality in Indonesia. No studies reveal the coverage rates required to achieve such effects, nor is there evidence that small children and pregnant women represent high-risk groups for malaria morbidity or mortality. Among Javanese transmigrants in Papua, for example, adults had a fourfold higher risk of developing severe malaria than their children (Baird et al., 1995d). Risk of a poor outcome probably varies among ethnic groups and among the very many endemic settings in Indonesia. A critical examination of ITN efficacy using a prospective, randomized and well-controlled study design of sufficient size to measure all-cause morbidity and mortality should be carried out in a setting typical of most malarious areas in Indonesia, that is, in a hypo- to mesoendemic area.

2.4.4.2.2. House screening: Ease of mosquito access to human dwellings profoundly impacts on the risk of malaria. The screening of windows, doors and open eaves represents an effective barrier to entry by feeding anophelines. Evidence shows that even simple modifications to the design of indigenous houses can protect people from mosquitoes and malaria (Kirby et al., 2009; Lindsay et al., 2002).

According to the National Economic and Social Survey (Badan Pusat Statistik, 2008) which was conducted by the Indonesian Centre of Statistics in 2008 and which surveyed over 270,000 households, 65% of houses were made of brick/cement (urban: 81% vs. rural: 51%), 23% of wood (urban: 13% vs. rural: 33%), 10% of bamboo (urban: 5% vs. rural: 15%) and 2% of other materials. Wooden and bamboo-walled houses were common in rural settings. In western Indonesia, more houses were made of brick/cement than in eastern Indonesia (western Indonesia: 65% vs. eastern Indonesia: 42%; $p = 0.002$). Wooden-walled houses were more common in eastern Indonesia (46% vs. 28%; $p = 0.044$). Bamboo walls were similarly rare in eastern and western Indonesia (6% vs. and 8%; $p = 0.719$). In West Sumba (Lesser Sundas archipelago), where stable transmission of malaria occurs, the most common type of housing consisted of wooden plank walls and dried palm leaf roofing (Ompusunggu et al., 2006). Mosquitoes enjoy free access into these traditional homes through gaps in the walls, open doors and windows or eaves.

Sanjana et al. conducted a survey of KAP towards and against malaria in and around the Menoreh Hills (Purworejo, Central Java) in 2001 (Sanjana et al., 2006). One thousand respondents were interviewed and it was reported that the walls of their houses were constructed of a variety of materials, including brick (25%), cement (20%), wooden planks (12%), bamboo (10%) or a combination of these materials (31%). Only 2% of the 1000 houses surveyed had screens over the window openings, but 72% had some or all window areas covered with glass or plastic. It also became apparent that the physical make-up of the homes was different according to whether the respondents were residents of hills/forested areas or were living in rice paddies or urban areas. Paddy/urban homes were more often

made with mixed materials than forest/hill homes (37% vs. 29%; $p = 0.007$), whilst forest/hill homes were more likely to be made from wood (15% vs. 9%; $p < 0.001$). Those living in paddy/urban homes used more glass window coverings than those in forest/hill homes (32% vs. 23%; $p = 0.003$). Cement or brick constructions were shown to afford greater protection against malaria illness than all other building materials (OR = 0.6, $p < 0.0001$). Partial glass or no glass over windows increased malaria risk (OR = 1.8, $p < 0.0001$). These findings strongly suggest that house construction and barriers to mosquito access should be targeted in malaria prevention strategies.

Roosihermiatie et al. conducted an unmatched case control study in Bacan Island, North Maluku in 1998 (Roosihermiatie et al., 2000). The residents of 11 villages made up the sample population. One hundred individuals from each village confirmed as malaria positive were selected as cases and those confirmed as malaria negative were selected as controls. A positive association between house quality and malaria was described but was extremely age-dependent. Children under 15 years of age living in temporary houses were at a higher risk of contracting malaria than children of the same age living in more permanent housing (OR = 8.7, 95% CI 1.2–386). Among adults, no such difference existed (OR = 0.7; 95% CI 0.1–3.0).

Several studies have evaluated house construction in malaria endemic areas. Sekartuti et al. conducted a cross-sectional KAP survey in two malaria endemic villages in South Lampung in 2003 (Sekartuti, 2003). Malaria prevalence in both sites combined was 17% (95/549), with a dominance of *P. falciparum* (64%). Of the 420 households interviewed, over 90% of houses lacked screens and the owners did not associate these with the prevention of malaria. Arsunan et al. conducted a KAP survey in Pangkajene Island (South Sulawesi) in 2003 (Arsunan et al., 2003). It is unclear why, but the investigators sampled only one person per household, not only for the interview, but also for the blood film examination. Among 264 households randomly selected, 8% of households were malaria positive. The authors also made a note of the characteristics of the surveyed homes and found that only 3% (8/264) used window or door screens. Suharjo et al. also conducted a KAP survey in two sub-districts in Banjarnegara (Central Java) in 2003 (Suharjo et al., 2004). One hundred households were randomly selected. Only three of these used screening. However, none of these studies analysed the possible association between house screening and the risk of malaria.

The screening of homes, where practical, may represent an effective means of avoiding the risk of malaria. This principle also extends to other effective barriers applied to floors, walls and roofing in more traditional Indonesian homes. For example, the simple act of placing inexpensive plastic floor sheeting over wood plank flooring would largely close off an otherwise easy means of entry. The availability of insecticide-treated eave covers and curtains may also dramatically reduce ease of access to humans by night-feeding anophelines. One rarely encounters these materials in rural Indonesia and awareness of their effectiveness in preventing malaria appears to be very low, as documented in the studies discussed above. More evidence from a range of ecoepidemiological settings will be needed to convince policy makers that this intervention is broadly applicable throughout malarious areas in Indonesia.

2.4.4.2.3. Personal protection: Personal protection against biting mosquitoes represents a potentially important means of diminishing the risk of malaria. Individuals may take any number of a wide range of steps to do so. The primary means of avoidance is behavioural, that is, avoiding being at locations where and when malaria transmission is likely to occur. Although of limited value to residents of endemic areas, this is an important means of risk reduction for travellers. For example, the person aware of seasonal malaria risk at any given

location avoids scheduling travel during that season and avoids being in the countryside after dusk. These measures alone may almost completely eliminate risk. The use of repellents, long sleeve shirts, pants and shoes with socks also diminish risk, and tend to be more practical for travellers than for residents.

Fumigant insecticides, like burning mosquito coils, may be effective and practical for both travellers and residents. Indeed, these represent the most common form of personal protection used in Indonesia. Several studies have documented that coil usage rates in endemic areas range from 50% to 83% (Arsunan et al., 2003; Pribadi et al., 1997; Santoso et al., 1991, 1992). Mosquito coils are inexpensive and widely available in endemic settings (Santoso, 1988). Saikhu and Gilarsi used secondary data from the BES conducted in four districts in Central Java; Banjarnegara, Pekalongan, Kebumen and Jepara (Saikhu and Gilarsi, 2003). The survey had 15,901 respondents of all ages from 4032 households. Among the 6485 expressing awareness of malaria, the most popular method of malaria prevention was the use of mosquito coils (72%). There was a small correlation between the knowledge of mosquito coils as a means of malaria prevention and a protective effect against malaria ($p = 0.035$; OR = 1.5, 95% CI 1.03–2.2). Like the KAP study in Purworejo (Sanjana et al., 2006), this survey does not serve as a demonstration of the efficacy of coils against malaria. However, the results at least suggest that mosquito coils may have some impact upon the risk of malaria.

People in Indonesia also burn rubbish, clove tree foliage or coconut leaves in a deliberate effort to repel night-feeding mosquitoes, but according to a number of studies, only between 1% and 28% of people do so (Mardiana and Santoso, 2004; Pribadi et al., 1985, 1997; Santoso, 1988; Santoso et al., 1991, 1992). People in Indonesia's rural endemic zones also use insecticide spray dispensers at rates varying between 4% and 37% (Mardiana and Santoso, 2004; Santoso and Kasnodihardjo, 1991; Santoso et al., 1991; Sukowati et al., 2003). They also tend to wear long-sleeved clothing when they go outdoors at night (Santoso and Friskarini, 2003). One study in Eastern Indonesia (Sekartuti et al., 2004c) reported that 19–42% of respondents did so. Ompusunggu et al. supposed that relatively low prevalence among infants was attributable to clothing worn during the night (Ompusunggu et al., 2006). Yahya et al. described the willingness of mothers to use mosquito coils and wear appropriate clothing to protect their children (Yahya et al., 2006). Nonetheless, few children actually wore the most effective protective clothing. For example, they would wear a jacket or sarong, but would have no shoes or socks.

As with household screening, personal protection appears to hinge upon awareness of malaria and the means of its transmission. In contrast to household screening, however, personal protection measures among residents of endemic Indonesia seem varied and quite common, which is likely to be driven by the nuisance factor of night-feeding mosquitoes. The rates of mosquito coil usage, for example, seem unusually high in light of the correspondingly low rates of both bed net usage and screening. Coils are not provided through government programs (in contrast to ITNs), and are relatively inconvenient (igniting the coil and enduring its smoky product). Leveraging this positive behaviour to improving barriers to entry into homes and beds seems an obvious means of ramping up the effectiveness of malaria control.

