

Developing Evidence-Based Strategic Plans

For Malaria Control And Elimination In Indonesia

A thesis submitted for the degree of

Doctor of Philosophy

by

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Kellogg College, University of Oxford

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Controlling and eliminating malaria in Indonesia is a challenging endeavour. Evidence-based strategic plans should be critically formulated to overcome a complex mosaic of infection risk across the 5000-km-long archipelago of thousand islands and distinctive habitats. This project aimed to thoroughly explore the challenges and opportunities for controlling/eliminating malaria and present the application of malaria cartographic tools to allow malaria control agencies and their partners to comprehensively assess the prospects for reaching pre-elimination, monitor and evaluate the effectiveness of future strategies against the baseline generated.

First, the historical context of malaria in Indonesia and important methods of control and their impact in the context of the political systems that supported them was comprehensively described. A series of distribution maps of twenty *Anopheles* malaria vector mosquitoes in Indonesia were also produced, supported by comprehensive reviews of each species' bionomics and susceptibility to insecticides.

Then, the application of malaria cartographic tools for malaria control/elimination in Indonesia was explored. The first high spatial resolution (1 x 1 km) baseline endemicity maps of *Plasmodium falciparum* and *P. vivax* malaria were generated, together with corresponding estimates of population at risk and clinical burdens of each species in 2010. Low malaria prevalences of these parasites were predicted in western areas, with high prevalences in eastern Indonesia. Over 132 million people in Indonesia lived at risk of *P. falciparum* transmission with 70% of them in areas of unstable transmission and 30% in stable transmission. There were an estimated 7.7 million *P. falciparum* clinical cases across the populations at risk. Meanwhile, nearly 130 million people lived at risk of *P. vivax* malaria with 79% living in unstable and 21% in stable transmission areas. This infection caused 1.5 million estimated clinical cases in 2010. Both estimates were 30-fold and 6-fold higher than routinely reported numbers, respectively.

Finally, this project revealed the substantial multi-faced problems that impede current efforts towards the pre-elimination agenda. High rates of undiagnosed clinical cases, insufficient competence of malaria microscopy, inadequate primaquine dosing against *P. vivax* malaria infections, insufficient evidence of vector control interventions, wide diversities of vector mosquitoes and their bionomics, mosquito resistance against insecticides and inadequate malaria surveillance systems are challenging the task of controlling and eliminating malaria. A diverse range of strategies enabling locally-specific approaches must be implemented for controlling and eliminating malaria in Indonesia. Strategic recommendations are listed and future research priorities are proposed for further study.

Statement of Contribution

My research project began in September 2009. I have been responsible for formulating the research questions, conceiving, designing, performing and analyzing the experiments. All my research questions were aligned with the objectives of the Malaria Atlas Project (MAP). I, Prof Simon Hay and Dr J. Kevin Baird designed the analytical plans for each of the research chapters. Dr Peter Gething, Dr Anand Patil and Dr Samir Bhatt primarily performed the spatial modelling and provided the highly technical statistical knowledge to my research. I conducted all of the spatial analyses in this thesis with advice from Dr Peter Gething, Dr Anand Patil and Dr Samir Bhatt. All of the chapters in this thesis, aside from Chapters 1, 6, and 7 are modified from manuscripts that have been published in peer-reviewed journals. I wrote the first draft and am the first author of all papers and take ultimate responsibility for their contents. I received editorial comments from co-authors and these have been incorporated into the thesis chapters. The co-authors are gratefully acknowledged at the end of each chapter.

This thesis uses data from a wide range of sources. I conducted the literature reviews, extracted and analysed data for the two review chapters (Chapters of 2 and 3). Chapters 2 and 3 are based on published and unpublished malaria studies from the early 1900s up to 2011. Chapter 3 uses the national insecticide susceptibility database which was collected from the published literature and unpublished experimental data carried out by the Indonesian National Vector Control Program. These data were compiled, validated and cleaned by myself. The final manuscript texts were edited and approved by all authors. These chapters have been published and are included here in their final form.

Elyazar IRF, Hay SI, Baird JK. 2011. Malaria distribution, prevalence, drug resistance and control in Indonesia. *Adv Parasitol*. 74: 41-175. *A modified version of this article appears as Chapter 2 of this thesis*.

Elyazar IRF, Sinka M, Gething PW, Tarmidzi SN, Surya A, Kusriastuti R, Winarno, Baird JK, Hay SI, Bangs MJ. 2013. The distribution and bionomics of *Anopheles* malaria vector mosquitoes in Indonesia. *Adv Parasitol*. 83: 171-264. *A modified version of this article appears as Chapter 3 of this thesis*.

This project provided me with opportunities to present my research and develop a collaborative network with my research partners in the Indonesian Ministry of Health (MoH). This productive relationship between the Malaria Atlas Project via this work has created opportunities to guide the development of technological instruments of greatest possible utility to the government agencies executing malaria control activities. I and a team in the MAP and MoH have obtained consensus on specific technological goals and the research activities forming our collaboration.

Chapters 4, 5 and 6 use the national parasite incidence data which were assembled by me and my colleagues in the Indonesian National Malaria Control Program (NMCP) from provincial and district reports. Chapter 4 and 5 also use the national parasite prevalence surveys which were contributed primarily by the Indonesian NMCP and by a large number of malaria researchers in Indonesia. All contributors are gratefully acknowledged on the MAP website. The parasite incidence and prevalence data were scrutinized with a team of the MAP. These chapters are examples of the application of malaria cartographic tools for controlling and eliminating malaria. Chapters 4 and 5 have been published and are included here in their final form. I was responsible for writing the first draft of the manuscripts. The final manuscript text was edited and approved by all authors.

Elyazar IRF, Gething PW, Patil AP, Royagah H, Kusriastuti R, Wismarini DM, Tarmizi SN, Baird JK, Hay SI. 2011. *Plasmodium falciparum* malaria endemicity in Indonesia in 2010. *PLoS ONE*. 6: 6. *A modified version of this article appears as Chapter 4 of this thesis*.

Elyazar IRF, Gething PW, Patil AP, Rogayah H, Sariwati E, Palupi NW, Tarmizi SN, Kusriastuti R, Baird JK, Hay SI. 2012. *Plasmodium vivax* malaria endemicity in Indonesia in 2010. *PLoS ONE*. 7:5. *A modified version of this article appears as Chapter 5 of this thesis*.

Much of my technical knowledge about malaria epidemiology and geostatistical modelling came from working with my supervisors during my research project. Parallel publications which I have been involved with but which are not directly integrated into this thesis include:

Hay SI, Guerra CA, Gething PW, Patil AP, Tatem AJ, Noor AM, Kabaria CW, Manh BH, **Elyazar IRF**, Brooker S, Smith DL, Moyeed RA, Snow RW. 2009. A world malaria map: *Plasmodium falciparum* endemicity in 2007. *PLoS Med*. 6: 3.

Gething PW, **Elyazar IRF**, Moyes CL, Smith DL, Battle KE, Guerra CA, Patil AP, Tatem AJ, Howes RE, Myers MF, George DB, Horby P, Wertheim HFL, Price RN, Müeller I, Baird JK, Hay SI. 2012. A long neglected world malaria map: *Plasmodium vivax* endemicity in 2010. *PLoS Negl Trop Dis*. 6:9.

Battle KE, Gething PW, **Elyazar IRF**, Moyes CL, Sinka ME, Howes RE, Guerra CA, Price RN, Baird JK, Hay SI. 2012. The global public health significance of *Plasmodium vivax*. *Adv Parasitol*. 80: 1-111.

Qi Q, Guerra CA, Moyes CL, **Elyazar IRF**, Gething PW, Hay SI, Tatem AJ. 2012. The effects of urbanization on global *Plasmodium vivax* malaria transmission. *Malar J*. 11: 403.

Guerra CA, Howes RE, Patil AP, Gething PW, Van Boeckel TP, Temperley WH, Kabaria CW, Tatem AJ, Manh BH, **Elyazar IRF**, Baird JK, Snow RW, Hay SI. 2010. The international limits and population at risk of *Plasmodium vivax* transmission in 2009. *PLoS Negl Trop Dis*. 4:8.

Sutanto I, Tjahjono B, Basri H, Taylor WB, Putri FA, Meilia RA, Setiabudy R, Nurleila S, Ekawati LL, **Elyazar I**, Farrar J, Sudoyo H, Baird JK. 2013. Randomized, open label trial of Primaquine against vivax malaria relapse in Indonesia. *Antimicrob Agents Chemother*. 57: 1128-1135.

Nurlela, SN, Syafruddin D, **Elyazar IRF**, Baird JK. 2012. Serious and fatal illness associated with falciparum and vivax malaria among patients admitted to hospital at West Sumba in Eastern Indonesia. *Am J Trop Med Hyg*, 87: 41-49.

Sinka ME, Bangs MJ, Manguin S, Chareonviriyaphap T, Patil AP, Temperley WH, Gething PW, **Elyazar IRF**, Kabaria CW, Harbach RE, Hay SI. 2011. The dominant *Anopheles* vectors of human malaria in the Asia-Pacific region: occurrence data, distribution maps and bionomic précis. *Parasit Vectors*. 4: 89.

Hay SI, Sinka ME, Okara RM, Kabaria CW, Mbithi PM, Tago CC, Benz D, Gething PW, Howes RE, Patil AP, Temperley WH, Bangs MJ, Chareonviriyaphap T, **Elyazar IRF**, Harbach RE, Hemingway J, Manguin S, Mbogo CM, Rubio-Palis Y, Godfray HCJ. 2010. Developing global maps of the dominant *Anopheles* vectors of human malaria. *PLoS Med*. 7:2.

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As his supervisors, we certify that the statements of contribution listed here are a fair representation of Iqbal Elyazar's work.

Prof Simon I. Hay Dr J. Kevin Baird Dr Peter W. Gething

12th July 2013

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I greatly appreciate Prof Simon I. Hay, Dr J. Kevin Baird and Dr Peter W. Gething for their substantial amount of time and efforts towards mentoring me and providing me expertise in malaria epidemiology and spatial modelling. Learning from them has been one of the most exhilarating experiences of my life, through which they have enriched me with their wisdom: (a) be critical, (b) be responsible and (c) be independent. They simply demonstrated the living role models of world-class scientists.

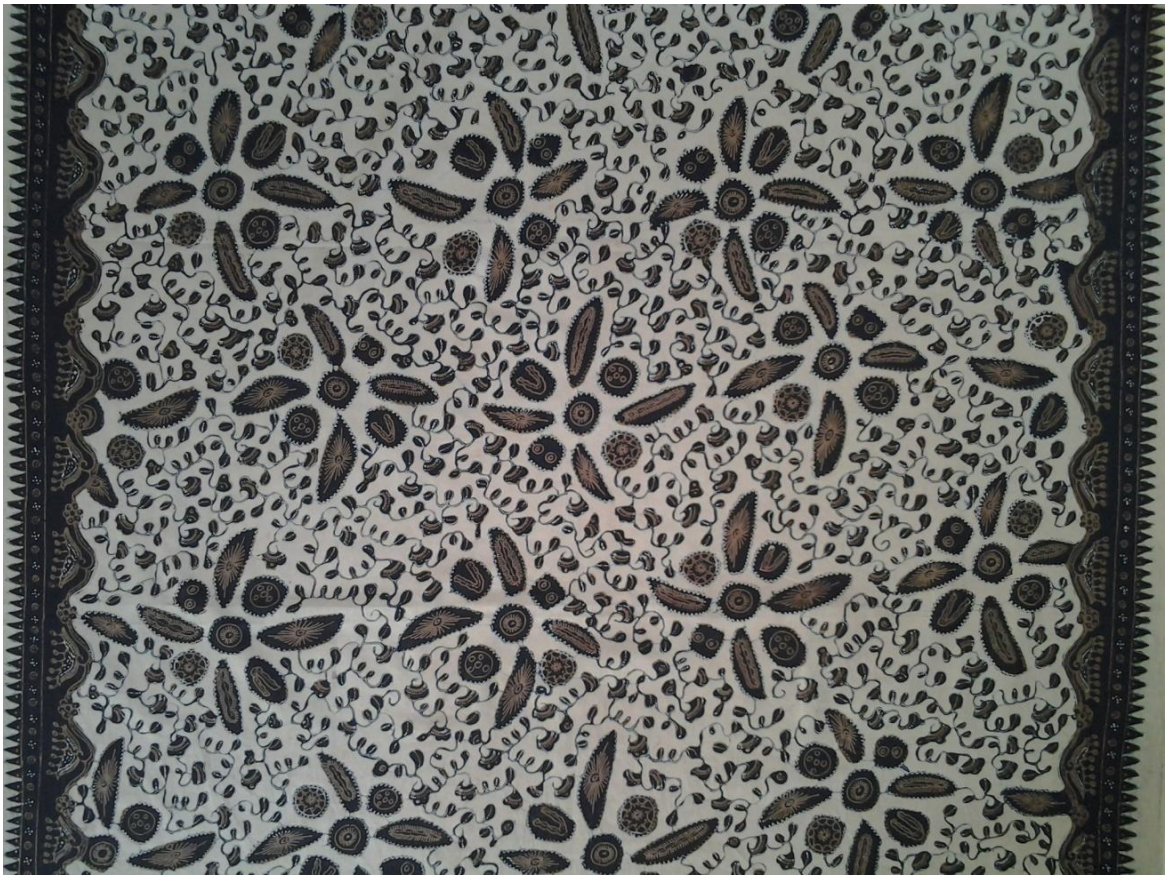
I sincerely express my gratitude to the University of Oxford - Li Ka Shing Foundation Global Health Program, the Oxford Tropical Network and the United States of Naval Medical Research Unit, Jakarta (NAMRU-2) for tremendous provision towards my studentship. Studying at the University of Oxford has been a huge opportunity for me by having extraordinarily wide online access to scientific journals. I also thank the Library of the U.S. NAMRU-2, Jakarta and the Library of the Eijkman Institute for Molecular Biology, Jakarta for giving me free access to their collections of the scientific literature published in Dutch from early 1900s to pre-1942.