2.4.4.2.4. Zooprophylaxis: Zooprophylaxis is defined by the WHO as 'the use of wild or domestic animals, which are not the reservoir hosts of a given disease, to divert the blood-seeking mosquito vectors from the human hosts of that disease' (Bouma and Rowland, 1955). It may be active or passive. Active zooprophylaxis is a reduction in malaria or human biting resulting from the deliberate deployment of domestic animals as a barrier between mosquito breeding sites and human settlements (Bouma and Rowland, 1955; Seyoum et al.,

2002). Passive zooprophylaxis is the serendipitous reduction in malaria purported to occur when cattle density increases within a community (Bulterys et al., 2009; Giglioli, 1963). Several studies in Indonesia have explored the possibility of zooprophylaxis as a malaria control tool.

Kirnowardoyo and Supalin evaluated the association between cattle shelter location and *A. aconitus* contact with humans (Kirnowardoyo and Supalin, 1982). At three villages in Wonosobo and four villages in Purworejo (both in Central Java) in 1981–1982, it was found that those people who had cattle shelters in or attached to their homes had man-landing rates which were 4.6 times higher than the rates for people who had their cattle shelters separated from the house (3.2 vs. 0.7 mosquito/man-hour; $p = 0.076$). The proportion of captured anophelines found to have taken a human blood meal was higher among homes with cattle shelters attached (5.9% vs. 0.5%; $p = 0.076$). Kirnowardoyo and Supalin concluded that the placement of cattle away from human dwellings appeared to divert *A. aconitus* and reduce man-mosquito contact (Kirnowardoyo and Supalin, 1986). This species of mosquito is known to prefer feeding on animals rather than humans, which will certainly have had an impact on the outcome of this evaluation. When mosquito preferences lean toward human biting, outcomes may be radically different and the strategies concerning cattle placement would thus also be completely different.

Boewono et al. investigated the effect of cattle shelter placement on indoor densities of *A. aconitus* in Kendal (Central Java) in 1986 (Boewono et al., 1991). In the study area, the ratio of people to cattle was 12:1. They studied four groups: houses with cattle shelter inside (4), houses with cattle shelter attached (4), houses with cattle shelter 20 m from dwelling (4) and houses with no cattle shelter (2). They found a sixfold higher mosquito density in homes with an indoor cattle shelter than in the homes with a distant cattle shelter, as well as the two homes with no cattle shelter. This value was fourfold when compared to homes with a cattle shelter attached. This accords with the zoophilic feeding behaviour of *A. aconitus*.

2.4.4.3. Control of adult mosquito

2.4.4.3.1. Indoor residual spraying: IRS is the application of long-acting chemical insecticides on the walls, doors and ceilings of all houses and domestic animal shelters in a given area in order to kill the adult vector mosquitoes that land and rest on these surfaces (World Health Organization, 2006a). The indoor spraying of chemicals that have a relatively long residual effect, typically 2–6 months, remains a vitally important means of reducing the risk of malaria (World Health Organization, 2008e). In addition to possible protection arising from the excito-repellancy of some insecticides (i.e. the scent of the insecticide forces mosquitoes to fly away from the house), insecticide kills mosquitoes that rest on interior surfaces before or, more often, after feeding on humans. The efficacy of IRS thus hinges upon the feeding behaviour of the local anopheline species responsible for malaria transmission. Some species do not prefer feeding indoors (exophagic), or they may tend to fly directly outdoors without resting on interior walls. Efficacy also depends upon the dose and degree of coverage of the interior surfaces of the home. Moreover, as with ITNs, protection improves if more homes in any given area are covered by this form of control. One of the greatest pitfalls of IRS is the infrastructure required to deliver it safely and effectively. The selection of insecticide and its safe application requires relatively large numbers of people with highly specialized training and equipment (Oemijati, 1980).

Table 2.12 shows the evolution of recommended insecticides for malaria control in Indonesia. According to the WHO expert committee on pesticides (often referred to as WHOPES) in 2009, 12 insecticides belonging to four chemical classes are recommended for IRS (World Health Organization, 2007a). These insecticides included the pyrethroid class (alpha-cypermethrin, bifentrin, cyfluthrin, deltamethrin, etofenprox and lambda-

cyhalothrin), carbamate class (bendiocarb, propoxur), organophosphates (fenitrothion, malathion, pirimiphos-methyl) and organochloride (DDT). According to the Indonesian MoH released in 2003 and 2010 (Departemen Kesehatan, 2003c, 2010), six insecticides belonging to two of these classes may be applied for IRS: pyrethroids (alpha-cypermethrin, bifentrin, deltamethrin, etofenprox and lambda-cyhalothrin) and carbamates (bendiocarb). Earlier, the Indonesian MoH had recommended organophosphates for IRS (fenitrothion, malathion, pirimiphos-methyl).

According to the Indonesian MCP guidelines, IRS is targeted at endemic areas with an API > five cases per 1000 population, areas with malaria positive infants or areas with a high potential of malaria outbreak (Departemen Kesehatan, 2006a). The guidelines suggest that IRS be conducted 2 months prior to the median peak of malaria case numbers. The median value is derived from the last 3–5 years of monthly malaria cases. Alternatively, spraying should be done 1 month before the peak density of the local malaria vector (Departemen Kesehatan, 2006a). IRS is aimed at houses, ‘dangau/saung’ (small wooden or bamboo shelters in ricefields where farmers wait for the rice harvest), animal shelters and public places where evening activities are common. The guidelines recommend full coverage with IRS to a height of 3 m. Several studies in Indonesia have explored the effects of this application of insecticides against malaria vectors.

The following sections (Sections 2.4.4.3.1.1–2.4.4.3.1.12) include insecticide-specific summaries of the available published evidence for efficacy and tolerability of these chemicals in Indonesia. Some useful information may be gleaned from these many studies with respect to guidance on dosage and manner of application. However, we have found no published reports of village-randomized trials of these interventions. Although many of the available data do suggest good levels of efficacy and tolerability, one may argue that convincing evidence of this has yet to be generated in Indonesia.

2.4.4.3.1.1. Alpha-cypermethrin: Alpha-cypermethrin is a synthetic pyrethroid. It has a high-knockdown effect and a strong excito-repellent effect on anophelines (Najera and Zaim, 2001). It acts by blocking nerve impulses by stopping the passage of sodium ions through channels in the nerve membranes. This insecticide is classified by the WHO as a moderately hazardous chemical (World Health Organization, 2006b). Typically, intoxication of the mosquito results in a rapid knockdown effect and high-mortality rate (World Health Organization, 2007b). The dosage recommended by the WHO is 0.02–0.03 g/m^2, giving a residual effect of 4–6 months (World Health Organization, 2007a). The Indonesian MoH recommended alpha-cypermethrin wettable powder (WP) at a dosage of 0.02 g/m^2 for IRS (Departemen Kesehatan, 2003c, 2010). Several studies in Indonesia have explored the application of this insecticide against malaria vectors.

Barodji et al. conducted a village-scale trial of cypermethrin 20% WDP applied as a residual spray at a dosage of 0.5 g/m^2 against DDT-resistant *A. aconitus* in Semarang (Central Java) in 1981 (Barodji, 1982; Barodji et al., 1983). IRS was carried out for 479 households with insecticide usage averaging 0.58 kg/house. *A. aconitus* mosquitoes were collected indoors and outdoors 1 week before application and then every week after the application for 21 weeks. A direct contact test at dosage 0.5 g/m^2 of cypermethrin on wooden and bamboo surfaces was conducted every 3 weeks for 24 weeks. It was found that cypermethrin did not reduce indoor mosquito landing (before application: 0.5 vs. after: 0.7 mosquito/man-hour) or outdoor landing (before: 1.4 vs. after: 1.3 mosquito/man-hour). There was an increase of 35% in morning resting density (before: 3.4 vs. after: 4.6 mosquito/man-hour). Only a 9% reduction of the natural outdoor resting density was achieved (before: 95 vs. after: 86 mosquito/man-hour). A direct contact test showed that the insecticide residue could last for 15 weeks on wooden and bamboo surfaces (mosquito mortality rate 91% on both surfaces).

Barodji et al. concluded that cypermethrin was ineffective against *A. aconitus* in Central Java.

Barodji et al. experimented with the IRS application of alphamethrin 5% water dispersible powder (WDP) at a dosage of 0.1 g/m^2 against DDT-resistant *A. aconitus* at Kendal (Central Java) in 1985 (Barodji et al., 1989). The IRS program involved the spraying of 1254 houses with an average of 0.02 kg insecticide/house. *A. aconitus* mosquitoes were collected indoors and outdoors 2 weeks before application and every 2 weeks after application for 12 weeks. A direct contact test at a dosage of 0.02 g/m^2 alphamethrin on wooden and bamboo surfaces was conducted 2 weeks after application and measured monthly afterwards. It was revealed that the insecticide reduced the indoor mosquito landing density by only 16% (before: 0.45 vs. after: 0.38 mosquito/man-hour) and did not reduce outdoor mosquito landing rate, but rather seemed to cause an increase of 57% (before: 0.37 vs. after: 0.95 mosquito/man-hour). A reduction of 46% in morning resting density was found (before: 2.8 vs. after: 1.5 mosquito/man-hour), while at natural outdoor resting sites a more modest decrease of 15% occurred (before: 57.5 vs. after: 49.1 mosquito/man-hour). A direct contact test showed that on day 16 the mosquito mortality rate had reduced from 100% to less than 60% on wood and less than 20% on bamboo surfaces. Alphamethrin therefore appears to be ineffective when applied on wooden or bamboo surfaces. As in the previous study, this insecticide was ineffective in reducing *A. aconitus* mosquito landing density in Kendal (Central Java). The low efficacy of alphamethrin may have been caused by the relatively low dosage compared to the trial at Semarang, Central Java (Barodji, 1982; Barodji et al., 1983). However, the authors did not explain the rationale of using a lower dosage in this trial.