Contribution and acceptance from the Indonesian Ministry of Health is greatly appreciated: (a) the Directors of Indonesian Malaria Control Program: Dr Rita Kusriastuti, Dr Asik Surya, Dr Made Wismarini, Dr Nadia Tarmizi, Dr Ferdinand Laihad and Dr Arbani for allowing me to access massive unpublished data sets, program reports and providing the context of local malaria control and (b) Director of the Indonesian Vector Control Program: Dr Winarno for sharing unpublished data and discussion on vector control activities.

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Malaria Batik. Batik has notable meanings rooted to the Javanese conceptualization of the universe. The craft of batik is intertwined with cultural identity and the expression of creativity and spirituality through the symbolic meanings of its colours and designs. This handmade malaria batik was originally drawn by Dr Purnomo Prodjodipuro (NAMRU-2) and illustrates the life cycle of malaria. The brown colour (Javanese, “sogan”), dynamic patterns (“isen-isen”), and mango flowers-shaped border ("kembang mangga") are typical batik features from Yogyakarta and Central Java. A special thank you goes to Lenny Ekawati (NAMRU-2 Batik, Jakarta) for this image.

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Abbreviations

ABER	Annual Blood Examination Rate
ACD	Active Case Detection
ACT	Artemisinin Combination Therapy
AM	Artemether
AQ	Amodiaquine
AS	Artesunate
AUC	Area Under Curve
AVHRR	Advanced Very High Resolution Radiometer
BES	Benefit Evaluation Study
BHS	Basic Health Survey
BIC	Bayesian Information Criteria
BTI	*Bacillus thuringensis israelensis*
CFR	Case Fatality Rate
CI	Confidence Interval
COI	Cytochrome Oxidase I
CQ	Chloroquine
CMS	Civil Medical Service
CSP	Circumsporozoite Protein
DDT	Dichlorodiphenyltrichloroethane
DHA	Dihydroartemisinin
DNA	Deoxyribonucleic acid
DX	Doxycycline
DVS	Dominant Vector Species
EIR	Entomological Inoculation Rate
ELISA	Enzyme-linked Immunosorbent Assay
ENSO	El Nino Southern Oscillation
G6PD	Glucose-6-Phosphate Dehydrogenase
G6PDd	Glucose-6-Phosphate Dehydrogenase deficiency
GDP	Gross Domestic Product
GIS	Geographic Information System
GRUMP	Global Rural Urban Mapping Project
HBI	Human Blood Index
HHS	Health Household Survey
HRP-2	Histidine-Rich Protein-2
ID	Incidence Density
IDHS	Indonesian Demographic and Health Survey
IDR	Incidence Density Ratio
IM	Intramascular
IRS	Indoor Residual Spraying
ITN	Insecticide Treated Nets
ITS-2	Internal Transcibed Spacer 2
IV	Intavenous
KAP	Knowledge, Attitude and Practice
KDR	Knockdown resistance
KOPEM	Komando Operasi Pembasmian Malaria
LC	Lethal Concentration
LD	Lethal Dosage
LLIN	Long Lasting Insecticide-treated Net

MAE	Mean Absolute Error
MAP	Malaria Atlas Project
MBG	Model based geostatistics
MBS	Mass Blood Survey
ME	Mean Error
MFS	Malaria Fever Survey
MIR	Middle Infra-Red
MoH	Ministry of Health
NDVI	Normalized Difference Vegetation Index
NGO	Non-Governmental Organization
NICA	Netherlands Indies Civil Administration
NIHRD	National Institute of Health Research and Development
NMCP	National Malaria Control Program
NMES	National Malaria Eradication Services
OR	Odds Ratio
PCD	Passive Case Detection
PCR	Polymerase Chain Reaction
*Pf*API	*Plasmodium falciparum* Annual Parasite Incidence
*Pf*PR	*Plasmodium falciparum* Parasite Rate
$PfPR_{2-10}$	*Plasmodium falciparum* Parasite Rate of age-standardized 2-10 year old
POLRI	Polisi Republik Indonesia (Police of Republic of Indonesia)
PQ	Primaquine
Puskesmas	Pusat Kesehatan Masyarakat (Community Health Centre)
*Pv*API	*Plasmodium vivax* Annual Parasite Incidence
*Pv*PR	*Plasmodium vivax* Parasite Rate
$PvPR_{1-99}$	*Plasmodium vivax* Parasite Rate of age-standardized 1-99 year old
QN	Quinine
RBM	Roll Back Malaria
RDT	Rapid Diagnostic Test
ROC	Receiver Operating Characteristics
RR	Risk Ratio
SP	Sulfadoxine-pyrimethamine
SPR	Slide Positivity Rate
SPRS	Sistem Pelaporan Rumah Sakit (Hospital Reporting System)
TC	Tetracycline
TFA	Temporal Fourier Analysis
TNI	Tentara Nasional Indonesia (Armed Forces of Indonesia)
UKBM	Upaya Kesehatan Berbasis Masyarakat (Community-based health efforts)
UKS	Usaha Kesehatan Sekolah (School Health Unit)
UNFPA	United Nations Population Fund
US NAMRU-2	United States Naval Medical Research Unit No 2
USAID	United States Agency for International Development
VCP	Vector Control Program
VOC	Vereenigde Oost-Indische Company
WDP	Water Dispersible Powder
WHO	World Health Organization
WHOPES	World Health Organization Pesticide Evaluation Scheme
WMR	World Malaria Report
WP	Wettable Powder

CHAPTER 1

Introduction

1.1. General Background

Eliminating malaria is an ultimate goal of controlling malaria. Controlling malaria is the deliberate action to reduce malaria incidence to a locally acceptable and manageable level [1], while eliminating malaria is the deliberate action to reduce local malaria incidence to zero within a delimited geographical areas [2]. Control must be sustained to maintain the reduction, while elimination must be sustained to stop re-introduction. The most important operational difference between controlling and eliminating is the concentration of activities to identify and attack foci of clinical and asymptomatic infections [3].

Eliminating malaria is achievable at the national level. Within three decades nearly 30 countries have been certified as malaria-free by the World Health Organization [4]. To date, there are 39 malaria-eliminating countries [5]. The important lessons learnt from the countries that are making remarkable progress towards malaria elimination may be summarized as follows: (a) clear understanding of the epidemiological situation in each area, (b) understanding population movement, (c) tailoring interventions to local conditions, (d) establishing and maintaining cost-effective surveillance systems, (e) maintaining strong political commitment, adequate funding, domestic human resource capacity at sufficiently high levels for long periods, and (f) establishing integral coordination between intervention activities and research [6-14].

These lessons indicate that each country should have their own evidence-based strategy for eliminating malaria based on their local situation and a critical feasibility assessment. Politically motivated or intuitive approaches should be avoided in reaching this commitment [5].

Challenges within a country, such as lack of commitment, human and financial capital, increasing parasite and insecticide resistance, a threat of malaria resurgence, may vary and demand unique solutions [5]. All provinces/districts pursuing low-controlled or pre-elimination stages should comprehensively assses their constraints. Sophisticated spatial analyses, mathematical modelling and computational technology can provide answers regarding assessments of feasibility [15,16]. Any elimination program will need plans with defined time limits and concrete operational targets expressing well-defined parasitological, entomological, and epidemiological endpoints as metrics of progress and success [16]. This work requires assembly of a great deal of relevant data, addressing the issues with appropriate models, and making refined maps capable of guiding specific action at national and sub-national levels [1]. Figure 1.1. presents the considerable evidence-base requirements [17], including information about the intensity of endemic transmission, human population distribution, intensity of endemic transmission, malaria importation risk and local political and financial environments, health-system capacity and the size of populations at risk of malaria.

Understanding *Anopheles* malaria vector dynamics in different epidemiological settings is important as controlling mosquitoes is a main attack weapon for reducing malaria transmission [18]. The deployment of vector control must be carefully adapted both the biology of the local species of vector mosquitoes and the local epidemiology of malaria [19]. Ferguson *et al*. listed ecological obstacles to vector control [20], including vector biodiversity, variation in mosquito behaviour, insecticide resistance, behavioural

avoidance, dispersal and mating behaviour, competitive and food web interactions and enviromental change (Figure 1.2).

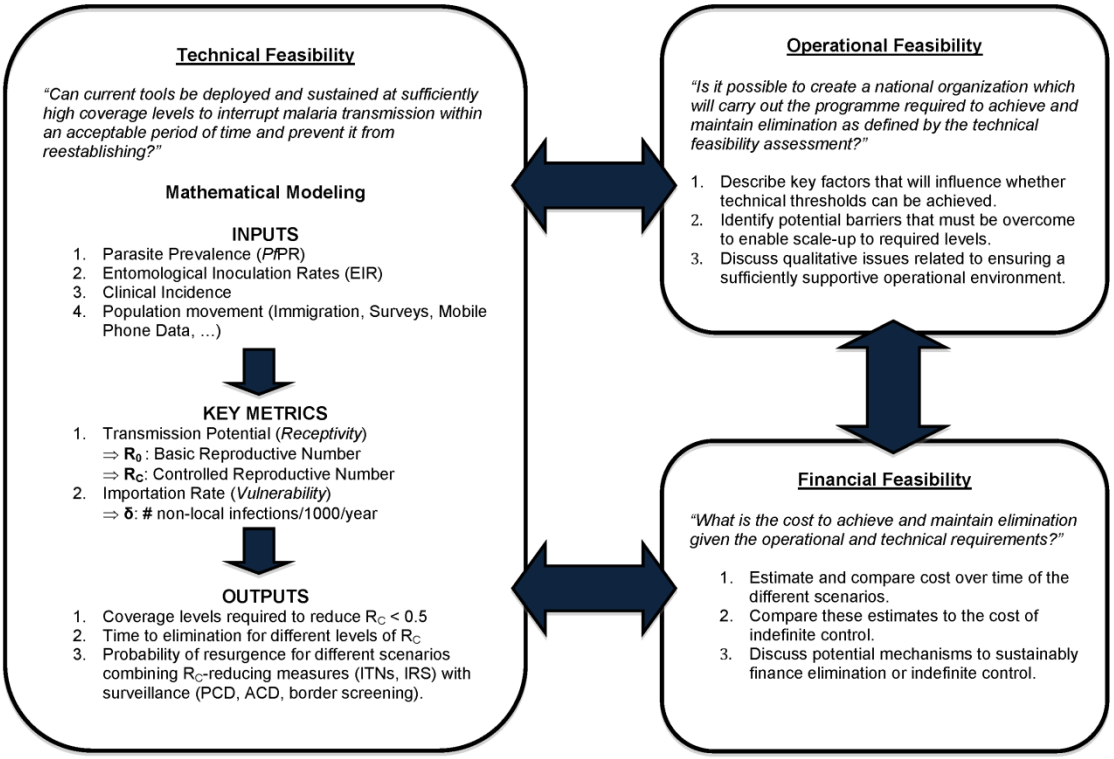


Figure 1.1. Framework for assessing the feasibility of malaria elimination. Technical feasibility identifies requirements for achieving and maintaining elimination under different scenarios, operational feasibility involves the administrative and programmatic capacity to meet those requirements, and financial feasibility examines the costs involved. Figure 1.1 reproduced with permission from Moonen *et al*. [17].

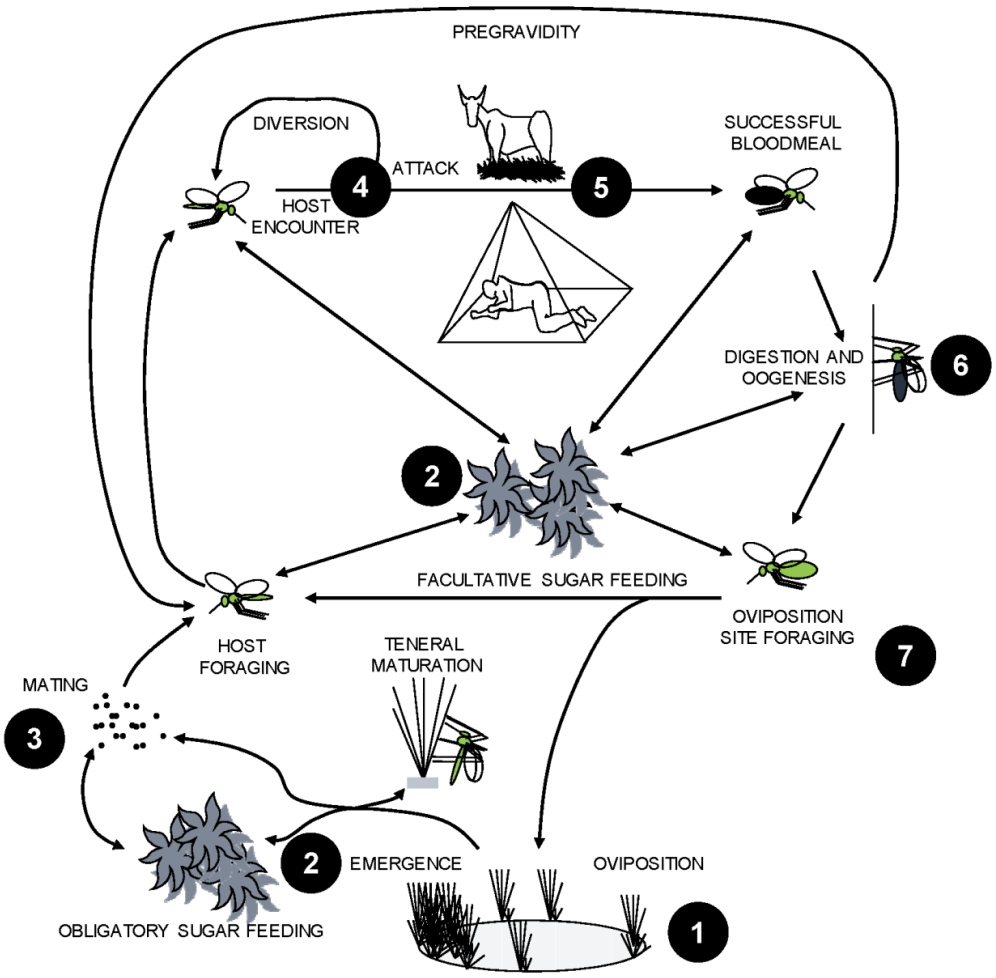


Figure 1.2. The life cycle components of *Anopheles* malaria vectors and corresponding examples of target for intervention strategies. Examples of intervention target include: (1) larvicide application by direct means or by auto-dissemination via adults, and environmental management, (2) insecticide application to natural sugar sources, toxic sugar baits and para-transgenic bacteria, (3) pheromone trapping and release of genetically modified or sterile males, (4) spatial and contact repellents, (5) zooprophylaxis, insecticide-treated cattle and odour-baited traps, (6) adult contamination with biological and chemical agents which may be auto-disseminated and (7) enviromental management of water resources for adult vector control. Figure 1.2 reproduced with permission from Ferguson *et al*. [20].

The understanding of spatial epidemiology of malaria and its mosquito vectors is essential for malaria program managers and research communities to focus their efforts to interrupt sources of residual transmission and in limiting importation risk in areas that have been cleared of malaria. Consequently, efficient allocation of finite resources, expertise, together with social and political capital, demands an evidence-based quantification of need [21] and spatial maps has been considered important in coordinating these resources [15,22-29].

With over 17,000 islands straddling the equator, stretching 5,200 km from western Malaysia to Papua New Guinea and covering a land area of 1.9 million km^2 [30], the Indonesian archipelago was home to over 230 million people in 2010 [31] and harboured 20 known anopheline vectors of malaria transmitting all four of the species of *Plasmodium* that routinely infect humans [32]. Taking into account all considerations above, this thesis raises the following questions: (1) What challenges and opportunities exist towards controlling/eliminating malaria in Indonesia, (2) What are the prospects of reaching pre-eliminating phases of malaria control within the country and (3) How may cartographic tools contribute to assessing the pre-elimination prospects.

1.2. The scope of the thesis

The thesis is structured as a series of submitted/published manuscripts, with introductory and concluding chapters synthesizing the overall thesis objectives, findings and conclusions. The key outputs of this research are evidence-based maps of the endemicity of *Plasmodium. falciparum* (Chapter 4), *P. vivax* (Chapter 5), and estimates of clinical incidence of both species (Chapter 6). These maps are supported by comprehensive literature reviews on malaria distribution, prevalence, drug resistance and control (Chapter 2) and the distribution of *Anopheles* and their bionomics (Chapter

3). This research required literature reviews of the epidemiology of malaria in Indonesia and its *Anopheles* vectors, together with extensive data abstraction and geo-positioning processes. Geostatistical methods, developed in a Bayesian framework, were then used to generate continuous maps informed by the assembled datasets. The nature of the statistical design meets the demand for both objective evidence-based products and provision of uncertainty metrics. The methodological steps involved here are common to both the *P. falciparum* and *P. vivax* malaria endemicity maps and clinical burden estimates. These methods are fully discussed in Chapter 4, 5 and 6.

Chapter 2 details the historical context of malaria in Indonesia and important methods of control and their impact in the context of the political systems that supported them. A complex mosaic of infection risk across this 5000 km-long archipelago of thousands of islands and distinctive habitats that seriously challenges efforts to control malaria is explored. The prospects for malaria control in Indonesia, a decentralized and democratized country with multi-drug resistant malaria and greatly sub-optimal capacities for integrated malaria control management programs, is examined. Finally, suggestions for useful and practical areas of scientific research aiming at better equipping malaria control and elimination decision makers in Indonesia are listed and discussed. This work was published in *Advances in Parasitology* entitled “Malaria distribution, prevalence, drug resistance and control in Indonesia” in 2011.

Several extensive works have described the geographical distribution of the malaria vectors in Indonesia [32-40] but no comprehensive and contemporary map of their ranges currently exists. Recent work by the Malaria Atlas Project (www.map.ox.ac.uk), defining the spatial distributions of the dominant vector species (DVS) of human malaria worldwide [41-44], have begun to address the need for geographical species-specific information. Chapter 3, therefore, closely examines both the past and current

state of knowledge of many of the anopheline malaria vectors present in this environmentally diverse archipelago. Geographical distribution maps of the malaria vectors, specifically for Indonesia, will be an important guide to the local vector control services and, in addition, will help define bio-geographic zones with which to stratify the islands for endemicity mapping. This work was published in *Advances in Parasitology* entitled “The distribution and bionomics of *Anopheles* malaria vector mosquitoes in Indonesia” in 2013.

Chapter 4 and 5 aim to define the spatial limits of *P. falciparum* and *P. vivax* transmission and to map their endemicity within the stable transmission limits in Indonesia. Systematic approaches have been developed to achieve this on a global scale using geo-positioned assemblies of national surveillance data, various other public health data and biological limits of transmission suitability [15,45]. This global-level work has been conducted at a relatively crude spatial scale but here is increased to the district level in Indonesia. The most contemporary case reports available from the national health management information system (2005-2008 inclusive) are used to define the spatial limits of *P. falciparum* and *P. vivax* transmission. Then, a huge assembly of parasite rate (PR) survey data is used to generate the continuous malaria endemicity surface using a model based geostatistics (MBG) framework. These works have been published in *Public Library of Science ONE* entitled “*Plasmodium falciparum* malaria endemicity in 2010” in 2011 and “*Plasmodium vivax* malaria endemicity in 2010” in 2012.

Decision-makers require accurate and timely information on malaria burden to effectively allocate their limited resources to allow maximum impact [46,47]. The malaria burden in Indonesia, as in so many nations, is under-reported and its true level is poorly known [48-50]. In order to provide more reliable estimates of malaria burden,

the MAP has implemented techniques to estimate incidence from endemicity maps [15]. A comparison between burden estimates and national reported data is made using robust evidence-based morbidity estimates derived for both *P. falciparum* and *P. vivax*. This analysis has important global implications as Indonesia contributes substantially to the global malaria burden estimates. This work is described in Chapter 6.

This project aims to determine the challenges and opportunities in controlling/eliminating malaria in Indonesia, the prospect of eliminating malaria within the country and the exploration of the application of cartographic tools in providing evidence-based assessments of future prospects. Chapter 7 lists pertinent and practical strategic plans aimed at better equipping malaria control and elimination decision-makers in Indonesia as well as future research priorities.

CHAPTER 2

Malaria distribution, prevalence, drug resistance and control in Indonesia

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 paper 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.

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 5,200 km from west Malaysia to

Papua New Guinea (Figure 2.1). The country consists of 17,504 islands, (only 6,000 of which are inhabitated), covering a land area of 1.9 million km^2 [30,51]. The archipelago is comprised of 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, 6,093 sub-districts and 73,067 villages [52]. Census authorities in 2007 estimated a population of 227 million people, with an average density of 118 people per km^2 [52]. The annual population growth rate was 1.3% [53]. 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 lived 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 ($\geq$ 65 years old). Life expectancy at birth for Indonesians increased from 52 years in 1980 to 69 years in 2007 [52]. 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%) [54]. The highest illiteracy rates occurred in Papua (23%; rural 32% and urban two percent) and West Nusa Tenggara provinces (18%; rural 20% and urban 13%) [52]. 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[53]. However, according to a global poverty map, based on night light brightness from satellite imagery, and the criterium of a US$ two per day poverty line, Elvidge *et al*. estimated that 73 million of Indonesia's population (32%) lived in poverty in year 2006 [55]. 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) [56]. The International Monetary Fund estimated that the annual Indonesian Gross Dosmestic Product (GDP) per capita in 2008 was US$ 2,239, a significant increase from US$ 516 in 1998 [57]. About 88% of the population spent less than US$ 50 per month (rural 96%; urban 76%) [53]. 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 [52].

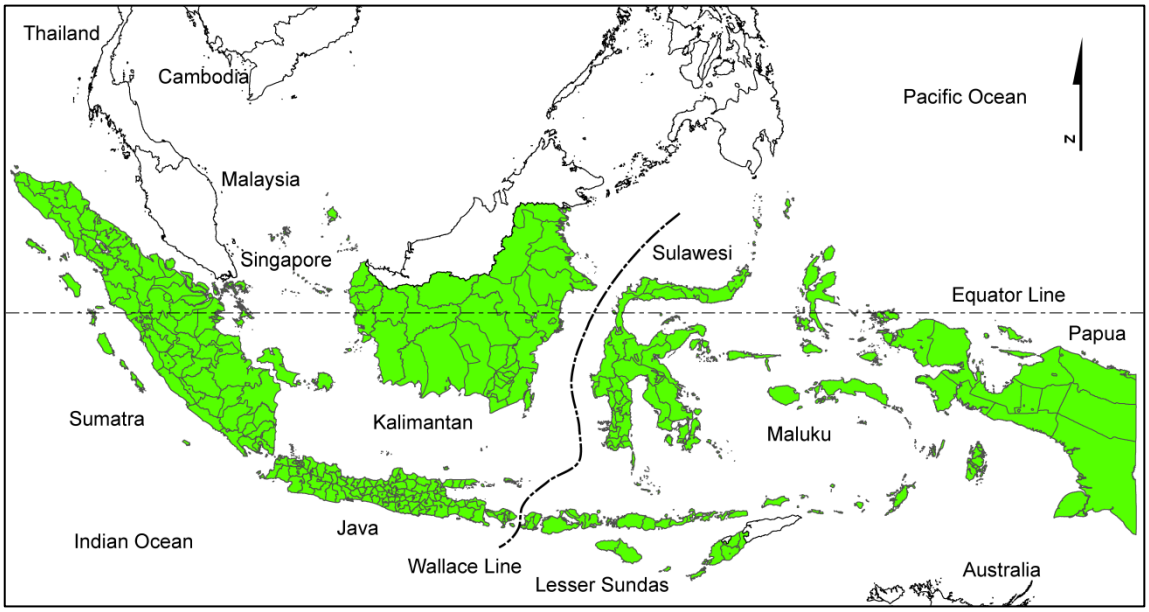


Figure 2.1. The map of Indonesian archipelago.

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 [58-60]. However, government expenditures on health recovered and even surpassed pre-crisis figures at US$ 8 per capita per year by 2007 [61]. In 2007, the health budget reached 18.5 trillion rupiah (approximately US$ 19 billion) [52], 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 three-fold 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 health care 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 8,234 primary health centres, with a centre serving, on average, about 27,400 people [52]. The number of primary health centres increases at a rate of about 2.7% per year. The service coverage by province ranged from 8,000 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 1,000 km^2.

The number of hospitals was 1,319 in 2007, which provided a total of 142,707 hospital beds [52]. Ownership of these hospitals was 49% private and 51% public and government operated. The overall ratio of population to each hospital bed was 1,581:1. The Indonesian Ministry of Health (MoH) declared the ideal ratio to be 1,000 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 approximately 7.8% of them being referred from lower levels of health care delivery, including primary health centres [54].

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 [52]. 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 9,598 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 1,634 small, traditional drug companies in the production sector [52]. 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 2,493 wholesalers, 10,275 dispensaries, and 7,056 drugstores [52]. 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 [52]. 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 health care centres [52].

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 [56,57,62,63]. 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 seventeen 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 fifteen 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 three to forty-five 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: the National Institute of Health Research and Development, the Directorate General of Disease Control and Health Environment and 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.

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$)	2008	823	2,239	4,116	8,118	38,972
Population below poverty line (%)	2005	68	54	12	8	0
Health expenditure per capita (US$)	2006	30	39	113	259	1,017
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 percapita were derived from World Economic Outlook Database-October 2009 [57]. The number of population below poverty line was acquired from World Bank Development Indicators in 2008 [56]. Annual growth rate, life expectancy at birth, health expenditure percapita, and all indicators in healthcare delivery systems were regained from World Health Statistics Report 2008 and 2009 [62,63].

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 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 174 billion rupiah (approximately US$ 2 million) and spent 25% on research and development, 72% on human resources and facilities development and 3% on research results dissemination [64].

The NIHRD organizes health surveys. The Basic Health Research, called Riskesdas or Riset Kesehatan Dasar project, initiated in 2007, is an example of this. 258,366 households and 987,205 invidual 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 [65].

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 [66]. In addition, the National Family Planning Bureau also conducts Indonesian Demography and Health Surveys (SDKI, Survey Demografi dan Kesehatan Indonesia) every three years (this began in 1981). The surveys are designed to collect data on fertility, family planning, and maternal and child health. 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) [66].

The Directorate General of Disease Control consists of five directorates: (a) the Directorate of Epidemiology Surveillance (144 personnel), (b) the Directorate of Direct 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 [67].

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) [68]. Primary health centres generate monthly malaria reports from outpatient services and malaria case detection activities. Primary health centres are responsible for analyzing 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 [69-71]. 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 [72], 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, along with the dates of bed net distribution are also reported. As well as larviciding activity which includes: the coverage area, the amount of larvicide used and the date of the activities. 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 the number of fish introduced and the dates of these activities [73].

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 [74,75]. 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 2,366 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 [76]. Since then, the presence of this parasite has been recorded at 1,915 (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 five percent (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 *Plasmodium falciparum*, *P. vivax* is the most common of the *Plasmodium* in Indonesia. To the present day, it has been reported at 1,786 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 three percent (ranging from 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 2,366 survey locations, the presence of these two species was confirmed at 1,606 locations (68%). *Plasmodium 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 co-existed 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 [76]. 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 two percent (ranging from 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 [77]. 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 occuring 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* [78]. The samples were taken from patients with severe and uncomplicated malaria. Initially, the blood samples were morphologically diagnosed by microscopy as *P. falciparum*. *Plasmodium knowlesi* was then determined using a nested 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*), pigtailed macaques (*Macaca nemestrina*) and banded leaf monkeys (*Presbytis malalophos*) [79,80]. The *Anopheles leucosphyrus* group of mosquitoes (about 20 distinct species) transmits *P. knowlesi* very efficiently [81]. In Malaysian Borneo, *P. knowlesi* has been found to affect in particular those humans inhabiting the natural habitat of the simian hosts [82]. *Plasmodium knowlesi* has been reported in humans from the Philippines [83], Thailand [84], China [85] and Singapore [86]. 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) [87]. It seems very likely that the absence of reports of *P. knowlesi* in humans represents a failure to conduct sufficiently sensitive surveys [88]. 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 [82].

Table 2.2. The distribution of human *Plasmodium* throughout the Indonesian archipelago. Sources from which the database of distribution of human *Plasmodium* was regained are listed in the Appendix to Chapter 2.