Boewono et al. conducted excito-repellency tests of alpha-cypermethrin at dosages of 0.0125, 0.025 and 0.05 g/m^2 against *A. sundaicus* at Purworejo (Central Java) in 2000 (Boewono et al., 2002) The box interior was coated with insecticide. The test ran for 60 min with eight replications. Each replication used 25 mosquitoes, giving a total of 200 mosquitoes evaluated at each dose. The number of mosquitoes able to exit the test box was recorded. Slightly more mosquitoes exited the test box at a dosage of 0.05 g/m^2 (17%) compared to the dosage of 0.025 g/m^2 (12%; $p = 0.16$), the dosage of 0.0125 g/m^2 (9%; $p = 0.02$) and the control (9.5%; $p = 0.027$). In other words, at higher doses, mosquitoes tend to avoid the insecticide sprayed surfaces. By considering the dosage recommended by the WHO (0.03 g/m^2; World Health Organization, 2007a) and the closest dosage evaluated, that is, 0.025 g/m^2, about 88% of the mosquitoes would be expected to die after exposure. The authors concluded that an IRS program with alpha-cypermethrin would be likely to be effective against *A. sundaicus* in coastal areas of Purworejo (Central Java).

2.4.4.3.1.2. Bifentrin: This insecticide is classified by the WHO as moderately hazardous (World Health Organization, 2006b). The dosage recommended by the WHO is 0.025–0.05 g/m^2 and should remain effective up to 6 months (World Health Organization, 2007a). The Indonesian MoH recommends bifentrin 10% WP at a dosage of 0.025 g/m^2 for IRS (Departemen Kesehatan, 2003c, 2010). Several studies in Indonesia have explored the application of bifentrin against malaria vectors.

Barodji et al. measured the efficacy of bifentrin 10% WP at doses of 0.025, 0.05, 0.1 and 0.15 g/m^2 against *A. maculatus* at Salatiga (Central Java) in 2000 (Barodji et al., 2000). Mosquito mortality was observed weekly for 6 months. At 6 months post-application, the dosage of 0.15 g/m^2 was effectively killing *A. maculatus* on wood (98%), bamboo and cement surfaces (100%). Also at 6 months post-application, the dosage of 0.1 g/m^2 bifentrin was killing 84% of mosquitoes on wood, 100% on bamboo, but was less effective on cement (48%). The dosage of 0.05 g/m^2 was ineffective on wood (40%) and cement (46%), but remained effective on bamboo surfaces (96%). At the lowest dose (0.025 g/m^2), bifentrin

was ineffective on all types of surfaces (mortality < 14%). Barodji et al. recommended the use of a dosage of 0.1 or 0.15 g/m^2 against *A. maculatus* in Central Java.

In 2006, Sunaryo et al. evaluated the effect of bifentrin spraying (with a dosage of 0.025 g/m^2) in Kebumen (Central Java) 35 days after application in response to a malaria outbreak driven by *A. maculatus*, *A. aconitus* and *A. balabacensis* (Sunaryo et al., 2007). Wood, bamboo and cement surfaces from six houses were sprayed. Mortality was observed for 24 h. They found 94% mortality on wood, 83% on bamboo and 64% on cement surfaces. It appears that cement surfaces absorbed more insecticide than other surface types and the insecticide remaining on the surface was insufficient to effect a kill.

2.4.4.3.1.3. Cyfluthrin: Cyfluthrin is a synthetic pyrethroid insecticide which is effective against a wide variety of agricultural and public-health pests (World Health Organization, 2003c). Its mode of action is characterized by interference with nerve signalling by inhibition of the membrane sodium channel systems in the target organism. Cyfluthrin is mainly a contact insecticide classified as moderately hazardous (World Health Organization, 2006b). It has a very high-knockdown and low excito-repellent effect (Najera and Zaim, 2001). It is also known by the name baythroid (World Health Organization, 2003c). The WHO recommends a dosage of 0.02–0.05 g/m^{2,} giving a residual effect lasting three up to 6 months (World Health Organization, 2007a). The Indonesian MoH does not recommend this insecticide for IRS as part of its insecticide rotation cycle policy (Departemen Kesehatan, 2003c). Several studies have explored the application of cyfluthrin against malaria vectors in Indonesia.

Barodji et al. investigated the impact of cyfluthrin IRS against *A. barbirostris*, *A. subpictus* and *A. sundaicus* in East Flores (Lesser Sundas) in 1996 (Barodji et al., 2004b). They applied a dosage of 0.05 g/m^2 with a single application. Indoor and outdoor human-landing collections were measured before application, and then again 3 and 6 months after application. No physical complaints were reported from villagers or sprayers. For *A. barbirostris*, they found that the indoor man-landing rate declined from 6.4 mosquito/man-hour before application to 4.6 mosquito/man-hour at 3 months (reduction: 28%) and 4.8 mosquito/man-hour at 6 months (reduction: 25%). The outdoor man-landing rate reduced from 5.2 mosquito/man-hour before application to 4.4 mosquito/man-hour at 3 months (reduction: 16%), but increased again by 33% to 5.4 mosquito/man-hour at 6 months. For *A. subpictus*, the indoor man-landing rate reduced from 14.3 mosquito/man-hour before application to 7.9 mosquito/man-hour at 3 months (reduction: 45%) and 2.6 mosquito/man-hour at 6 months (reduction: 86%). The outdoor man-landing rate decreased from 20.5 mosquito/man-hour before application to 16.7 mosquito/man-hour at 3 months (reduction: 19%) and to 1.5 mosquito/man-hour at 6 months (reduction: 93%). For *A. subpictus*, the indoor man-landing rate declined from 14.3 mosquito/man-hour before application to 7.9 mosquito/man-hour at 3 months (reduction: 45%) and 2.6 mosquito/man-hour at 6 months (reduction: 86%). The outdoor man-landing rate decreased from 20.5 mosquito/man-hour before application to 16.7 mosquito/man-hour at 3 months (reduction: 19%) and to 1.5 mosquito/man-hour at 6 months (reduction: 93%). For *A. sundaicus*, the indoor man-landing rate declined from 4.2 mosquito/man-hour before application to zero at 3 and 6 months after application (reduction: 100%). The outdoor man-landing rate reduced from 4.5 mosquito/man-hour before application to 0.04 mosquito/man-hour at 3 months (reduction: 99%) and to zero at 6 months (reduction: 100%). They concluded that cyfluthrin at a dosage of 0.05 g/m^2 was effective in reducing man-vector contact in the case of *A. sundaicus*, but not in the case of *A. barbirostris* and *A. subpictus*. The SPR among residents in the area sprayed was 39% (63/162) before spraying. This fell to 11% (16/145) at 3 months post-application and to 3% (4/158) at 6 months.

2.4.4.3.1.4. Delthamethrin: Deltamethrin is a synthetic pyrethroid which has been used in malaria control in Indonesia since the late 1970s (Najera and Zaim, 2001; World Health Organization, 2008d). Its mode of action is primarily upon the basal ganglia causing repetitive nerve action (Najera and Zaim, 2001). This insecticide is classified by the WHO as a moderately hazardous insecticide. It is used at dosages of 0.02–0.025 g/m^2, giving a residual effect of three up to 6 months (World Health Organization, 2007a). The Indonesian MoH recommends deltamethrin 5% WP at a dosage of 0.2 g/m^2 for IRS (Departemen Kesehatan, 2003c, 2010). We found no published IRS study of deltamethrin against malaria vectors in Indonesia.

2.4.4.3.1.5. Etofenprox: Etofenprox is a synthetic non-ester pyrethroid which has high vapour pressure and low water solubility (World Health Organization, 2006g). It is classified by the WHO as unlikely to pose an acute hazard in normal use as a residual insecticide (World Health Organization, 2006b). It disturbs nerve impulses in insect nerve axons (Najera and Zaim, 2001). The WHO recommends a dosage of 0.1–0.3 g/m^2, giving a residual effect of three up to 6 months (World Health Organization, 2007a). The Indonesian MoH recommends etofenprox 20% WP at a dosage of 0.1 g/m^2 for IRS (Departemen Kesehatan, 2003c, 2010). An operational study has affirmed good results for etofenprox in Indonesia.

Nalim et al. conducted a trial of etofenprox in East Flores (Lesser Sundas) in 1994 (Nalim et al., 1997). They applied 0.2 g/m^2 three times at 6-month intervals. The suspected vectors were *A. sundaicus*, *A. barbirostris*, *A. flavirostris* and *A. maculatus*. Human-landing rates and resting densities were measured every 2 weeks for 16 months. A direct contact test was conducted on wooden and bamboo surfaces. Mosquito mortality was observed for 24 h in the 240 sprayed homes. The direct contact test showed that the insecticide remained efficient for up to 4 months on wooden surfaces and for 5 months on bamboo. The human-landing rate decreased from 0.91 mosquito/man-hour before application to 0.23 mosquito/man-hour at 6 months, 0.004 mosquito/man-hour at 12 months and zero at 18 months. Likewise, the indoor resting density dropped from 0.9 mosquito/man-hour before application to 0.1 mosquito/man-hour at 6 months, dropping further to zero and remaining there at 12 and 18 months of IRS. Despite this apparently superb activity, they found no significant reduction in SPR among residents in the earlier stages of implementation: 30.6% before spraying; 30% at first cycle; and 21% ($p = 0.054$) at second cycle. However, a significant reduction of SPR was observed at 18 months after application (8%; $p < 0.001$). No physical complaints were reported from villagers or sprayers. Nalim et al. concluded that their study was a good demonstration of the efficacy and tolerability of this insecticide.