Islands	Year of sample	No. Sites	No. Exam	No. *Pf* (%)	No. *Pv* (%)	No. *Pm* (%)	No. *Po* (%)
Sumatra	1919-2009	676	239,109	8,487 (3.5%)	7,057 (2.9%)	494 (0.2%)	-
Java/Bali	1900-2006	114	105,734	3,387 (3.2%)	2,773 (2.6%)	221 (0.2%)	-
Kalimantan	1975-2005	17	7,367	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	5,311 (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%)	9,343 (4.8%)	1395 (0.7%)	40 (0.02%)
Indonesia	1900-2009	2,366	1,062,259	61,415 (5.8%)	52,336 (4.9%)	2,299 (0.2%)	51 (0.005%)

2.2.2.2. Reported *vs*. 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 [49,89]. In contrast, the MoH reported only 191 deaths

in 1995 and 1,774 deaths in 2001 [90]. 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 to 1,774 deaths occurred in Indonesia per year between 1994 and 2003 [90].

Lederman *et al*. reported that malaria in Jakarta, the capital city, is not rare and significantly underestimated [50]. 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 [91]. However, in the same period, the MoH reported no malaria data in Jakarta province [92]. 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 [48]. The WHO estimated that there were 2.5 million cases of malaria in Indonesia in 2006 [48]. 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 three thousand 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.

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).

Year	Reported malaria cases			Reported malaria deaths	
	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

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 [93]. The 87 malaria endemic countries into countries were devided with a low risk of transmission (unstable transmission: *Pf* Annual Parasite Incidence (API) < 0.1 cases per 1,000 people) and countries with a moderate or high risk of transmission (stable transmission: *Pf*API $\geq$ 0.1 cases per 1,000 people). In countries with unstable transmission, the researchers assumed a uniform annual clinical incidence rate of 0.1 cases per 1,000 people and multiplied this by population sizes to get disease burden estimates. In countries with stable transmission, they used a modeled 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 of 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 [94]. 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, two million occurred in areas with stable transmission and 2.4 million in areas with unstable

transmission. 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* co-exist. 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 ten districts with 19,483 cases and 66 deaths (CFR 0.3%) [95]. Between 2000 and 2005, there were outbreaks in 19 provinces, covering 65 districts/municipalities, with 58,152 malaria cases and 536 reported deaths (Case Fatality Rate, CFR, 0.9%) [67]. In 2006, outbreaks occurred in eight provinces with 3,705 cases and 30 reported deaths (CFR 0.8%) [96]. Later, between 2007 and 2008, outbreaks were reported in 11 provinces, covering 20 districts, with 1,864 cases and 93 reported deaths (CFR 5%) [97].

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 two months after their arrival [98]. 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) [99]. 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 *An. balabacensis* has played an important role in the persistence of hypoendemic malaria on Java [100]. 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 [95]. 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 *Anopheles sundaicus* [95]. In Kulonprogo [101] 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. 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 [102]. Microscopic diagnostic services in the epidemic zone were found to be unreliable [102].

2.2.2.4. Malaria treatment policy and practice

2.2.2.4.1. Treatment of uncomplicated *Plasmodium falciparum*

The evolution of Indonesia's malaria treatment policy is shown in Table 2.4 [103,104]. 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 three days, 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 four mg/kg weight/day, ten 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 three days, with a single dose of PQ (gametocytocidal) given on the first day (DHA+PP+PQ). The dosages of DHA, PP and PQ are two to four 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 one 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.

Table 2.4. Malaria treatment policy and practice in Indonesia.

Year	Clinical malaria	*P. falciparum*		*P. vivax*	*P. malariae*	*P. ovale*	Prevention during pregnancy	Chemo-prophylaxis
		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) ASU (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 theraphy; AM, Arthemeter; AQ, Amodiaquine; AS, Artesunate; CQ, Chloroquine; DHA, Dihydroartemisinin; DX, Doxycycline; PQ, Primaquine; IM, Intramuscular; IV, Intravenous; SP, Sulfadoxine-pyrimethamine; QN, Quinine; TC, Tetracyline.

The second line of treatment is a combination of quinine (QN), doxycyline (DX) or tetracycline (TC) and primaquine (QN+DX+PQ or QN+TC+PQ). Quinine is given orally three times a day for seven days at ten mg/kg weight/medication. Doxycyline is given orally two times a day for seven days with adults receiving a dosage of four mg/kg weight/day and children of 8-14 years receiving a dosage of two mg/kg weight/day. If DX is not available, then TC is given orally four times a day for seven days at four to five mg/kg weight/medication. However, Doxycyline and tetracycline are not recommended for the treatment of malaria in pregnant women or in children under eight years of age.

Malaria treatment for *P. falciparum* where diagnostic facilities are available but AS and AQ is not, is a single dose of sulfadoxine and pyrimethamine at 25 mg/kg weight 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 [105] and a single dose of PQ as gametocytocide. Chloroquine is given once daily for three days: at ten mg base/kg weight on the first two days and at five 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 confirmation [48]. 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 [106]. 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 1,000-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 seven and thereafter. In addition, serious adverse events were noted in 3 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 seven

and his symptoms resolved over the subsequent eight days. He had a recurrence of *P. falciparum* infection on day 21 and was re-treated 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. falcifarum* malaria in children and adults [107]. The study was conducted in Timika (Papua) between 2004-2005. A combination of DHA and PP was administered at a dosage of 2.25 mg/kg weight/day 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 Polymerase Chain Reaction [108] correction, the risks was 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 [109]. They reported that, of 103 malaria patients treated, 101 had recovered completely by day seven, one had retained parasitemia up to day 14, and the remaining two participants showed the reappearance of parasites on day 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 seven. 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 [110]. One hundred and thirty-five patients were given AS at a dosage of four mg/kg weight and AQ at a dosage of ten mg/kg weight for three 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 Sumatera) in 2006 [111]. The study involved 111 volunteers who were given quinine orally three times a day at ten mg/kg weight/medication for four days and continued at five mg/kg weight/medication for three days. Doxycyline was given orally at dosage of two mg/kg weight/day for seven days. Malaria smears were taken on day 0, 2, 7 and 28. The study showed that only two of 111 volunteers had malaria on day two 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 Sumatera for children. Similar results were also reported by Lubis in Natal (North Sumatera) in 2007 [112]. The study showed that only two of 123 volunteers had malaria on day two, but they found no parasitemia after day seven 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 Sumatera for children.

Tarigan investigated the efficacy of QN+TC against uncomplicated *P. falciparum* infection in Natal (North Sumatera) in 2002 [113]. After randomization, 100 people received QN three times a day for five 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 group for seven 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 seven days resulted high efficacy than those of Q5 ($p < 0.001$). The most commonly complaints reported were tinnitus (78%) and balance disorder (62%), but the difference between groups was not significant. The study concluded that giving QN+TC for seven days was more effective against uncomplicated *P. falciparum* infections in North Sumatera, than giving QN only for five days.

2.2.2.4.2. Treatment of complicated *Plasmodium falciparum*

The first line of treatment for complicated *P. falcifarum* malaria is the administration of artesunate by intramuscular (IM) or intravenous (IV) route and artemether intramuscular (IM) [103]. Artesunate with a dosage of 2.4 mg/kg weight is given on admission, then at 12 hour, 24 hour, and thereafter once daily until oral medication could be taken reliably. Every 60 mg vial contain anhydrous artesunic acid, which is dissolved in 0.6 ml 5% natrium bicarbonate and then mixed with three to five 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% [103]. The quinine drip is administered over eight hours and then followed by 10 mg/kg weight injected every four hours 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 eight hour to provide a total quinine course of seven days (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 [103]. Quinine HCl at a dosage of 10 mg/kg weight is dissolved in the amount of five percent dextrose or NaCl 0.9% normally used for a dosage of 75-100 ml/kg weight/24 hours. This dosage is administered for every eight hour. This treatment is repeated each day until the patient is conscious and able to accept oral medication. If the child is younger than two months, then the dose is reduced from 10 mg/kg weight to six to eight 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 [114]. 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 hour, 24 hour, 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 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 two mg salt/kg weight/day was administered to complete a total course of seven 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 hour (in 500 ml 5% dextrose water or 0.9% saline), followed by 10 mg/kg weight infused over two to eight hour 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 eight hour to provide a total quinine course of seven 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 [115]. Two group of thirty 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, disolved in 10 ml/kg weight five percent dextrose, for first four hours, 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 eight hour to provide a total quinine course of seven 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 *Plasmodium vivax*

The current first line of treatment for *P. vivax* is AS+AQ or DHA+PP [103]. A combination of AS+AQ or DHA+PP is taken orally for three 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 mg/kg weight 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 three 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) [103]. Quinine is given orally three times a day for seven 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 [106]. 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 1,000-patient weeks) than with AS+AQ treatment (36.5 cases per 1,000-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 prolonged 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 2004-2005 [107]. A combination of DHA and PP was administered at a dosage of 2.25 mg/kg weight/day 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 a 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) [116]. Secondly, in 1995, Baird *et al*. documented the therapeutic failure of CQ+PQ in Arso (Papua) in 5% and 15% of cases, on day 14 and 28, respectively [117]. Then, in 1997, Fryauff *et al*. evaluated the efficacy of CQ+PQ as a treatment for *P. vivax* in Arso X/XI (Papua) [118]. 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 [119]. 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 [120].

2.2.2.4.4. Treatment of *Plasmodium malariae* and *Plasmodium ovale*

The treatment for *P. malariae* is CQ once daily for three days at a total dosage of 25 mg base/kg weight [103]. 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 seven 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 two mg/kg weight for two days before traveling to endemic areas, and throughout the duration of stay in an endemic area. Such dose can be taken for periods up to four to six weeks [103]. As a chemoprophylaxis against *P. vivax* infection, the MoH guidelines recommend a weekly dose of five mg/kg weight of CQ to be administered a week prior to entering an endemic area, and to take whilst remaining in the area [104]. 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 [121]. 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) [122]. Forty-five subjects received PQ at 0.5 mg/kg weight every other day and 54 people in the same village received five mg of CQ base/kg weight for 16-19 weeks. A blood film was taken from each subject once a week. The study showed the risk of malaria among people taking CQ relative to that of subjcts 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 sudy 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 [123]. 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 volunter 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 was 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 were 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 one 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 [124]. They found that only one of *P. falciparum* and no *P. vivax* infections occured during the first month after ending PQ prophylaxis. In contrast, six *P. falciparum* and three *P.vivax* infections occured within one 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 attact 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 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 were uniform. The authors concluded that there was no indication that a daily use of PQ or weekly dose of CQ for one year placed subjects at greater risk of malaria infection or to more severe clinical symptoms of malaria than subject 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) [125]. 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 twelve 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 crosschecked 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 health care providers an excellent option to standard suppressive prophylactics for travelers 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 [126]. 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 supresses the usage of PQ as a prophylactic measure.

2.2.2.5. Resistance to antimalarials

Effective treatment is an essential element of malaria control [127]. 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 [48]. Tests for treatment efficacy can be used to help establish whether an antimalarial drug is still effective [128]. Such tests in Indonesia reveal that drug resistance poses a major threat to malaria control efforts [129]. As resistance to one or more antimalarial drugs becomes more prevalent, the malaria control program 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 [130,131]. 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 Supplementary Table S1. Our analysis of the data, extracted from *in-vivo* and *in-vitro* tests, shows that 52% (1,539/2,967) and 59% (1,022/1,743) of the tests, respectively, revealed resistance to CQ. Table 2.5 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%, 1,122/2,006 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 Supplementary Table S2. Eighteen percent (184/998) of the *in-vivo* tests and 64% (310/487) of the *in-vitro* tests revealed resistance to SP. Table 2.5 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, $p < 0.001$).

Supplementary Table S3 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 2.5 presents that only a small number of *in-vivo* tests were carried out. One case of *P. falciparum* resistance to QN were 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.

Supplementary Table S4 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 2.5 shows that the resistance of *P. vivax* in eastern Indonesia was significantly higher than in western Indonesia (57%, 288/502vs. 23%, 43/185; Z-test, $p < 0.001$).

Table 2.5. *Plasmodium falciparum* and *P. vivax* resistance to chloroquine, sulphadoxine-pyrimethamine and quinine by region.

Parasite	Drug	Test	Western Indonesia			Eastern Indonesia			P-value (Z-test)
			No. examined	No. Resistance	Resistance (%)	No. examined	No. Resistance	Resistance (%)	
P. falciparum	CQ	*In-vivo*	961	417	43	2,006	1,122	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**

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 2.6 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. *Plasmodium falciparum* resistance to SP was revealed in eight percent (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 inviduals 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 [132]. 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 seven-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 [133,134]. A year later, Ebisawa and Fukuyama reported two cases of resistance in Manokwari (Papua) [135]. 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) [136]. In 1981, Pribadi *et al.*documented *P. falciparum* resistance to CQ in Southern Sumatra [137]. Treatment with 1,500 mg doses of CQ base failed to

cure the patients, as did increased doses up to 2,250 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 [138]. 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 [130].

Rumans *et al*. first reported *P. falciparum* resistance to SP in 1979 in Jayapura (Papua) [139]. 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 [140,141].

2.2.2.5.1.2. *Plasmodium vivax*

Dondero *et al*. carried out two *in-vivo* tests in the Seruwai Plantation, Labuan Deli (North Sumatra) in 1973 and 1974 [132]. However, a total of sixteen individuals with *P. vivax* infections, they found no resistance to CQ during their seven-day follow up. Guldelfinger *et al*. also reported similar results on 12 individuals in Belu (Lesser Sundas) in 1973 [77].

2.2.2.5.2. Evaluations since 1985

2.2.2.5.2.1. *Plasmodium falciparum*

Table 2.6 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% (1,475/2,715) 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% (960/1,617) 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 not different between 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 [142]. They reported that 60% (6/10) of isolates required higher doses of QN to achieve 50% inhibition of schizont development.

2.2.2.5.2.1. *Plasmodium vivax*

Table 2.6 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 [143]. 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 eight 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. *Plasmodium malariae*

The susceptibility of *P. malariae* to anti-malarial 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 [144]. 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). *Plasmodium malariae* was the most common parasite, accounting for a majority of malaria cases (41% in Selusung 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 100 micro grams per litre) on day eight 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, *i.e.*, the 36 hour cycle of *P. vivax vs*. the 48 hour cycle of *P. falciparum* malaria. However, Siswantoro *et al*. made different findings during research conducted in Timika (Papua) in 2005 [145]. 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 seven (0/42) and day 28 (0/27).

2.2.2.5.2.4. *Plasmodium ovale*

Siswantoro *et al*. evaluated the efficacy of CQ as a treatment in 14 subjects with *P. ovale* malaria in Timika (Papua) [145]. 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. Ministry of Health 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.

Table 2.6. *Plasmodium falciparum* and *P. vivax* resistance to chloroquine, sulphadoxine-pyrimethamine and quinine throughout the Indonesian archipelago.

Parasite	Drug	Test	Prior 1985			Since 1985			P-value (Z-test)
			No. examined	No. Resistance	Resistance (%)	No. examined	No. Resistance	Resistance (%)	
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**

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 [146]. 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 two hundred 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 present 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 [147]. Van der Brug claims that malaria explains, to a large extent, the high incidence of morbidity and mortality in 1733 in Batavia [147]. Up until 1733 approximately 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 approximately 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 (2,000 – 3,000 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 *An. sundaicus*, a species which is an efficient and notorious vector of coastal malaria.

Doolan *et al*. reviewed naturally acquired immunity to malaria [148]. In the review, they summarised 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) [76]. 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) [149]. 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 lifelong uninterrupted exposure [150]. 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 [150].

The Civil Medical Service (CMS) was founded in 1826 [146], and then reorganized in 1911 [151]. 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 combatting 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 sub-division 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, i.e., building out or away from anopheline breeding sites. The Central Malaria Bureau offered training to over a hundred 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 [152]. Watson had visited Swellengrebel in Sumatra in 1913 and introduced him to the working concepts of species sanitation

[153]. 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 *Anopheles 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; 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 [153]. Swellengrebel embraced this approach [152], 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 [153]. 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) [153]. Out

of all the sites across Indonesia, 41 dealt with a total of eight malaria vectors: *An. sundaicus* (26 sites), *An. aconitus* (nine sites), *An. maculatus* (six sites), *An. sinensis* (three sites), *An. hyrcanus* (two sites), *An. minimus* (one site), *An. bancrofti* (one site) and *An. 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 *An. sundaicus* (13 sites), *An. aconitus* (three sites), *An. maculatus*, *An. sinensis*, *An. bancrofti* and *An. 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 *An. 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 1,000 of the population per year after implementation in Sibolga (North Sumatra).

The sanitation measures implemented in Sibolga are exemplary of anti-malaria 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 eight percent 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 *An. 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 [153]. This solution cost five times the amount that De Vogel had had in mind. Nonetheless the project roughly halved the spleen index.

Schüffner introduced a new form of species sanitation in 1916-1917 [152,153]. 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 fish ponds harbouring breeding sites for *An. 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 one 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 fish ponds 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 *An. 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 [151,152]. 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 5,000 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 [153]. 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 *An. aconitus* as the vector in Cihea [154]. Later in the same year, Mangkuwinoto, as health officer for the region, confirmed *An. 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 occured in fields where rice had been harvested and the remaining stalks simply trampled down [152]. These rice fields were still being deliberately flooded in preparation for the next planting. Mangkuwinoto's recommendations resembled those of Van Gorkom [153]. 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 two weeks thereafter, the irrigation supply to the area of the first scheme was reduced by 1/6 before being completely stopped on April 15 [153]. 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 [152]. 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 *An. 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 [151]. The annual all cause death rate fell significantly from 34 per 1,000 population (1919) to 15 per 1,000 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 [153]. 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 1942-1945, during the Japanese occupation of Java [152]. The Japanese occupiers identified *An. 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 approximately 30%. At some later date, probably during the Global Eradication campaign of the 50s and 60s, 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 [155]. Between 1989 and 1999, not a single case of malaria was reported by the two primary health centres (Bojongpicung and Ciranjang). *An. 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 [91] 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 [153]. His investigations led him to identify ricefields and marine fishpods 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 [156]. They noted that the mortality rates and spleen indices among communities surrounding marine fishponds were higher than in other communities. *An. 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 fish ponds, 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 [153]. 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 meters) had been much greater than it was here (one meter).

In Pasuruan (East Java), in 1922, Reijntjes disproved the notion that cultivated fish depended on the water plants at the surface of the fish pond for food [153]. He showed that the bluegreen 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 hectares of fishponds were sanitized against *An. 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 1,000 population (1925-1929) to 27 per 1,000 population (1931).

As far as the use of quinine as a malaria treatment and a method of control was concerned, Indonesia was well-known as being the most productive producer of chinchona 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) [157]. 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 [158]. 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 Goverment. The British Government refused and George then sold one 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 [159]. 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 possiblity of controlling malaria during the Japanese invasion of 1942 to 1945 [160]. 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 [161]. 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 labor 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%; 926/7,677) was higher than it was in either Sumatra (8.9%; 3,142/35,115) or Java (5.1%; 87/1,696). The prevalence of *P.vivax* was also higher in Papua (6.1%; 469/7,677) than it was in Sumatra (3.4%; 1,196/35,115) or Java (3.3%; 56/1,696). However, the prevalence of *P. malariae* was much higher in Java (13%; 221/1,696) than in either Sumatra (1.2%; 421/35,115) or Papua (0.5%; 38/7,677).

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 health care 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 multi-dimensional 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 re-introduction of Dutch military rule and authority. In 1947 and 1948, the nationalists fought against the re-introduced Netherland 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 [160]. 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 1,200 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 re-organized 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 [161,162].

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 *An. aconitus* and *An. subpictus* for 6 months in Cianjur (West Java) [163]. In 1950 Bonne-Wepster and Swellengrebel reported that the residual effect of DDT on *An. sundaicus* lasted for five months in Tanjung Priok (north Jakarta) [164]. 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) [165]. The results of these studies showed the way towards an era of attacking endemic malaria.

The malaria control program of the fledgling Republic of Indonesia received generous support from their counterparts abroad. Suparmo detailed the difficulty in acquiring DDT and sprayers [166]. Mainly, the malaria control program 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 a Malaria Control Program (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 [167].

In 1954, however, DDT-resistance in mosquitoes was reported. Crendell discovered DDT-resistant *An. sundaicus* at Cirebon (West Java) [168]. In 1956, Chow and Soeparno reported that, in Semarang (Central Java) and Surabaya (East Java), *An.*

sundaicus had become 23-27 times more resistant to DDT than when the insecticide had first been implemented [169]. Dieldrin was introduced to combat this DDT resistance. *An. sundaicus* gradually disappeared from the northern coastal area of Java [170]. 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, *An. 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 two gr/m^2 dosage of 5% DDT wettable powder [171]. The parasite rate fell from 47% (736/1,566) to 20% (260/1,301) in hyperendemic areas and from 16% (346/2,162) to 6% (81/1,350) in mesoendemic areas. Meanwhile, in control areas (in Nimboran), the parasite rate dropped from 87% (871/1,001) to 64% (495/773). In experiment areas, the sporozoite rate fell from 1.2% (9/744) to 0.2% (4/1,657) in the punctulatus group of mosquitoes. Metselaar found that the spraying did not completely prevent transmission as a few sprozoite-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 [172]. 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 [162,173]. 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% (700/2,363) to 7% (90/1,346). 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 [174] and Dumoga (North Sulawesi) in 1951 and 1952. In Metro, the prevalence of malaria in infants (0-12 months) fell from 21% (392/1,849) before spraying to two percent (27/1,506) after spraying [175].

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. Health care 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 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 a Malaria Control Program 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) one year of pre-eradication, (2) three years of attack and three 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 [170]. With re-infection no longer an issue, all remaining malaria cases were to be treated and cured. Only a few cases would then

remain after three years. Any relapses or imported cases were to be detected and cured. DDT spraying operations were conducted twice a year. Over nine thousand 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. *An. sundaicus* and *An. aconitus* were found to be resistant to the DDT replacement, dieldrin. The first record of dieldrin-resistance in *An. sundaicus* was on the coast near Yogyakarta in 1959. *An. aconitus* was found to be resistant to dieldren in Subah (Central Java) in the same year [176]. Reports of dieldrin-resistance came from South Sumatra and all of Java. It became apparent that dieldren-resistance was spreading in *An. sundaicus* and *An. 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 1,000 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 1,000 of the population between 1963 and 1968 [153]. Unfortunately, no malaria data was reported between 1959 and 1962. Passive case detection never reached the minimal 10% of annual blood examination rate (ABER) as recommended by the WHO [177]. In 1966, the number of malaria cases increased and within two years the number was 4 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 [170]. In the period of violence that followed the attempted coup d'état in 1965, the NMES discontinued all its activities [153] 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 Malaria Control Program (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 ouside 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 passive case detection (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. Indoor residual spraying 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 1986-1988, 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 insectides included fenitrothion, deltamethrin, bendiocarb, lamda-cyhalotrine and malathion.

Another vector control tool used in Indonesia was larviciding. Larviciding was first conducted in Bali in 1974 using kerosene [178,179]. It was estimated that, as a result of these operations, 0.7 million people were protected and 70 hectares of larval habitat across Bali were treated. During this period, larviciding was conducted in areas where *An. sundaicus* was found; fenithrothion was used at a dosage of one 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 *An. aconitus* [180]. 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 *An. 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 hectares in 2000 [181]. Only 2.6 million hectares 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 *An. sundaicus*. This is not merely conjecture; in the past the loss of mangrove forests has brought on malaria epidemics at Teluk Betung Port (1915) [182], Batavia (1919) [156], Pariaman (1921) [182], Belawan Port (1922) [183], Nias (1929) [184], Tanjung Priok (1939) [182], Cilacap (1984) [185] and South Lampung (1992) [182]. 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 five years, as well as reducing the density of the vector population [186].

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 [187]. They suggested ten 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 three 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 insecticide-treated mosquito nets, 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 behavior [188,189].

In summary, control activities during the period 1969-1999 were centered 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 (2000 - present)

During this period, two global events affected malaria control policy in Indonesia. The first was the Roll Back Malaria (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, 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 activites: (1) active and passive case finding coupled with periodic mass surveys, including a mass fever survey, a mass blood survey and a malariometric survey (all of which require community participation at the designated village malaria post), (2) case management with effective drugs, 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 [190]. Malaria elimination activities are to be conducted in 4 stages. These stages include: Stage 1) The thousand Islands [91], 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 establised to store, analyze 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 [2,5,191-193].

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 [69], case detection activities cover active and passive case detection, mass fever surveys, mass blood surveys, malariometric surveys, migration surveillance and contact surveys. Active case detection 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 1,000 per annum) or medium case incidence (API $\geq$ one case per 1,000 per annum) biweekly and monthly home visits, respectively, are prescribed by the MoH. In contrast, passive case detection 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 1,000 people (or an annual rate of 36/1,000), 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). A mass blood survey 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 active case detection (ACD) by village malaria workers and passive case detection (PCD) by health facilities in Jepara (Central Java) during the years 1994-1998 [194]. They found that ACD detected more cases than PCD (ratio 1.4 : 1), covered a broader geographical area (4.7 vs. 4.1 kms; $p < 0.05$) 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 seven 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 [195]. 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 no malaria surveys were conducted during this period and neither 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) [195]. Each group of ten houses elected a leader to report suspected malaria cases to the community malaria cadre (who each represented four groups of ten 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 hours 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 one year, it was found that the Dasa Wisma scheme resulted in the collection of significantly more slides (24%; 538/2,225) than the village malaria worker scheme (19%; 212/1,124) ($p < 0.001$). 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 two years showed that Dasa Wisma continued to perform better (13%; 297/2,225) than the village malaria worker scheme (3%; 37/1,124) ($p < 0.001$). 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 two 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 continous 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 [196]. A program of weekly chemoprophylaxis was instigated, with chloroquine being administered to about 700 residents by nine cadres. Assessment after one 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 [197]. 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 [198]. 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 [199].

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 [69]. Therefore, improving PCD represents an important goal in supporting malaria control in those relatively high endemic settings. Sekartuti *et al*. reported efforts aimed at improving PCD, i.e., improving treatment seeking behaviour among residents, in Banjarnegara (Central Java). They used slide shows for school children and patients [200]. Shinta *et al*. , in turn, noted the important role played by community leaders in Purworejo (Central Java) [201,202]. Improving the

effectiveness of PCD provides additional benefits such as improving microscopy competency, and community awareness [203].

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 [204]. 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 responsility 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 center staff would give radical treatment. Hunt *et al*. noted the advantages and constraints involving UKS in passive case detection. 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 is 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 [205]. 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, i.e., 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 lauched under Dutch administration in 1905 [206]. 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 [206]. 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 33-69 per 1,000 of the population [207]. In 1998, the highest numbers were reported from Papua (274/1,000), East Nusa Tenggara (120/1,000) and West Nusa Tenggara (95/1,000). 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 [208]. 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) [209]. Residents of Arso XIV came predominantly from Java (83 % of residents),

where the risk of malaria has been less than one infection per 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 four infections/person-year. They found that the overall incidence of evacuation was 7.5/100 person-years. 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; $p < 0.001$). Relative risk (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 is 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 [187]. Malaria blood survey of those sites showed 30% to 70% prevalence of parasitemia with virtually universal symptomic malaria. Even several years after settlement, the incidence of malaria at Arso ranged from two to five infections per person per year [210], 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 [187]. 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 [211]. This estimate agreed with the measurements of force of infection [210].

Baird *et al*. observed that nurses in transmigration villages at that time relied almost entirely upon a clinical diagnosis of malaria [187]. Therefore, asymptomatic carriers went undetected and fueled the conditions for an epidemic. Baird *et al*. concluded that new tranmigrants 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 [212]. During the 34 months of their continuous observation, the health clinic they had established received over 22 thousand visits (an average of 700 visits per month) from both indigenous Papuan people and the Javanese transmigrants. They found 3,631 new cases of malaria in the Javanese transmigrants. In other words, approximately 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 - 1.5 infections/person-year [213]. 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 [214].

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 [215]. Dakung *et al*. evaluated 3,506 fever patients in Jakarta who were seen between 1964 and 1980, and found that 357 (10%) had malaria [216]. 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 [50]. 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 one week of travel is much more common in civilian travelers (5/26) than in military travelers (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 [217]. They found a slide positivity rate of 0.4% (11/3,106). 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 [218]. 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. Travelers 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 Malaria Control Program of Indonesia lists three diagnostic tools for routine use: clinical diagnosis, microscopic diagnosis, and rapid diagnostic tests [69].