2.4.4.3.1.6. Lambda-cyhalothrin: Lambda-cyhalothrin is a synthetic pyrethroid (World Health Organization, 2006e). It has a low vapour pressure, is essentially insoluble in water, and has low volatility (Najera and Zaim, 2001). The WHO classifies this insecticide as moderately hazardous (World Health Organization, 2006b). It is used at a dosage of 0.02–0.03 g/m^2, giving a residual effect of 3–6 months (World Health Organization, 2007a). The Indonesian MoH recommends lambda-cyhalothrin 10% WP at a dosage of 0.025 g/m^2 for IRS (Departemen Kesehatan, 2003c, 2010). We found no publications about the use of lambda-cyhalothrin against malaria vectors in Indonesia.

2.4.4.3.1.7. Bendiocarb: Bendiocarb is a carbamate insecticide (World Health Organization, 2008a). It has a low vapour pressure and low odour (Najera and Zaim, 2001). The WHO classifies it as moderately hazardous (World Health Organization, 2006b). The WHO recommends a dosage of 0.1–0.4 g/m^2, giving a residual effect of two up to 6 months (World Health Organization, 2007a). The Indonesian MoH recommends bendiocarb 80%

WP at a dosage of 0.2 g/m^2 for IRS (Departemen Kesehatan, 2003c, 2010). Three studies have been performed, documenting the efficacy of bendiocarb in Indonesia.

Fleming et al. conducted a village-scale trial of bendiocarb against *A. aconitus* in Central Java in 1981 (Fleming et al., 1983). Bendiocarb 80% WP at a dosage of 0.4 g/m^2 was only effective in reducing human-vector contact with *A. aconitus* within the first 2 months. Residual efficacy by direct contact test lasted less than 2 weeks when sprayed on wooden or bamboo surfaces. However, in natural resting catches, bendiocarb was effective for 8 weeks.

Barodji et al. evaluated the efficacy of bendiocarb at a dosage of 0.4 g/m^2 against *A. maculatus* and *A. sinensis* between 1996 and 1997 (Barodji et al., 1997). *A. maculatus* mosquitoes used for the test were obtained from Kulonprogo (Yogyakarta) and *A. sinensis* from Nias (North Sumatra). Mosquito mortality rates were observed 2 weeks post-application, and then monthly for 6 months. The mortality rates for *A. maculatus* and *A. sinensis* were 100% on wooden, bamboo and cement surfaces for up to 4 months. However, at 5 months mortality rates for *A. maculatus* decreased to 37% on wood, 33% on bamboo and 83% on cement. Mortality rates for *A. sinensis* were reduced by 53% on wood, 70% on bamboo and 83% on cement. Wooden and bamboo surfaces failed to retain residual activity. The authors concluded that bendiocarb spraying at 0.4 g/m^2 on cement surfaces was effective against *A. maculatus* and *A. sinensis*.

Bonsall et al. conducted safety studies of bendiocarb in a field trial in 1981 (Bonsall et al., 1981). Two of 16 sprayers experienced mild toxic effects of short duration. Although no complaints were received from the villagers after the spraying of over 800 homes, 39 ducklings died and this was attributed to spraying.

2.4.4.3.1.8. Propoxur: Propoxur is a carbamate insecticide which has been used for IRS since the early 1970s (Najera and Zaim, 2001). The WHO classifies it as a moderately hazardous chemical (World Health Organization, 2006b). Propoxur inhibits acetylcholinesterase activity (World Health Organization, 2003b). Acetylcholinesterase is an enzyme which is responsible for hydrolysis of the neurotransmitter acetylcholine (Carlier et al., 2008). Acetylcholine is a nerve system which sends messages between nerves. The recommended dosage is 1–2 g/m^2, giving a residual effect of 3–6 months (World Health Organization, 2007a). The Indonesian MoH does not recommend this insecticide for IRS as part of its insecticide rotation cycle policy (Departemen Kesehatan, 2003c). We found no publications describing the use of propoxur in Indonesia.

2.4.4.3.1.9. Fenitrothion: Fenitrotion is an organophosphate insecticide used extensively in IRS since the 1970s (Najera and Zaim, 2001). The WHO classifies it as a moderately hazardous chemical (World Health Organization, 2006b). The recommended dosage is 2 g/m^2, giving a residual effect of three up to 6 months (World Health Organization, 2007a). The Indonesian MoH does not recommend this insecticide for IRS on the basis of the perception of a low margin of safety (Departemen Kesehatan, 2003c). Nonetheless, several studies have examined the application of fenitrotion against malaria vectors in Indonesia.

Joshi et al. conducted a village-scale fenitrotion trial against *A. aconitus* in Semarang (Central Java) in 1976 (Joshi et al., 1977). A dosage of 2 g/m^2 retained residual lethal activity for 23 and 25 weeks on bamboo and wooden surfaces, respectively. Other studies in the 1980s reported that insecticide activity would only last 14–18 weeks on similar surfaces (Bang et al., 1981; Sukowati et al., 1979).

Suwarto et al. measured the efficacy of fenitrothion 40% WDP at a dosage of 2 g/m^2 against *A. aconitus* between full (0–300 cm above floor) versus selective (10–85 cm above floor)

coverage in Banjarnegara (Central Java) in 1981 (Suwarto et al., 1987). Spraying was conducted in two cycles at 6-month intervals. The number of houses sprayed in each cycle was 12,763 (full coverage) and 10,699 (selective coverage). The amount of insecticide used for selective coverage was of course much less than full coverage (0.48 vs. 1.4 kg/house; $p < 0.001$). In other words, there was a potential saving of 65%. The average number of houses sprayed each day using selective coverage was two times the number sprayed using full coverage (12 vs. 6 house/day; $p < 0.001$). A further 50% of cost savings could therefore be made. Indoor mosquito landing rates declined from 0.49 mosquito/man-hour before application to zero at 12 months post-application using full coverage (reduction 100%) and from 1.29 to 0.16 mosquito/man-hour using selective coverage (reduction 88%). Outdoor mosquito landing rates declined from 3.79 mosquito/man-hour before application to 0.03 at 12 months post-application using full coverage (reduction 99%), and from 0.37 to 0.04 mosquito/man-hour using selective coverage (reduction 89%). Natural outdoor mosquito landing rates decreased from 14.4 mosquito/man-hour before application to 0.04 at 12 months post-application using full coverage (reduction 99%) and from 7.3 mosquito/man-hour to 0.04 mosquito/man-hour using selective coverage (reduction 99%). Selective coverage provided a substantial impact on man-vector contact. The authors recommended that full coverage should be applied only during the first cycle, with selective coverage applied during the subsequent cycles. Gandahusada et al. reported that there were no serious cases of intoxication among the sprayers (Gandahusada et al., 1984). However, of 203 sprayers, a small number were hospitalized for observation because of minor complaints, which might possibly have been associated with exposure.

Barodji et al. measured the efficacy of fenitrotion at 1 g/m^2 against *A. maculatus* and *A. sinensis* between 1996 and 1997 (Barodji et al., 1997). *A. maculatus* mosquitoes were obtained from Kulonprogo (Yogyakarta) and *A. sinensis* from Nias (North Sumatra). The mosquito mortality rate was recorded at 2 weeks post-application, and then monthly for 6 months. Against *A. maculatus*, they found 100% mortality up to 3 months on wood, 2 months on bamboo and 1 month on cement. At 6 months after application, mortality of *A. maculatus* was 63% on wood, 67% on bamboo and 60% on cement. Against *A. sinensis*, they found 100% mortality up to 2 months post-application on wood, and a month on either bamboo or cement. At month 3, mortality of *A. sinensis* reached only 7% on all types of surfaces. Fenitrotion IRS at 1 g/m^2 was only really effective against *A. maculatus* and *A. sinensis* on wood surfaces (on bamboo and cement the duration of lethal activity was unacceptably brief).

Barodji et al. conducted an operational-scale trial of fenitrotion in East Flores (Lesser Sundas) in 1995 (Barodji et al., 2004c). The local vectors were *A. sundaicus*, *A. barbirostris*, *A. flavirostris* and *A. maculatus*. In three sub-villages in Lewo Bunga, they applied full coverage at 1 g/m^2 for one single cycle in a year, and in three sub-villages in Ebak, they applied 0.5 g/m^2 for two cycles with a 6-month interval. Indoor and outdoor human-landing collection and indoor resting density were measured every 3 months for 12 months. Direct contact tests were conducted on wooden and bamboo surfaces. At the 1 g/m^2 dosage, at 12-months post-application, the indoor human-landing rate fell from 15.8 to 0.2 mosquito/man-hour (reduction: 99%). Likewise, the outdoor human-landing rate fell from 19.9 to 0.1 mosquito/man-hour (reduction: 99%). Resting density decreased from 0.05 mosquito/man-hour to zero (reduction: 100%). At the 0.5 g/m^2 dosage, 12 months post-application, the indoor human-landing rate decreased from 0.92 to 0.25 mosquito/man-hour (reduction: 73%). The outdoor man-landing rate fell from 1.97 to 0.02 mosquito/man-hour (reduction: 99%). The indoor resting density decreased from 1.7 mosquito/man-hour to zero (reduction: 100%). The 1 g/m^2 dosage effectively reduced mosquito density. Direct contact tests showed that 1 g/m^2, at 2 months post-application, achieved 100% mortality on wooden, but only 70% on bamboo surfaces. Mortality fell to 90% on wood and 40% on bamboo at 3

months. Effective mortality lasted only 1 month on bamboo. At 9 months post-first application, the apparent effects upon SPR in the treated villages were very similar for 1 g/m^2 (before application: 26%, 35/134 vs. at 9 months post-first application: 9%, 11/123; $p < 0.001$) and for 0.5 g/m^2 (30%, 38/127 vs. 8%, 10/124; $p < 0.001$). No complaints from residents or sprayers were noted.

2.4.4.3.1.10. Malathion: Malathion is an organophosphorus insecticide widely used in malaria control since the 1960s (Najera and Zaim, 2001). It has low vapour pressure, moderate water solubility and low toxicity (World Health Organization, 2003d). It has quite a strong and generally unpleasant odour. The WHO classifies it as a slightly hazardous insecticide (World Health Organization, 2006b) and recommends a dosage of 2 g/m^2, giving a residual effect of 2–3 months (World Health Organization, 2007a). The Indonesian MoH does not recommend this insecticide for IRS against malaria vectors, but it does recommend it for Aedes control (Departemen Kesehatan, 2003c, 2010). In general, this insecticide is applied as a quick knockdown of adult mosquitoes in outbreak settings.

A study in the 1980s explored the application of malathion as IRS in Jombang (East Java; Martono, 1988). The investigators applied full coverage, at 2 g/m^2 for one cycle, lasting a year, to 1100 houses. Human landing and indoor resting densities were measured before application and at 3 months post-application. The indoor human-landing rate fell from 0.6 mosquito/man-hour to 0.06 mosquito/man-hour (reduction: 90%). Likewise, the outdoor human-landing rate fell from 4.5 to 0.5 mosquito/man-hour (reduction: 89%). The morning resting density decreased from 1.3 to 0.4 mosquito/man-hour (reduction: 69%). The SPR dropped significantly at 3 months post-application (before application: 2.3%, 22/951 vs. after: 0.2%, 2/1015; $p < 0.001$). Although the authors declared this insecticide to be very effective, the powerful and unpleasant odour of this chemical probably explains why the MoH does not recommend it for IRS.

2.4.4.3.1.11. Pirimiphos-methyl: Pirimiphos-methyl is an organophosphorus insecticide (World Health Organization, 2006i). It is classified by the WHO as a moderately hazardous chemical (World Health Organization, 2006b). Application of 1–2 g/m^2 gives a residual effect for 2–3 months (World Health Organization, 2007a). The Indonesian MoH does not recommended this insecticide for IRS as part of its insecticide rotation cycle policy, but it does recommend it for *Aedes* control (Departemen Kesehatan, 2003c, 2010). Trials were carried out with a 25% WDP formulation at a dosage of 2 g/m^2 (Shaw et al., 1979) and with a 50% EC formulation at dosage of 1 g/m^2 (Supalin et al., 1979). Shaw et al. reported that the pirimiphos-methyl maintained better than 70% mortality for about 12 weeks. Supalin et al. reported essentially similar findings.

2.4.4.3.1.12. DDT: DDT is the only organochlorine still recommended for IRS. Other organochlorines, for example, dieldrin, were abandoned due to relatively high toxicity to humans (Najera and Zaim, 2001). The WHO classifies it as a moderately hazardous chemical (World Health Organization, 2006b). A 1–2 g/m^2 application gives a residual effect of more than 6 months (World Health Organization, 2007a). DDT resistance has been reported from Indonesia (Bangs et al., 1993; Soerono et al., 1965). The Indonesian MoH does not recommend this insecticide for any purpose (Departemen Kesehatan, 2003c, 2010). The environmental contamination from DDT, caused by the illegal diversion of the insecticide to agricultural use (Najera and Zaim, 2001), underpins the government's prohibition of DDT. The last application of DDT in Indonesia was in 1992 (World Health Organization, 1998). A study in the 1980s (Martono, 1988) documented modest effects on SPR (3.7% vs. 1.4%; $p = 0.006$), a relatively modest decrease in indoor human-landing rates (0.4 to 0.1 mosquito/man-hour) and a sharp increase in outdoor human-landing rates (2.9 to 6.8 mosquito/man-hour), the latter observation being consistent with the well-known

powerfully repellent properties of DDT. In 1982, Gandahusada et al. also reported that the application of DDT had no impact on the malaria tranmission between treated sites and non-treated sites (5%, 91/1,807 vs. 6%, 77/1,254; Z-test, p = 0.187) during three years of study (1979-1981) in South Kalimantan (Gandahusada et al., 1982).

2.4.4.3.2. Cattle shelter indoor residual spraying: During the 1980s, investigators in Indonesia investigated the impact of cattle shelter spraying as a supplement to IRS of human dwellings. Today, the MoH recommends cattle shelter IRS (Departemen Kesehatan, 2006a). According to the BHS (National Institute of Health Research and Development, 2008) in 2007, 9% of Indonesian households raised livestock such as cattle and horses. One percent of households kept the cattle shelters inside the house and about 8% kept them outside the house.

Barodji evaluated the impact of cattle shelter spraying on *A. aconitus* at Jepara (Central Java) in 1983 and 1984 (Barodji, 1985). Two villages in Mlonggo sub-district were selected as intervention sites. DDT-resistant *A. aconitus* has been reported at those sites. SPR at the intervention sites was 12% (1516/9509). In the first year, fenitrotion IRS was applied monthly at 2 g/m^2, and in the second year of the study, it was applied every 2 months. A census was carried out on population homes, cattle and their shelters. The ratio of people to cattle was 14:1 and the ratio of homes to shelters was 7:1. Cattle shelters were typically either attached to the owner's home or standing nearby. *A. aconitus* is characteristically zoophilic and occurs in greatest abundance in and around cattle shelters. Approximately 3000 cattle shelters were sprayed monthly. Barodji found that within a year, reductions of human-vector contact occurred at human dwellings; five times lower indoors (from 0.15 to 0.03 mosquito/man-hour), nine times lower outdoors (from 0.77 to 0.09 mosquito/man-hour) and eight times lower in cattle shelters (from 9.5 to 1.2 mosquito/man-hour). However, when the frequency application was reduced from monthly applications to bimonthly applications, human-vector contact increased once again among human dwellings becoming four times higher indoors (from 0.03 to 0.13 mosquito/man-hour), three times higher outdoors (from 0.09 to 0.29 mosquito/man-hour) and three times higher in cattle shelters (from 1.2 to 3.5 mosquito/man-hour). They also found that, following monthly application, SPR fell significantly from baseline levels (baseline: 15.9%, 1516/9509 vs. monthly: 5.8%, 797/13,724; $p < 0.001$). During the bimonthly cycles, SPR increased slightly (monthly: 5.8%, 797/13,724 vs. bimonthly: 7.5%, 869/11,524 vs; $p < 0.001$). Cattle shed IRS did not seem to cause *A. aconitus* to become less zoophilic or more anthropophilic, that is, to switch its feeding preferences from the protected cattle to unprotected humans. The proportion of mosquitoes with animal blood in their gut was not significantly different before versus after application (92%, 92/100 vs. 87%, 215/248; $p = 0.165$). Contact susceptibility tests of fenitrothion against *A. aconitus* after 15 applications showed 100% mortality. Repetitive applications did not decrease susceptibility of *A. aconitus* to fenitrothion. Monthly cattle shelter IRS for 12 months brought a saving of 78% of insecticide compared to two cycles IRS applied in a year (Barodji, 2003). The authors concluded that cattle shelter IRS could diminish the risk of malaria in areas where *A. aconitus* represents an important vector of malaria. Nalim reported similar findings at Banjarnegara (Central Java) in 1985 (Nalim, 1986).

2.4.4.4. Community knowledge—IRS is by its nature invasive upon private citizens, and community support represents an essential and sometimes hard-won element of success. Several studies in Indonesia have explored this dimension of IRS. Saikhu et al. used secondary data from the BES by the Indonesian National Institute for Health Research and Development and the Centre of Statistics in 2001 (Saikhu and Gilarsi, 2003). The study surveyed 15,902 people from 4032 households in four districts (Banjarnegara, Kebumen, Jepara and Pekalongan) in Central Java. Only 11% understood that IRS was a tool for

malaria control. No association was found between ignorance of the utility of IRS and the risk of malaria (OR = 0.06; 95% CI 0.9–5), nor was there any association between the latter and attitude regarding IRS (OR = 1.3, 95% CI 0.6–3.0). Four percent of respondents did not want IRS due to its effects on the home, that is, foul smell, fouling the furniture and fear of toxicity.

The KAP study by Sanjana et al. at Purworejo (Central Java) involved 1000 randomly selected households (Sanjana et al., 2006). Among the 50 villages sampled, 15–100% of households had been sprayed in the past year. Paddy/urban residents reported less spraying activity in the past year compared to hill/forest residents (10% vs. 30%). Most malaria transmission during the malaria epidemic occurred in the hills and forested areas. The odds of malaria illness in the past year for houses sprayed with insecticide within that year were significantly higher than among houses sprayed more than 1 year ago (OR = 1.6, $p = 0.03$). This is not evidence of the poor efficacy of IRS, but it points instead to a selection bias imposed by the health authorities who direct their limited resources to the areas at highest risk. Spray operations were often sporadic in response to ongoing malaria outbreaks. There was no universal coverage. When asked if respondents would be willing to pay Rp. 30,000 (~US$ 3) to have their house sprayed, only 45 respondents (5%) said yes; however, 989 respondents (99%) would agree to have their house sprayed if the service was offered at no charge. The acceptability of IRS during a period of epidemic malaria may be at its zenith.