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 [219]. A diagnosis of clinical malaria was based on fever or history of fever in the last 48 hours 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 have been acknowledged and in their plans for malaria elimination, Indonesian health authorities call for all primary health centres to confirm malaria using microscopy [190]. The Indonesian National Institute of Health Research and Development [205], 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 [220], 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 [205]. 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 [48]. The World Malaria Report of 2008 reported that 1,246,324 microscopic or RDT diagnoses had been made in Indonesia throughout 2006 [48]. 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 [221] 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 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 6 districts in eastern Indonesia had microscopes [205].

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 [222]. 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 [223]. 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 [198]. Ompusunggu *et al*. reported similar problems in West Sumba (Lesser Sundas) [224]. 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 health care centres in Sambas (West Kalimantan) involving 41 laboratory workers, paramedics and heads of clinics [225]. 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 [226].

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 rapid diagnostic tests or RDTs [221,227], and all employing antigen capture by monoclonal antibodies. Like the extremely simple take-home pregnancy test kits, the malaria RDT produces a colored line within 5-20 minutes. 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 [228]. The WHO has recently published a systematic evaluation of the performance of 41 commercially available RDTs from 21 manufacturers [229]. 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 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 2,000 or 5,000 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 [230]. 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 $\leq$ 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 $\leq$ 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 [231]. 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 500–1,000 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 [219]. 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 [232]. 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 Sumatera) in 2006 [233]. 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 [234,235]. 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 [222]. 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 [198]. Correct microscopy requires persistence, experience and dedication by the microscopists and the systems supporting them [222].

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 [236]. 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 4 readers with demerit points greater than one standard deviation above the mean. A composite diagnosis and parasite density was 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 per 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. 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 [65]. 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 [65]. Table 2.7 shows the accessibility to health facilities by region throughout the Indonesian archipelago. 48% of those households sampled were located within one km of health services (western: 49% vs. eastern: 46%). Another 46% were located between one and 5 km from the services (western: 47% vs. eastern: 46%). Accessibility varied widely among provinces, e.g., the percentage of households within one km from a health facility ranged from 27% to 73% [65]. About two thirds of households were within 15 minutes of a health facility (western: 71% vs. eastern: 56%) and most of the remainder were between 15 and 30 minutes (western: 22% vs. eastern: 27%). Only 9% of households reported needing over 30 minutes 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 2.7 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 kilometer of UKBM (western: 80% vs. eastern: 76%). Eighty-five percent of households were within 15 minutes of a UKBM (western: 88% vs. eastern: 81%). Seventy nine percent of households were within a kilometer of a UKBM, compared to just 48% which were within a kilometer 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 [65]. The effectiveness of the village drug post

in providing easier access to antimalarials cannot be adequately assessed until more such posts are established.

Table 2.7. 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 minutes 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 minutes of UKBM	88%	81%	85%

2.4.3.2. Treatment seeking behaviors

People exhibit distinct behavior in seeking treatment for malaria or a malaria-like illness. Such behavior 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) [237].

Sanjana *et al*. assessed malaria knowledge, attitudes, and practices in communities experiencing epidemic malaria in Purworejo (Central Java) in 2001 [238]. They surveyed 1,000 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 approximately 100 meters 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%). 358 (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 health care providers (22%). The median time required to reach the place of consultation was 15 minutes (range: 0–240 minutes). The modes of transport employed to reach the source of treatment were: 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 6,000 rupiah (US $ 0.6) and 7,250 rupiah (US$ 0.7), respectively.

Karyana *et al.* also conducted a cluster randomized survey of malaria treatment seeking practices in Timika in 2007 [239]. They reported that 26% (302/1,177) of the people surveyed did not seek treament when they had febrile illness as they did not feel unwell enough (62%, 198/302). Of those people with febrile illness who did seek treament, 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 National Institute of Health Research and Development and the Indonesian Centre of Statistics [66]. The survey selected 9,082 households and 41,764 respondents were interviewed across all provinces [240]. Of these, 3,947 respondents were under five 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%) [241].

In contrast, Kasnodihardjo *et al*. found a high rate of consultation of health professionals among respondents with malaria in Sumatra [242]. 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 [243]. 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 [244]. About one percent 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 [204]. Most of them (77%) did not go to school or working when they had malaria-like syptoms. As a result, on average, they missed five days of working or school. Mardiana *et al.* reported that, in Jepara (Central Java), in 2000, 24% of 100 people interviewed waited one or two days after they had fever before visiting a health facility [245]. 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 [246]. About 25% of the 100 respondents would visit a health facility within the first three days of being ill. Three percent of repondents 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 6,484 respondents in four districts in Central Java in 2001, 75% could not describe treatments for malaria [247]. However, of those repondents who had already had malaria, only two percent 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 1,577 health personnel in pregnancy clinics had received training on malaria treatment and prevention [205]. This proportion was even lower in hospitals (0.4%, 6/1,245) 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 [248]. 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., behavioral 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 insecticide-treated bed nets (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 [248]. 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 malaria control program recommends insect growth regulators (methoprene, pyriproxyfen) and microbial insectides (the bacterium *Bacillus thuringensis israelensis* or BTI) as the preferred larvacidal measures. Methoprene [249] and pyriproxyfen [250] 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 [251], 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 *An. aconitus* [252-256], *An. barbirostris* [257-259], *An. maculatus* [260,261], and *An. sundaicus* [262-266]. However, BTI application is 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 [248]. Once this has been done, the task would be to determine the sufficient dosage of larvacidal component [262]. 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 *An. aconitus* larvae in Semarang (Central Java) in 2000 [256]. They administered at 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 three 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 first three 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 two 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 *An. aconitus* larvae until three days.

In 1994, Blondine *et al*. executed a trial of BTI against *An. barbirostris* in East Flores (Lesser Sundas archipelago) [257]. 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 four weeks. It was revealed that, within 24 hours, 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 [258]. The study used three intervention ponds and one control pond. The tested dosages were 0.06 ml/m^2, 0.075 ml/m^2, 0.1 ml/m^2 and 0.12 ml/m^2. They found that mean larval densities within 24 hours in intervention ponds fell from 55 to seven larvae per 20 dips at dosages ranging from 0.06 ml/m^2 to 0.12 ml/m^2. No village-scale study of BTI against *An. barbirostris* has been reported from Indonesia.

Munif and Pranoto conducted a trial of BTI against *An. maculatus* at Kulonprogo (Jogyakarta, Java) in 1994 [260]. They evaluated three distinct means of application: sprayers, plastic bags, and direct pouring into streams. The sprayer application used a dosage of 1.5 liters per ha. Spraying was done evenly on river pool surfaces. The plastic bag application was done by placing a 1.5 liter per 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 liters of water. The water was then allowed to flow into the river at an upstream location. Each method was repeated 4 times over 21 days, with a weekly interval between each run. Larvae were collected at one hour prior to treatment, 24 hours post treatment, and then again after weeks one, two and three. They found that the spraying application reduced larval density from 95 to 3 larvae on day one, a figure which increased to 8 larvae (week one), dropped again to one larvae (week two) and finally increased to 21 larvae (week three). In other words, the mean reduction of larval density relative to pre-treatment was above 96% up until week two, but only 34% in week three. The plastic bag application reduced larval density from 95 larvae to none on day one, but this increased to 7 larvae (week one), 23 larvae (week

two) and finally 61 larvae (week three). The plastic bag application therefore reduced larval density relative to pre-treatment by about 90% up until week two, but only by 36% in week three. The direct pouring technique prompted larval density to fall from 79 larvae to one larva (day one), which dropped further to none (week one) and then increased to four (week two) and seven (week three). This technique took longer to take effect, i.e., the reduction of larvae was only 7% on day one and 58% after week one. However, a reduction rate of 98% was reached after weeks two and three. 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 *An. maculatus* larvae in Kulonprogo [101] in 2008 [261]. 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 hours (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 x LC90) and 5.9 ml/100 ml water (10 x 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 day 1, 2, 4, week one, week two and week three 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 two days, then decreased from 78% on day 4 to 37% on week three after application. At dosage of 2.95 ml/100 ml water, the reduction of larvae density relative to control was 99-100% on first two days, then decreased from 87% on day 4 to 41% on week three after application. At a dosage of

5.9 ml/100 ml water, the reduction of larvae density relative to control was 100% on first two days, then decreased from 87% on day 4 to 61% on week there 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 was effective against *An. maculatus* larvae.

Various studies consistently show that BTI effectively reduces densities of *An. sundaicus* larvae in Indonesia. Kirnowardoyo *et al*. evaluated the efficacy of 3 distinct BTI H-14 formulations (liquid, granule and briquette) against *An. sundaicus* larvae in Banyuwangi (East Java) and Jembrana (Bali) in 1984 [262]. Active BTI 100 ml was diluted into 8 liters 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, six hours prior to treatment and then again 24 hours after treatment. They found that the larval density had fallen from 27.3 to 3.5 larvae/10 dips (reduction = 87%) 24 hours after the first application. The mean reduction of larval density for each application ranged from 76% to 100%. The second (granule) formulation containing 500 grams of BTI was dispersed over a 10,000m^2 water surface. The evaluation of this formulation was done by collecting larvae every three days for a month. The granule formulation of BTI H-14 effected a reduction from 38 larvae/10 dips to 0.2 larva/10 dips (reduction 99%) on the first day after treatment. After three days, however, the larval density increased to 54 larva/10 dips. Between day 6 and day 25 larval density ranged from 29–59 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 three meters. 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 hours after the treatment. The effect of the briquettes remained satisfactory (approx. 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 *An. sundaicus*, whilst the granule formulation was less successful.

Blondine *et al*. examined the efficacy of the liquid formulation of BTI cultured in coconuts against *An. sundaicus* larvae in Cilacap (Central Java) in 2003 [263]. 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 gram) 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 hours. 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 was observed a day before application, then on days one, two and four, and week one and two after application. The reduction of larvae relative to control was 100 % on day one, 91% after week one, and 84% after week two. 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 *An. sundaicus* larvae.

Hakim *et al*. studied the residual effect of granule and liquid BTI formulations in Ciamis (West Java) in 2005 [264]. Fifteen *An. sundaicus* larvae were caught in shrimp ponds

and put into the plastic containers. The larval mortality was observed after 24 hours. Probit analysis showed LD90 at dosage of 0.869 kg/ha for granule and 1,795 ml/ha for liquid formulation. Then authors tested the LD90 and two other doses: 0.5 gram/ha (granule) and 1,000 ml/ha (liquid). For granule formulation, they found 100% mortality at dosage of LD90 and the recommended dosage on day 1. After two 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 two 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 four 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 [101] in 1993 [267]. 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 *An. maculatus*, *An. flavirostris* and *An. 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%, 35/1,257 vs.

control: 86%, 472/552, $p < 0.001$) and 0.05 ppm (intervention: 1.3%, 13/1,033 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 five-fold presented no apparent advantage.

Mardiana reported the efficacy of methoprene against *An. farauti* larvae at laboratory-scale in 1996 [268]. 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 *An. farauti* larvae at least in laboratory-scale.

Waris evaluated the efficacy of pyriproxyfen as larvicidal control of *Anopheles subpictus* in South Kalimantan in 2003 [269]. A total of 1,200 *An. subpictus* larvae were kept in groups of 150 in 25 x 20 x 3.5 cm containers for each concentration plus a control group. A dosage of 2 grams pyriproxyfen 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 *An. 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 *An. aconitus* in Banjarnegara (Central Java) in 1994 [270]. They evaluated a 900 m² 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 *Metarhizium anisopliae* is an effective control agent. However, the further documentation of the entomopathogenic fungus in community-based larvaciding studies are still lacking.

In terms of community support for the application of larvicides, Blondine *et al*. interviewed 60 people in Cilacap (Central Java) in 2003 [263]. 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 [271-276]. This approach has been most effectively applied in man-made mosquito breeding sites. It has a long history and constituted the core of malaria control program strategies before the introduction of DDT [127,273]. 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 [277]. In 1984, Sharma identified 315 species of larvivorous fish [278]. 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 [279,280]. Many authors suggest the same steps in fielding fish aimed at reducing the risk of malaria [280-285]. 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 behavior 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 malaria control program in Indonesia provides guidelines for the introduction of larvivorous fishes [286]. The recommended larvivorous fish in Indonesia are *Poecilia reticulata* (Indonesians call these ikan guppy), *Aplocheilus panchax* (ikan kepala timah)

and *Gambusia affinis* [286]. In Central Java, Nalim *et al*. investigated the potential of *Poecilia reticulata*, first introduced into Indonesia in 1961, as a method of control against the *An. aconitus* mosquito, which is found in rice fields [287-289]. The study involved 92 farmers cultivating 24 hectares 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 one-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 two fish fry per 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 *Poecilia reticulata* reduced *An. aconitus* emergence from over 3 mosquitoes/m^2/day to 0.01 mosquitoes/m^2/day. More importantly, the slide positivity rate for malaria among residents dropped from 17% to 0.2% in the five 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 [290], to control the fishpond mosquito *An. Sundaicus* [291]. Fishponds were found in many locations in the study area. Each of three ponds (6 x 7 meter) was allocated as treatment and control ponds. The ponds were filled with water to a height of 30-50 cm. After four weeks all ponds had grown water plants and *An. sundaicus* larvae were found in all of the ponds. *Oreochromis niloticus* fish were distributed at 3 fish/m^2 or 126 fish/pond. The size of these fish ranged from 6-8 cm in length and their weight ranged from 10-12 gram. 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 one percent of 636 respondents interviewed in three sub-districts in Central Java recognized of the role of fish in paddy-field for the control of mosquito larvae [204]. 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 [198]. Similar findings were reported from Eastern Indonesia [205]. 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 2.2.3.1. 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 [292]. She evaluated the impact of draining two rice paddies; one selected as an intervention plot and the other as a control plot (three km^2 each). The two sites were six km apart but both had a similar ecological setting. Larval

densities were measured twice a week from the beginning of planting until the harvest five 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 three days after two months of rice growth, and were then flooded again for 10 days. A month after the paddy had been flooded, all species (*An. aconitus*, *An. annularis*, *An. vagus*, *An. indefinitus*), except *An. barbirostris* (larvae density: 0.04 larvae/dip; adult density: 0.61 mosquitoes/day/m^2) were absent. The author concluded that three 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 *An. sundaicus* in shaded and unshaded fish farming ponds in North Sumatra in 1986 [293]. Four fish ponds were shaded for the experiment. The size of these ponds was 2.5 m in width and 7 to 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 larvae/10 dips 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 larvae/10 dips 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 fish ponds, as nipa palm fronds are typically about two meter in length. This measure also requires the monthly replacement of the Nipa leaves.