Sekartuti et al. conducted a cross-sectional KAP survey in two malaria endemic villages in South Lampung in 2003 (Sekartuti, 2003). They surveyed 420 people and only 10 (2%) knew of IRS being used as a malaria prevention tool. About 95% of participants responded favourably to IRS. In 2003, Arsunan et al. also documented that 71% of 264 respondents in Kapoposang Island (Pangkajene, Sulawesi) agreed to re-spraying 2 years after the last application (Arsunan et al., 2003). Sekartuti et al. also reported a KAP survey carried out in Banjarnegara (Central Java) in 2004 involving 219 respondents (Sekartuti et al., 2004b). They found that 75% of respondents were aware of the purpose of IRS as a malaria prevention tool. Over 95% reported that their house had been sprayed. Sixty-two percent of respondents agreed to place their cattle shelter at more than 20 m from their dwelling. In 1999, Sukowati et al. documented that 95% of 99 respondents in Lombok (Lesser Sundas) supported IRS as a malaria intervention tool (Sukowati et al., 2003). Santoso et al. evaluated a community participation program in Bintan (Riau Island, Sumatra) in 1991 and described complaints registered after a round of IRS (Santoso et al., 1992). They documented that 91% of 127 respondents had had their houses sprayed. Of 127 respondents, 31% complained of headaches and 38% reported negative effects of the insecticide on their furniture.

2.4.5. Malaria surveillance

According to the Indonesian MCP guidelines (Departemen Kesehatan, 2006b), malaria surveillance is needed to support three activities: early warning, outbreak management and post-outbreak management. Data collection is started from sub-primary health centres and aggregated by the upper levels. The monthly transfer of data from the primary health centres to the district health office is done by hand delivery, fax or email. The district health offices then use this data to create graphs showing trends, distribution and minimum–maximum case loads. The processing and analysing of data is conducted at primary health centre level. An increase in the number of malaria cases, which is more than twofold the number of cases during the normal period, was designated as the threshold of a malaria warning. Another important aim of such data collection is the informing of maps of malaria risk. The maps, in turn, inform the placement of the limited control resources precisely where and when they are needed. However, in 2007, Elyazar et al. showed that primary health centres did not have the sufficient capacity to analyse these data (Elyazar and Rachmat, 2004; Elyazar et al., 2007).

Effective surveillance of malaria in Indonesia requires important challenges to be overcome. As already described, only 13–16% of estimated clinical malaria cases come with a microscopic or RDT confirmation. In other words, 84–87% of clinical malaria cases are undetected by health facilities. This leads to the under-reporting of malaria case figures given by the MoH. The situation is also hampered by the existence of people with malaria who do not seek malaria treatment (21–26%) or people who treat themselves (10–31%). Therefore, the API data reported by district health offices is unreliable. There is no correction factor of API in their reports as high proportion of clinically diagnose malaria.

Another problem is the limited coverage of malaria cases treated by private clinics, physicians and hospitals. The ongoing malaria surveillance used by Indonesia's MCP has not accommodated data generated at those sources. The Indonesian Hospital Reporting System aggregates malaria data from all hospitals in Indonesia. The system reports the number of malaria cases without detailing the *Plasmodium*. The details are kept by each hospital. To assemble, these data would therefore mean to connect with over 1300 hospitals across the archipelago. There is no adjustment of API in the MCP reports to take into account the low contribution of data from clinics, physicians and hospitals.

2.5. OUTLOOK FOR MALARIA RESEARCH IN INDONESIA

This review summarizes the evidence demonstrating that malaria represents an important public-health challenge for Indonesia. After China and India, no other country has more people living at risk of malaria (150–220 million; Guerra et al., 2010; Hay et al., 2009). As can be seen by the work of many presented in this review, the risk and mechanics of infection sharply vary across the 5000-km archipelago and its many habitats. The social complexity of Indonesia's many distinct cultures, and their high mobility, imposes further difficulty. The daunting task faced by the organizations engaging the malaria problem is to place their limited resources precisely where and when needed, using proven tools, in this fantastically complex mosaic of risk.

Most malariologists emphasize the locality-specific character of malaria. In few places is this truer than among the islands of Indonesia. Control strategy must be tailored to localities, and this largely defines the difficulty of achieving gains against malaria at a national level. Experts in Jakarta may be in a poor position to prescribe effective control in, for example, Alor at the far eastern reaches of the Lesser Sundas archipelago; and health officers at Alor may lack the technical expertise to develop control strategies effectively suited to their unique transmission dynamics.

The instinct to consider as essential to progress the dissection and grasp of every nuance of malaria transmission across the many thousands of settings across Indonesia should be resisted by malaria experts working the problem. This would perhaps trend towards hopelessness and abandonment of effort. Research effort is desperately needed to better inform malaria control and elimination strategies, regardless of who carries it out: the MoH, Ministry of Science & Technology, local governments, universities, NGOs, and, ideally, informed and determined local citizens. The effort at gathering, digesting and summarizing the vast body of evidence in this chapter produced an appreciation of some conspicuous gaps in evidence. Most of these tend to reach across the daunting diversity of transmission dynamics and thus represent likely research aims that would inform control and elimination strategy, in almost any setting, with useful evidence. Working to fill in such gaps represents achievable steps forward for the malaria agenda in Indonesia.

We do not presume to list all such gaps. It is hoped that readers will identify further gaps in evidence perhaps more relevant to their individual areas of expertise. Nonetheless, we list

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here what we consider to be seven conspicuously useful and practical areas of research endeavour aimed at better equipping malaria control and elimination in Indonesia.

1. Characterization of antimalarial consumption by both survey instruments and objective observation, especially evaluating the extent of persisting therapeutic practice engaging chloroquine and sulfadoxine/pyrimethamine against both *P. falciparum* and *P. vivax* malaria in both the public and private sectors.
2. Assessing the extent of primaquine therapy being applied against both *P. falciparum* malaria (gametocytocide) and *P. vivax* malaria (hypnozoitocide), including objective measurements of rates of adherence to the latter.
3. Objective epidemiological measurement of the relative contribution of the hypnozoite reservoir to the burden of parasitemia in given communities with endemic *P. vivax* malaria.
4. Randomized, controlled trials assessing the efficacy of primaquine as a gametocytocide and hypnozoitocide, including the characterization of G6PD deficiency variant diversity, distribution and relative sensitivity to primaquine.
5. Randomized, controlled trials assessing the efficacy of ITN or IRS as an intervention against malaria in hypo- and mesoendemic settings.
6. Prospective hospital-based studies in various endemic settings aimed at identifying demographic groups at highest risk of severe and complicated malaria.
7. Development and evaluation of surveillance systems linked to geospatial mapping systems aimed at focusing control resources and effort where most needed or most likely to succeed.

Malaria in Indonesia will remain a problem for a span of time that will extend beyond the active careers of even the youngest physician or scientist in 2011. Achieving elimination will require advancements that fill the many gaps in understanding of this menace to the public. The malariologists responsible for more than 100 years of malaria research in Indonesia summarized in this review provided us a framework of understanding, imperfect and incomplete. It falls upon contemporary malariologists to leverage all of that effort in order to improve this understanding and thereby achieve greater impacts with smarter interventions against malaria.

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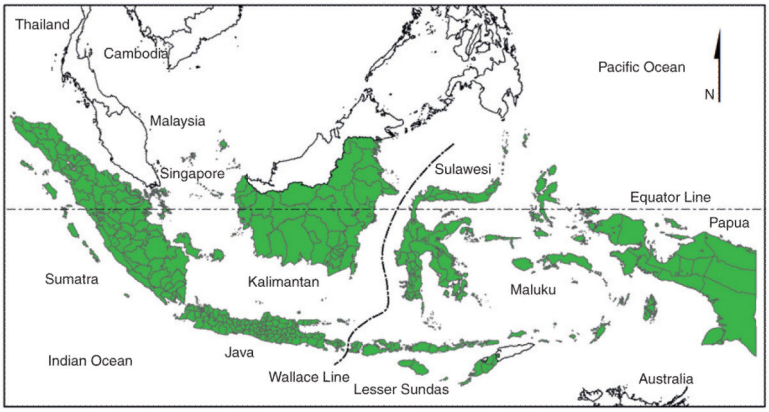

FIGURE 2.1.
The map of Indonesian archipelago.

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TABLE 2.1

Human population, economics and healthcare delivery system indicators for Indonesia and neighbouring countries

Indicators	Year	Cambodia	Indonesia	Thailand	Malaysia	Singapore
Human population						
Population (millions)	2008	14	227	66	27	5
Annual growth rate (%)	1997–2007	1.9	1.3	0.8	2	1.8
Life expectancy at birth (years)	2007	61	69	70	72	81
Economics						
GDP per capita, current prices (US$)	2008	823	2239	4116	8118	38,972
Population below poverty line (%)	2005	68	54	12	8	0
Health expenditure per capita (US$)	2006	30	39	113	259	1017
Healthcare delivery systems						
Hospital beds (per 10,000 population)	2000–2008	1	6	22	18	32
Physician (per 10,000 population)	2000–2007	2	1	4	7	15
Nurses and midwives (per 10,000 population)	2000–2007	9	8	28	18	44
Other health service providers (per 10,000 population)	2000–2007	<1	2	12	1	3

The population data and the estimates of GDP per capita were derived from World Economic Outlook Database–October 2009 (International Monetary Fund, 2009). The number of population below poverty line was acquired from World Bank Development Indicators in 2008 (The World Bank, 2008). Annual growth rate, life expectancy at birth, health expenditure per capita and all indicators in healthcare delivery systems were regained from World Health Statistics Report 2008 and 2009 (World Health Organization, 2008b, 2009a).

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TABLE 2.2

The distribution of human *Plasmodium* throughout the Indonesian archipelago

Islands	Year of sample	No. sites	No. exam	No. *Pf* (%)	No. *P.v.* (%)	No. *P.m.* (%)	No. *P.o.* (%)
Sumatra	1919–2009	676	239,109	8487 (3.5%)	7057 (2.9%)	494 (0.2%)	–
Java/Bali	1900–2006	114	105,734	3387 (3.2%)	2773 (2.6%)	221 (0.2%)	–
Kalimantan	1975–2005	17	7367	398 (5.4%)	248 (3.4%)	21 (0.3%)	–
Sulawesi	1972–2006	55	11,530	482 (4.2%)	316 (2.7%)	8 (0.1%)	–
Maluku	1997–2009	201	121,526	5311 (4.4%)	13,198 (10.9%)	3 (0.002%)	–
Lesser Sundas	1975–2009	609	383,950	23,502 (6.1%)	19,401 (5.1%)	157 (0.04%)	11 (0.003%)
Papua	1929–2009	694	193,043	19,848 (10.3%)	9343 (4.8%)	1395 (0.7%)	40 (0.02%)
Indonesia	1900–2009	2366	1,062,259	61,415 (5.8%)	52,336 (4.9%)	2299 (0.2%)	51 (0.005%)

The database of distribution of human *Plasmodium* was regained from 86% of unpublished data and 14% published sources. The malaria parasite rate data which acquired from published sources listed these following references:

Sumatra: (Bosh, 1925; Carney et al., 1974a, 1975a; Clarke et al., 1973; Cross et al., 1976; Dewi et al., 1996; Doi et al., 1989; Dondero et al., 1974; Doorenbos, 1931a, b; Fryauff et al., 2002; Gandahusada et al., 1981; Gerlach, 1935; Kaneko et al., 1987, 1989; Kirnowardoyo et al., 1993; Maguire et al., 2002b; Matsuoka et al., 1986; Mulder, 1936; Pribadi et al., 1985, 1994, 1997; Renny et al., 1989; Schuffner, 1919; Sekartuti et al., 2004a; Sieburgh, 1936; Soesilo, 1929; Stafford et al., 1977; Sudomo et al., 1997; Syafruddin et al., 2007; Tjitra et al., 1991).

Java/Bali: (Baird et al., 1996c; Clarke et al., 1973; Koch, 1900; Maguire et al., 2005; Ompusunggu et al., 1994, 2002, 2005; Pribadi et al., 1988, 1992; Ristiyanto et al., 2002; Schuurman and Huinink, 1929; Simanjuntak et al., 1981; Stafford et al., 1980b; Sudini and Soetanto, 2005; Tjitra et al., 1993b; Tjokrosonto et al., 1980; Utami et al., 2002; Verdrager and Arwati, 1975b).

Kalimantan: (Cross et al., 1975; Fryauff et al., 1998a; Ompusunggu et al., 1989b; Verdrager et al., 1975a).

Sulawesi: (Carney et al., 1974b,c, 1977; Chadijah et al., 2006; Clarke et al., 1974; Cross et al., 1972; Fryauff et al., 1998b; Joseph et al., 1978; Partono et al., 1973; Purnomo et al., 1987; Stafford et al., 1980a; Syafruddin et al., 1992; Tantular et al., 1999; Tjitra et al., 1995; Widjaya et al., 2006).

Maluku: (Fryauff et al., 1999; Roosihermiatie et al., 2000; Soekirno et al., 1997).

Lesser Sundas: (Baird et al., 1990; Barodji et al., 1994, 1996; Carney et al., 1975b; Dachlan et al., 2005; Fryauff et al., 1997b; Gundelfinger et al., 1975; Hoffman et al., 1984; Jalloh et al., 2004; Jodjana and Eblen, 1997; Joesoef and Dennis, 1980; Jones et al., 1993; Marwoto and Martono, 1991; Marwoto and Purnomo, 1992; Mucide et al., 1998; Nalim et al., 1997; Ompusunggu et al., 2006; Smrkovski et al., 1983; Susanto et al., 2005; Syafruddin et al., 2006, 2009; Tjitra, 2001).

Papua: (Andersen et al., 1997; Anthony et al., 1992; Baird, 1998; Baird et al., 1993, 1997b; Bangs et al., 1992; Barcus et al., 2003; Cross et al., 1977; De Rook, 1929; Dimpudus et al., 1981; Fryauff et al., 1997d, 2000; Hutapea, 1979; Kariadi, 1936; Karyana et al., 2008; Lee et al., 1980; Ling et al., 2002; Metselaar, 1956a, 1959; Meuwissen, 1961; Mooij, 1932; Pribadi et al., 1998; Purnomo et al., 1999; Sunaryo, 2006; Tjitra, 2001; Van der Kaay et al., 1973; Verdrager et al., 1976b; Voors, 1955).

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TABLE 2.3

Discrepancies of reported malaria cases and reported malaria deaths in Indonesia between the World Malaria Report 2008 (WMR2008) and the World Malaria Report 2009 (WMR2009)

	Reported malaria cases			Reported malaria deaths	
Year	**WMR2008**	**WMR2009-Profiles**	**WMR2009-Annex 3A**	**WMR2008**	**WMR2009**
1994	145,920		145,920	No data	No data
1995	123,226		123,226	No data	No data
1996	179,878		179,878	148	148
1997	161,285		161,285	199	199
1998	160,282		160,282	45	45
1999	No data		No data	No data	No data
2000	101,185		No data	No data	No data
2001	1,400,596	2,776,477	267,592	68	No data
2002	1,494,165	2,416,039	273,793	197	No data
2003	1,481,748	2,554,223	223,074	No data	No data
2004	1,494,636	3,016,262	268,852	No data	No data
2005	1,792,992	1,445,831	437,323	No data	No data
2006	1,327,431	1,320,581	347,597	494	494

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TABLE 2.4

Malaria treatment policy and practice in Indonesia

Year	Clinical malaria	*P. falciparum*		*P. vivax*	*P.m.*	*P. ovale*	Prevention during pregnancy	Chemoprophylaxis
		Uncomplicated	Complicated					
1991	CQ CQ + PQ	First line: CQ CQ + PQ Second line: SP + PQ Third line: QN + PQ	CQ (IV or IM) SP (IM) QN (IV or IM)	CQ + PQ	CQ+PQ	CQ+PQ	CQ	CQ
2004	CQ + PQ	First line: AS+AQ+PQ Second line: QN+DX+PQ QN+TC+PQ	First line: AS (IV or IM) AM (IM) Second line: QN (IV)	First line: CQ + PQ Second line: QN + PQ	CQ	CQ+PQ	No	DX CQ
2007	CQ + PQ	First line: AS + AQ + PQ DHA + PP + PQ Second line: QN + DX + PQ QN + TC + PQ	First line: AM (IM) AS (IM) or (IV) Second line: QN (IV)	First line: AS + AQ DHA + PP CQ + PQ (if ACT is absent) Second line: QN + PQ	CQ	CQ+PQ	No	DX

ACT, Artemisinin combination therapy; AM, Artemether; AQ, Amodiaquine; AS, Artesunate; CQ, Chloroquine; DHA, Dihydroartemisinin; DX, Doxycycline; PQ, Primaquine; IM, Intra- muscular; IV, Intravenous; SP, Sulfadoxine-pyrimethamine; QN, Quinine; TC, Tetracycline.

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TABLE 2.5

Plasmodium falciparum resistance to chloroquine in Indonesia throughout the Indonesian archipelago

			***In vivo* test**			***In vitro* test**			
Islands	**Year of sample**	**No. sites**	**No. examined**	**No. resistance**	**Resistance (%)**	**No. Sites**	**No. examined**	**No. resistance**	**Resistance (%)**
Sumatra	1973–2002	29	439	176	40	19	226	149	66
Java/Bali	1981–2002	18	365	179	49	12	378	163	43
Kalimantan	1973–2000	20	157	62	39	11	319	182	57
Sulawesi	1985–2003	12	405	172	42	9	149	64	43
Maluku	1985–1995	2	25	8	32	1	11	8	73
Lesser Sundas	1973–2002	9	270	80	30	6	174	98	56
Papua	1974–2005	26	1306	862	66	15	486	358	74
Total	1973–2005	116	2967	1539	52	73	1743	1022	59

The database of *P. vivax* resistance to CQ was retrieved from these following references:

Sumatra: (Azlin, 2003; Azlin et al., 2004; Dondero et al., 1974; Marwoto et al., 1985b; Maryatul et al., 2005; Ompusunggu et al., 1987, 1989a; Pribadi et al., 1981, 1997; Sutanto et al., 2010; Tjitra et al., 1997).

Java/Bali: (Baird et al., 1996b; Lederman et al., 2006a; Maguire et al., 2002a; Ompusunggu et al., 1987; Sekartuti et al., 1994, 2007; Simanjuntak et al., 1981; Tjitra et al., 1990, 1991, 1993b, 1997).

Kalimantan: (Ebisawa and Fukuyama, 1975; Fryauff et al., 1998a; Hananto et al., 2001; Ompusunggu et al., 1989b; Pribadi, 1992; Tjitra, 1991; Tjitra et al., 1992, 1993a, 1997; Verdrager and Arwati, 1974, 1975a; Verdrager et al., 1975a, 1976a).

Sulawesi: (Departemen Kesehatan, 1996; Fryauff et al., 1998b; Kaseke et al., 2004; Ompusunggu et al., 1987; Tjitra et al., 1997).