In Bintan, in 1993, Pribadi *et al*. studied the community's knowledge about, and attitude towards malaria, as well as the malaria prevention practices employed [294]. 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 was 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), the Ford Foundation and UNICEF [295]. 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 insecticide-treated mosquito nets (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 five years by ITN was low (3.3%). Fewer children under five 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 Health Household Survey (HHS) was implemented by the Indonesian National Institute for Health Research and Development and the Indonesian Centre of Statistics [66]. A stratified two-stage design was used to select 9,012 households. A total of 38,276 respondents were interviewed across all provinces [240]. 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 [238]. 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. 53% 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 [247]. The study was conducted in 4

districts in Central Java: Banjarnegara, Pekalongan, Kebumen and Jepara. There were 15,901 respondents of all ages from 4,032 households. The authors aimed to show the association between knowledge about malaria and the number of malaria cases. Remarkably, only 6,485 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 [238], 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) [244]. 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, i.e., obtaining and using mosquito netting. Sekartuti *et al*. conducted a health education intervention study at high risk sub-districts in epidemic Purworejo in 2000 [200]. 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 [296]. 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 [245]. The low income respondents prioritized spending money on food as opposed to buying a net. Ompusunggu *et al*. observed the behavior of 46 patients with a *P. falciparum* infection in Mbilur Pangadu, West Sumba (Lesser Sundas) in 2002 [297]. 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 behavior 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 [298]. 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 onself 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 practised 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 [299]. Most subjects tended to burn mosquito coils at night, starting at 8 pm. 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) [300]. The study took place in three villages with 1,790 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 two 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 [301] reported that a very low rate of health personnel ever received training in the use of impregnated nets (0.7%; 14/2,104) 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 [302]. 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 [303]. 138 Papuan inhabitants were recruited from a ITN treated vilage for serological investigation. Their sera were analyzed for total IgG before intervention and two years after intervention using synthetic peptides, i.e., $NANP_5$ and $EENV_4$-BSA. Analysis was then carried out only on individuals who were IgG positive before and after two 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 [304]. 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 approximately 2 x 2 x 2 meter were treated with a dosage of etofenprox at 0.2 g/m^2. Treatment was conducted by trained health workers every six months for 18 months. Nets were returned to participants after each treatment. The residual mortality against 90 *An. barbirostris* was evaluated for 24 hours after a 30-minutes exposure to the nets. The test were repeated on week one and two, and each month for five months. Night mosquito landing density was evaluated every night (18-24pm) and morning resting densities at 6-7 am. A malaria survey was conducted three months before intervention began and one 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 five months after treated the mosquito mortality rate was 100%. In the treated village, the indoor mosquito landing densities reduced from 0.29 mosquitoes/man-hour (before intervention) to 0.22 mosquitoes /man-hour (after six 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 term 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 six 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 *An. maculatus* and *An. barbirostris* [305]. 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 one day. Finally, the nets were sprayed using IRS sprayer and also dried naturally for one day. A direct contact test against *An. maculatus* and *An. barbirostris* was conducted by exposing 30 mosquitoes of each species for 3 minutes to each of the treated nets. The mosquitoes were then transferred into clean cups (no insecticide). The mosquito mortality rate was observed for 24 hours. Against *An. 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%). *An. maculatus* mortality rate in impregnated nylon nets (99%) was higher than sprayed nylon nets (87%) or crumpled nylon nets (48%). Against *An. 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%). *An. 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 *An. maculatus* and *An. barbirostris*.

Barodji *et al*. evaluated the the efficacy of ITN against *An. barbirostris*, *An. subpictus* and *An. sundaicus* in East Flores, Lesser Sundas in 1996 [306]. 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 (18-24pm). A malaria survey was conducted three months before the intervention and every three months after the ITN application. The study showed that the cyfluthrin treated nets provided impact in *An. sundaicus* and *An. subpictus*, but not *An. barbirostris*. Against *An. barbirostris*, indoor mosquito landing densities only reduced from 0.74 mosquitoes/man-hour (before intervention) to 0.68 mosquitoes/man-hour (after three months and six months). However, outdoors its landing densities increased from 0.4 mosquitoes/man-hour (before) to 0.8 mosquitoes/man-hour (after three months and six months). Against *An. subpictus*, indoor mosquito landing densities reduced from 7.7 mosquitoes/man-hour (before) to 2.5 mosquitoes/man-hour (after three months and six months). Outdoor mosquito landing densities decreased from 10.1 mosquitoes/man-hour (before) to 4 mosquitoes/man-hour (after three months and six months). Indoor and outdoor landing densities of *An. sundaicus* before intervention were 2.4 mosquitoes/man-hour and 1.3 mosquitoes/man-hour. Less than 0.03 indoor or outdoor mosquitoes/man-hour landing both three month or six months after intervention. In term of malaria prevalence, the authors reported that slide positivity rate reduced from 17% (48/275) before the ITN intervention to 13% (17/128) three months after application and 4% (11/250) six months after. However, the malaria prevalence increased to 7.5% (39/518) nine months to 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 *An. sundaicus* and *An. subpictus* in East Flores, and decreased malaria prevalence for three to six months after application.

Hakim *et al*. compared the mosquito mortality rate among permethrin, deltamethrin and lambda-cyhalotrine ITNs at dosage of 0.5 g/m^2 against *An. sundaicus* in Ciamis (West Java) in 2006 [307]. Each four-m^2 net was treated by those insecticides and mixed with adhesive glue contained 86% acrylic and 14% arthathrin. This acryclic 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 *An. sundaicus*. At five minutes intervals, the number of dead mosquitoes were recorded and after 40 minutes all remaining mosquitoes were moved to clean cup and observed for 24 hours. After the observations were completed, nets were washed with water and detergent for five minutes, 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. Lamda-cyhalotrine ITNs, mosquito mortality rate was 100% after 30 washes. The non-adhesive permethrin ITNs, mosquito mortality rate reduced from 100% before washing to 92% after one wash and diminished gradually to two percent after 30 washes. The study concluded that in the laboratoty at least, the presence of acrylic and arthathrin was effective to maintain ITN's efficacy against *An. sundaicus*.

Despite the distribution of 2.4 million ITNs from 2004 to 2007 [4], 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 four-fold higher risk of developing severe malaria than their children [98,187]. 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, i.e., in a hypo- to meso-endemic 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 [308,309].

According to the National Economic and Social Survey [310] 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 two percent 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 & 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 [297]. 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 [238]. 1,000 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 two percent of the 1,000 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 [299]. The residents of 11 villages made up the sample population. A 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 [198]. 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 [298]. 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 [296]. One hundred households were randomly selected. Only three of these used screening. However, none of these studies analyzed 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 behavioral, i.e., 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% [298,311-313]. Mosquito coils are inexpensive and widely available in endemic settings [314]. Saikhu and Gilarsi used secondary data from the Benefit Evaluation Study (BES) conducted in 4 districts in Central Java; Banjarnegara, Pekalongan, Kebumen and Jepara [247]. The survey had 15,901 respondents of all ages from 4,032 households. Among the 6,485 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 [238], 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 mosquitos, but according to a number of studies, only between 1% and 28% of people do so [197,245,294,313-315]. People in Indonesia's rural endemic zones also use insecticide spray dispensers at rates varying between 4% and 37% [197,245,312,316-318]. They also tend to wear long-sleeved clothing when they go outdoors at night [319]. One study in Eastern Indonesia [205] 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 [297]. Yahya *et al*. described the willingness of mothers to use mosquito coils and wear appropriate clothing to protect their children [320]. 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

behavior 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 [321]. 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 [321,322]. Passive zooprophylaxis is the serendipitous reduction in malaria purported to occur when cattle density increases within a community [323,324]. 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 *An. aconitus* contact with humans [325]. 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 mosquito/man-hour 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 *An. aconitus* and reduce man-mosquito contact [326]. 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 *An. aconitus* in Kendal (Central Java) in 1986 [327]. 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 meters from dwelling (4) and houses with no cattle shelter (2). They found a six-fold 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 four-fold when compared to homes with a cattle shelter attached. This accords with the zoophilic feeding behavior of *An. aconitus*.

2.4.4.3. Control of adult mosquito

2.4.4.3.1. Indoor residual spraying

Indoor residual spraying 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 [328]. The indoor spraying of chemicals that have a relatively long residual effect, typically two to six months, remains a vitally important means of reducing the risk of malaria [48]. 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 behavior 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 [329].

Table 2.8 shows the evolution of recommended insectides 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 [330]. These insecticides included the pyrethroid class (alpha-cypermethrin, bifentrin, cyfluthrin, deltamethrine, etofenprox and lambda-cyhalothrine), carbamate class (bendiocarb, propoxur), organophosphates (fenitrothion, malathion, pirimiphos-methyl) and organochloride (DDT). According to the Indonesian MoH released in 2003 and 2010 [331,332], six insecticides belonging to two of these classes may be applied for IRS: pyrethroids (alpha-cypermethrin, bifentrin, deltamethrine, etofenprox and lambda-cyhalothrine) and carbamates (bendiocarb). Earlier, the Indonesian MoH had recommended organophosphates for IRS (fenitrothion, malathion, pirimiphos-methyl).

Table 2.8. The World Health Organization (WHO) and the Indonesian Malaria Control Program (IMCP) recommended insecticides for indoor residual spraying against malaria vectors.

Insecticide	Class	WHO (2009)		IMCP (1993)		IMCP (2003, 2010)	
		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-cyhalotrin	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	-

According to the Indonesian Malaria Control Program guidelines, indoor residual spraying is targeted at endemic areas with an API > five cases per 1,000 population, areas with malaria positive infants, or areas with a high potential of malaria outbreak [286]. The guidelines suggest that IRS be conducted two months prior to the median peak of malaria case numbers. The median value is derived from the last 3-5 years of montly malaria cases. Alternatively, spraying should be done one month before the peak density of the local malaria vector [286]. 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 meters. 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. to 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 knock-down effect and a strong excito-repellent effect on anophelines [333]. 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 [334]. Typically, intoxication of the mosquito results in a rapid knockdown effect and high

mortality rate [335]. The dosage recommended by the WHO is 0.02 – 0.03 g/m^2, giving a residual effect of four to six months [330]. The Indonesian MoH recommended alpha-cypermethrin wettable powder [336] at a dosage of 0.02 g/m^2 for IRS [331,332]. 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 *An. aconitus* in Semarang (Central Java) in 1981 [337,338]. IRS was carried out for 479 households with insecticide usage averaging 0.58 kg/house. *An. aconitus* mosquitoes were collected indoors and outdoors one 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 three weeks for 24 weeks. It was found that cypermethrin did not reduce indoor mosquito landing (before application: 0.5 mosquito/man-hour vs. after: 0.7 mosquito/man-hour) or outdoor landing (before: 1.4 mosquito/man-hour vs. after: 1.3 mosquito/man-hour). There was an increase of 35% in morning resting density (before: 3.4 mosquito/man-hour vs. after: 4.6 mosquito/man-hour). Only a 9% reduction of the natural outdoor resting density was achieved (before: 95 mosquito/man-hour 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 *An. aconitus* in Central Java.

Barodji *et al*. experimented with the IRS application of alphamethrin 5% water dispersible water (WDP) at a dosage of 0.1 g/m^2 against DDT-resistant *An. aconitus* at Kendal (Central Java) in 1985 [339]. The IRS program involved the spraying of 1,254 houses with an average of 0.02 kg insecticide/house. *An. aconitus* mosquitoes were

collected indoors and outdoors two weeks before application and every two 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 two 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 mosquito/man-hour 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 mosquito/man-hour vs. after: 0.95 mosquito/man-hour). A reduction of 46% in morning resting density was found (before: 2.8 mosquito/man-hour vs. after: 1.5 mosquito/man-hour), while at natural outdoor resting sites a more modest decrease of 15% occurred (before: 57.5 mosquito/man-hour 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 *An. 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 [337,338]. 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 *An. sundaicus* at Purworejo (Central Java) in 2000 [340] The box interior was coated with insecticide. The test ran for 60 minutes 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) [330] and the closest dosage evaluated, i.e., 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 *An. 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 [334]. The dosage recommended by the WHO is 0.025 – 0.05 g/m^2 and should remain effective up to 6 months [330]. The Indonesian MoH recommends bifentrin 10 WP at a dosage of 0.025 g/m^2 for IRS [331,332]. 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 *An. maculatus* at Salatiga (Central Java) in 2000 [341]. Mosquito mortality was observed weekly for six months. At six months post-application, the dosage of 0.15 g/m^2 was effectively killing *An. maculatus* on wood (98%), bamboo and cement surfaces (100%). Also at six 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 inffective 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 *An. 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 *An. maculatus*, *An. aconitus* and *An. balabacensis* [342]. Wood, bamboo and cement surfaces from six houses were sprayed. Mortality was observed for 24 hours. 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 [343]. 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 [334]. It has a very high knock-down and low excito-repellent effect [333]. It is also known by the name baythroid [343]. The WHO recommends a dosage of 0.02 – 0.05 g/m^{2,} giving a residual effect lasting three up to six months [330]. The Indonesian MoH does not recommend this insecticide for IRS as part of its insecticide rotation cycle policy [331]. Several studies have explored the application of cyfluthrin against malaria vectors in Indonesia.