Maluku: (Tjitra et al., 1997)

Lesser Sundas: (Fryauff et al., 1997b; Gundelfinger et al., 1975; Hoffman et al., 1984; Smrkovski et al., 1983; Sutanto et al., 2004; Tjitra et al., 1997, 2001b).

Papua: (Baird et al., 1991b, 1995c, 1997b; Cylde et al., 1976; Dimpudus et al., 1981; Ebisawa and Fukuyama, 1975; Ebisawa et al., 1976; Fryauff et al., 1999; Gomez-Saladin et al., 1999; Maguire et al., 2001, 2006a; Nagesha et al., 2001; Pribadi et al., 1998; Ratcliff et al., 2007; Sumawinata et al., 2003; Taylor et al., 2001; Tjitra et al., 1996b, 1997, 2002; Verdrager et al., 1975b, 1976b).

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TABLE 2.6

Plasmodium falciparum resistance to sulphadoxine–pyrimethamine throughout the Indonesian archipelago

Islands	Year of sample	*In vivo* test				*In vitro* test			
		No. sites	No. examined	No. resistance	Resistance (%)	No. sites	No. examined	No. resistance	Resistance (%)
Sumatra	1984–2001	6	302	43	14	10	121	79	65
Java/Bali	1984–2001	4	135	26	19	7	89	62	70
Kalimantan	1987–1991	–	–	–	–	4	136	109	80
Sulawesi	1984–1995	3	106	2	2	4	60	33	55
Maluku	–	–	–	–	–	–	–	–	–
Lesser Sundas	1984–2002	2	52	4	8	1	1	1	100
Papua	1979–2005	13	403	109	27	8	80	26	33
Total	1979–2005	28	998	184	18	34	487	310	64

The database of *P. falciparum* resistance to SP was retrieved from these following references:

Sumatra: (Azlin et al., 2004; Fryauff et al., 2002; Kaneko et al., 1989; Marwoto et al., 1984, 1987; Ompusunggu et al., 1987, 1989a; Pribadi et al., 1997; Tjitra et al., 1997). Java/Bali:(Maguire et al., 2002a; Marwoto et al., 1984, 1985b, 1987; Ompusunggu et al., 1987; Sekartuti et al., 1994; Tjitra et al., 1990, 1991, 1993b).

Kalimantan: (Ompusunggu et al., 1989b; Pribadi, 1992; Tjitra, 1991; Tjitra et al., 1992).

Sulawesi: (Marwoto et al., 1984, 1985a; Ompusunggu et al., 1987; Tjitra et al., 1997).

Lesser Sundas: (Marwoto et al., 1984; Sutanto et al., 2004)

Papua: (Baird et al., 1991b; Fryauff et al., 1999; Hoffman et al., 1985, 1987; Nagesha et al., 2001; Pribadi et al., 1998; Rumans et al., 1979; Tjitra et al., 2001b, 2002).

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TABLE 2.7

Plasmodium falciparum resistance to quinine throughout the Indonesian archipelago

Islands	Year of sample	*In vivo* test				*In vitro* test			
		No. sites	No. examined	No. resistance	Resistance (%)	No. sites	No. examined	No. resistance	Resistance (%)
Sumatra	1997	–	–	–	–	1	1	0	0
Java/Bali	1983–1993	–	–	–	–	4	6	2	33
Kalimantan	1990–1995	–	–	–	–	3	142	5	4
Sulawesi	1991–1995	–	–	–	–	1	4	1	25
Maluku	–	–	–	–	–	–	–	–	–
Lesser Sundas	1983	–	–	–	–	1	1	1	100
Papua	1974–1992	1	3	1	33	8	75	6	8
Total	1974–1997	1	3	1	33	18	229	15	7

The database of *P. falciparum* resistance to Q was retrieved from these following references:

Sumatra: (Pribadi et al., 1997).

Java/Bali: (Hoffman et al., 1983; Kirnowardoyo et al., 1993; Tjitra et al., 1993b).

Kalimantan: (Pribadi, 1992; Tjitra, 1991; Tjitra et al., 1992).

Sulawesi: (Tjitra et al., 1997).

Lesser Sundas: (Hoffman et al., 1983).

Papua: (Baird et al., 1991b; Cylde et al., 1976; Pribadi et al., 1998).

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TABLE 2.8

Plasmodium vivax resistance to chloroquine throughout the Indonesian archipelago

		***In vivo* test**			
Islands	**Year of sample**	**No. sites**	**No. examined**	**No. resistance**	**Resistance (%)**
Sumatra	1974–2010	5	67	20	30
Java/Bali	1996–2002	2	91	11	12
Kalimantan	1998	1	27	12	44
Sulawesi	1998	1	11	1	9
Maluku	–	–	–	–	–
Lesser Sundas	1975–2009	6	87	37	43
Papua	1991–2008	12	404	250	62
Total	1974–2010	27	687	331	48

The database of *P. vivax* resistance to CQ was retrieved from these following references:

Sumatra: (Baird et al., 1996a; Dondero et al., 1974; Fryauff et al., 2002; Schwartz et al., 1991; Sutanto et al., 2010).

Java/Bali: (Baird et al., 1996b; Maguire et al., 2002a).

Kalimantan: (Fryauff et al., 1998a).

Sulawesi: (Fryauff et al., 1998b).

Lesser Sundas: (Fryauff et al., 1997b; Gundelfinger et al., 1975; Hanna, 1993; McCullough et al., 1993; Nurhayati, 2003; Sutanto et al., 2009).

Papua: (Asih, 2010; Baird et al., 1991a, 1995a, 1997a, 1997b; Fryauff et al., 1999; Murphy et al., 1993; Siswantoro et al., 2006; Sumawinata et al., 2003; Taylor et al., 2001).

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TABLE 2.9

Plasmodium falciparum and *P. vivax* resistance to chloroquine, sulphadoxine–pyrimethamine and quinine by region.

			Western Indonesia			Eastern Indonesia			
Parasite	**Drug**	**Test**	**No. examined**	**No. resistance**	**Resistance (%)**	**No. examined**	**No. resistance**	**Resistance (%)**	***p*-value (*Z*-test)**
P. falciparum	CQ	*In vivo*	961	417	43	2006	1122	56	<**0.001**
		In vitro	923	494	54	820	528	64	<**0.001**
P. falciparum	SP	*In vivo*	437	69	16	561	115	20	0.057
		In vitro	346	250	72	141	60	43	<**0.001**
P. falciparum	QN	*In vivo*	–	–	–	3	1	33	Not done
		In vitro	149	7	5	83	8	10	0.142
P. vivax	CQ	*In vivo*	185	43	23	502	288	57	<**0.001**

p-value < 0.05, significant.

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TABLE 2.10

Plasmodium falciparum and *P. vivax* resistance to chloroquine, sulphadoxine–pyrimethamine and quinine throughout the Indonesian archipelago

			Prior 1985			Since 1985			
Parasite	**Drug**	**Test**	**No. examined**	**No. resistance**	**Resistance (%)**	**No. examined**	**No. resistance**	**Resistance (%)**	***p*-value (*Z*-test)**
P. falciparum	CQ	*In vivo*	252	64	25	2715	1475	54	<**0.001**
		In vitro	126	62	49	1617	960	59	**0.026**
P. falciparum	SP	*In vivo*	272	21	8	726	163	22	<**0.001**
		In vitro	24	16	67	463	294	63	0.753
P. falciparum	QN	*In vivo*	3	1	33	–	–	–	Not done
		In vitro	3	3	100	226	13	6	Not done
P. vivax	CQ	*In vivo*	28	0	0	659	331	50	<**0.001**

p-value < 0.05, significant.

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TABLE 2.11

Accessibility to treatment centres by region throughout the Indonesian archipelago

Characteristics	Western Indonesia	Eastern Indonesia	Total
Number of households interviewed	167,141	91,225	258,366
Number of people interviewed	624,086	362,446	986,532
Accessibility			
Health service facilities			
Households located within 1 km of health services facilities	49%	46%	48%
Households located within 15 min of health service facilities	71%	56%	66%
Community-based health efforts (UKBM)			
Households located within 1 km of UKBM	80%	76%	79%
Households located within 15 min of UKBM	88%	81%	85%

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TABLE 2.12

The World Health Organization (WHO) and the Indonesian Malaria Control Program (IMCP) recommended insecticides for indoor residual spraying against malaria vectors

		WHO (2009)		IMCP (1993)		IMCP (2003, 2010)	
Insecticide	**Class**	**Recommended**	**Dosage (g/m^2)**	**Recommended**	**Dosage (g/m^2)**	**Recommended**	**Dosage (g/m^2)**
Alpha-cypermethrin	Pyrethroid	Yes	0.02–0.03	No	–	Yes	0.02
Bifentrin	Pyrethroid	Yes	0.025–0.05	No	–	Yes	0.025
Cyfluthrin	Pyrethroid	Yes	0.02–0.05	No	–	No	–
Deltamethrin	Pyrethroid	Yes	0.02–0.025	No	–	Yes	0.2
Etofenprox	Pyrethroid	Yes	0.1–0.3	No	–	Yes	0.1
Lambda-cyhalothrin	Pyrethroid	Yes	0.02–0.03	Yes	0.025	Yes	0.025
Bendiocarb	Carbamate	Yes	0.1–0.4	Yes	0.4	Yes	0.2
Propoxur	Carbamate	Yes	1–2	No	–	No	–
Fenitrothion	Organophosphate	Yes	2	Yes	1	No	–
Malathion	Organophosphate	Yes	2	Yes	1–2	No	–
Pirimiphos-methyl	Organophosphate	Yes	1–2	Yes	1	No	–
DDT	Organochloride	Yes	1–2	Yes	1–2	No	–