Barodji *et al*. investigated the impact of cyfluthrin IRS against *An. barbirostris*, *An. subpictus* and *An. sundaicus* in East Flores (Lesser Sundas) in 1996 [306]. 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 three months and six months after application. No physical complaints were reported from villagers

or sprayers. For *An. 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 three months (reduction: 28%) and 4.8 mosquito/man-hour at six months (reduction: 25%). The outdoor man-landing rate reduced from 5.2 mosquito/man-hour before application to 4.4 mosquito/man-hour at three months (reduction: 16%), but increased again by 33% to 5.4 mosquito/man-hour at six months. For *An. subpictus*, the indoor man-landing rate reduced from 14.3 mosquito/man-hour before application to 7.9 mosquito/man-hour at three months (reduction: 45%) and 2.6 mosquito/man-hour at six months (reduction: 86%). The outdoor man-landing rate decreased from 20.5 mosquito/man-hour before application to 16.7 mosquito/man-hour at three months (reduction: 19%) and to 1.5 mosquito/man-hour at six months (reduction: 93%). For *An. subpictus*, the indoor man-landing rate declined from 14.3 mosquito/man-hour before application to 7.9 mosquito/man-hour at three months (reduction: 45% ths) and 2.6 mosquito/man-hour at six months (reduction: 86%). The outdoor man-landing rate decreased from 20.5 mosquito/man-hour before application to 16.7 mosquito/man-hour at three months (reduction: 19%) and to 1.5 mosquito/man-hour at six months (reduction: 93%). For *An. sundaicus*, the indoor man-landing rate declined from 4.2 mosquito/man-hour before application to zero at three months and six 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 three months (reduction: 99%) and to zero at six 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 *An. sundaicus*, but not in the case of *An. barbirostris* and *An. subpictus*. The slide positivity rate [344] among residents in the area sprayed, was 39% (63/162) before spraying. This fell to 11% (16/145) at three months post-application and to 3% (4/158) at six 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 [333,345]. Its mode of action is primarily upon the basal ganglia causing repetitive nerve action [333]. 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 six months [330]. The Indonesian MoH recommends deltamethrin 5% WP at a dosage of 0.2 g/m^2 for IRS [331,332]. 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 [346]. It is classified by the WHO as unlikely to pose an acute hazard in normal use as a residual insecticide [334]. It disturbs nerve impulses in insect nerve axons [333]. The WHO recommends a dosage of 0.1 – 0.3 g/m^2, giving a residual effect of three up to six months [330]. The Indonesian MoH recommends etofenprox 20% wettable powder at a dosage of 0.1 g/m^2 for IRS [331,332]. 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 [347]. They applied 0.2 g/m^2 three times at 6 month intervals. The suspected vectors were *An. sundaicus*, *An. barbirostris*, *An. flavirostris* and *An. maculatus*. Human landing rates and resting densities were measured every two weeks for 16 months. A direct contact test was conducted on wooden and bamboo surfaces. Mosquito mortality was observed for 24 hours in the 240 sprayed homes. The direct contact test showed that the insecticide remained efficient for up to four months on wooden surfaces and for

five months on bamboo. The human landing rate decreased from 0.91 mosquito/man-hour before application to 0.23 mosquito/man-hour at six 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 six 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 slide positivity rate [344] 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-cyhalotrin

Lambda-cyhalothrin is a synthetic pyrethroid [348]. It has a low vapour pressure, is essentially insoluble in water, and has low volatility [333]. The WHO classifies this insecticide as moderately hazardous [334]. It is used at a dosage of 0.02 – 0.03 g/m^2, giving a residual effect of three to six months [330]. The Indonesian MoH recommends lambda-cyhalotrin 10% wettable powder at a dosage of 0.025 g/m^2 for IRS [331,332]. We found no publications about the use of lambda-cyhalotrin against malaria vectors in Indonesia.

2.4.4.3.1.7. Bendiocarb

Bendiocarb is a carbamate insecticide [349]. It has a low vapour pressure and low odour [333]. The WHO classifies it as moderately hazardous [334]. The WHO

recommends a dosage of 0.1 – 0.4 g/m^2, giving a residual effect of two up to six months [330]. The Indonesian MoH recommends bendiocarb 80% wettable powder at a dosage of 0.2 g/m^2 for IRS [331,332]. Three studies have been performed, documenting the efficacy of bendiocarb in Indonesia.

Fleming *et al*. conducted a village scale-trial of bendiocarb against *An. aconitus* in Central Java in 1981 [350]. Bendiocarb 80% wettable powder [336] at a dosage of 0.4 g/m^2 was only effective in reducing human-vector contact with *An. aconitus* within the first two months. Residual efficacy by direct contact test lasted less than two 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 *An. maculatus* and *An. sinensis* between 1996 and 1997 [351]. *An. maculatus* mosquitoes used for the test were obtained from Kulonprogo [101] and *An. sinensis* from Nias (North Sumatra). Mosquito mortality rates were observed two weeks post-application, and then monthly for sixmonths. The mortality rates for *An. maculatus* and *An. sinensis* were 100% on wooden, bamboo and cement surfaces for up to four months. However, at five months mortality rates for *An. maculatus* decreased to 37% on wood, 33% on bamboo and 83% on cement. Mortality rates for *An. 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 *An. maculatus* and *An. sinensis*.

Bonsall *et al*. conducted safety studies of bendiocarb in a field trial in 1981 [352]. 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 [333]. The WHO classifies it as a moderately hazardous chemical [334]. Propoxur inhibits acetylcholinesterase activity [353]. Acetylcholinesterase is an enzyme which responsible for hydrolysis of the neurotransmitter acetylcholine [354]. Acetylcholine is a nerve system which sends messages between nerves. The recommended dosage is one to two g/m^2, giving a residual effect of three to six months [330]. The Indonesian MoH does not recommend this insecticide for IRS as part of its insecticide rotation cycle policy [331]. We found no publications describing the use of propoxur in Indonesia.

2.4.4.3.1.9. Fenitrothion

Fenithrotion is an organophosphate insecticide used extensively in IRS since the 1970s [333]. The WHO classifies it as a moderately hazardous chemical [334]. The recommended dosage is 2 g/m^2, giving a residual effect of three up to six months [330]. The Indonesian MoH does not recommend this insecticide for IRS on the basis of the perception of a low margin of safety [331]. Nonetheless, several studies have examined the application of fenithrotion against malaria vectors in Indonesia.

Joshi *et al*. conducted a village-scale fenithrotion trial against *An. aconitus* in Semarang (Central Java) in 1976 [355]. 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 to 18 weeks on similar surfaces [356,357].

Suwarto *et al*. measured the efficacy of fenitrothion 40% WDP at a dosage of two g/m^2 against *An. aconitus* between full (0-300 cm above floor) versus selective (10-85 cm above floor) coverage in Banjarnegara (Central Java) in 1981 [358]. Spraying was conducted in two cycles at six-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 kg/house 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 mosquito/man-hour 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 mosquito/man-hour 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 [359]. 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 fenithrotion at one g/m^2 against *An. maculatus* and *An. sinensis* between 1996 and 1997 [351]. *An. maculatus* mosquitoes were obtained from Kulonprogo [101] and *An. sinensis* from Nias (North Sumatra). The mosquito mortality rate was recorded at two weeks post-application, and then monthly for six months. Against *An. maculatus*, they found 100% mortality up to three months on wood, two months on bamboo and one month on cement. At six months after application, mortality of *An. maculatus* was 63% on wood, 67% on bamboo, and 60% on cement. Against *An. sinensis*, they found 100% mortality up to two months post-application on wood, and a month on either bamboo or cement. At month three, mortality of *An. sinensis* reached only 7% on all types of surfaces. Fenithrotion IRS at 1 g/m^2 was only really effective against *An. maculatus* and *An. 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 fenithrotion in East Flores (Lesser Sundas) in 1995 [360]. The local vectors were *An. sundaicus*, *An. barbirostris*, *An. flavirostris* and *An. maculatus*. In three subvillages in Lewo Bunga, they applied full coverage at one g/m^2 for one single cycle in a year, and in three subvillages in Ebak, they applied 0.5 g/m^2 for two cycles with a six-month interval. Indoor and outdoor human landing collection and indoor resting density were measured every three months for 12 months. Direct contact tests were conducted on wooden and bamboo surfaces. At the one g/m^2 dosage, at 12-months post-application, the indoor human landing rate fell from 15.8 mosquito/man-hour to 0.2 mosquito/man-hour (reduction: 99%). Likewise, the outdoor human landing rate fell from 19.9 mosquito/man-hour 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 mosquito/man-hour to 0.25 mosquito/man-hour (reduction: 73%). The outdoor man landing rate fell from 1.97 mosquito/man-hour to 0.02 mosquito/man-hour (reduction: 99%). The indoor resting density decreased from 1.7 mosquito/man-hour to zero (reduction: 100%). The one g/m^2 dosage effectively reduced mosquito density. Direct contact tests showed that one g/m^2, at two 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 one month on bamboo. At nine months-post first application, the apparent effects upon SPR in the treated villages were very similar for one g/m^2 (before application: 26%, 35/134 vs. at nine 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 [333]. It has low vapour pressure, moderate water solubility and low toxicity [361]. It has quite a strong and generally unpleasant odor. The WHO classifies it as a slightly hazardous insecticide [334] and recommends a dosage of two g/m^2, giving a residual effect of two to three months [330]. The Indonesian MoH does not recommend this insecticide for IRS against malaria vectors, but it does recommend it for *Aedes* control [331,332]. In general, this insecticide is applied as a quick knock down of adult mosquitoes in outbreak settings.

A study in the 1980s explored the application of malathion as IRS in Jombang (East Java) [362]. The investigators applied full coverage, at two g/m^2 for one cycle, lasting a

year, to 1,100 houses. Human landing and indoor resting densities were measured before application and at three 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 mosquito/man-hour to 0.5 mosquito/man-hour (reduction: 89%). The morning resting density decreased from 1.3 mosquito/man-hour to 0.4 (reduction: 69%). The slide posivity rate dropped significantly at three months-post application (before application: 2.3%, 22/951 vs. after: 0.2%, 2/1,015; $p < 0.001$). Although the authors declared this insecticide to be very effective, the powerful and unpleasant odor 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 [363]. It is classified by the WHO as a moderately hazardous chemical [334]. Application of one to two g/m^2 gives a residual effect for two to three months [330]. 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 [331,332]. Trials were carried out with a 25% WDP formulation at a dosage of two g/m^2 [364] and with a 50% EC formulation at dosage of one g/m^2 [365]. 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, e.g., dieldrin, were abandoned due to relatively high toxicity to humans [333]. The WHO

classifies it as a moderately hazardous chemical [334]. A 1-2 g/m^2 application gives a residual effect of more than six months [330]. DDT resistance has been reported from Indonesia [176,366]. The Indonesian MoH does not recommend this insecticide for any purpose [331,332]. The environmental contamination from DDT, caused by the illegal diversion of the insecticide to agricultural use [333], underpins the government's prohibition of DDT. The last application of DDT in Indonesia was in 1992 [367]. A study in the 1980s [362] documented modest effects on SPR (3.7% vs. 1.4%; p = 0.006), a relatively modest decrease in indoor human-landing rates (0.4 mosquito/man-hour to 0.1 mosquito/man-hour) and a sharp increase in outdoor human landing rates (2.9 mosquito/man-hour to 6.8 mosquito/man-hour), the latter observation being consistent with the well known powerfully repellant 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 (1979-1982) in South Kalimantan [368].

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 [286]. According to the Basic Health Survey (BHS) [65] 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 eight percent kept them outside the house.

Barodji evaluated the impact of cattle shelter spraying on *An. aconitus* at Jepara (Central Java) in 1983 and 1984 [369]. Two villages in Mlonggo sub-district were selected as intervention sites. DDT-resistant *An. aconitus* has been reported at those

sites. SPR at the intervention sites was 12% (1,516/9,509). In the first year, fenithrotion IRS was applied monthly at two g/m^2, and in the second year of the study it was applied every two 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. *An. aconitus* is characteristically zoophilic and occurs in greatest abundance in and around cattle shelters. Approximately 3,000 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 mosquito/man-hour to 0.03 mosquito/man-hour), nine times lower outdoors (from 0.77 mosquito/man-hour to 0.09 mosquito/man-hour), and eight times lower in cattle shelters (from 9.5 mosquito/man-hour to 1.2 mosquito/man-hour). However, when the frequency application was reduced from monthly applications to bi-monthly applications, human-vector contact increased once again among human dwellings becoming four times higher indoors (from 0.03 mosquito/man-hour to 0.13 mosquito/man-hour), three times higher outdoors (from 0.09 mosquito/man-hour to 0.29 mosquito/man-hour) and three times higher in cattle shelters (from 1.2 mosquito/man-hour to 3.5 mosquito/man-hour). They also found that, following monthly application, SPR fell significantly from baseline levels (baseline: 15.9%, 1,516/9,509 vs. monthly: 5.8%, 797/13,724; $p < 0.001$). During the bi-monthly 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 *An. aconitus* to become less zoophilic or more anthropophilic, i.e., 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 vs. after application (92%, 92/100 vs. 87%, 215/248; $p = 0.165$). Contact susceptibility tests of fenitrothion against *An. aconitus* after 15 applications showed 100% mortality. Repetitive applications did not decrease susceptibility of *An. 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 [370]. The authors concluded that cattle shelter IRS could diminish the risk of malaria in areas where *An. aconitus* represents an important vector of malaria. Nalim reported similar findings at Banjarnegara (Central Java) in 1985 [371].

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 Benefit Evaluation Study by the Indonesian National Institute for Health Research and Development and the Centre of Statistics in 2001 [247]. The study surveyed 15,902 people from 4,032 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, i.e., foul smell, fouling the furniture and fear of toxicity.

The KAP study by Sanjana *et al*. at Purworejo (Central Java) involved 1,000 randomly selected households [238]. Among the 50 villages sampled, 15% to 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 was significantly higher than among houses sprayed more than one

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 [198]. They surveyed 420 people and only ten (two percent knew of IRS being used as a malaria prevention tool. About 95% of participants responded favorably to IRS. In 2003, Arsunan *et al*. also documented that 71% of 264 respondents in Kapoposang Island (Pangkajene, Sulawesi) agreed to re-spraying two years after the last application [298]. Sekartuti *et al*. also reported a KAP survey carried out in Banjarnegara (Central Java) in 2004 involving 219 respondents [372]. 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. 62% of respondents agreed to place their cattle shelter at more than 20 meters 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 [316]. Santoso *et al*. evaluated a community participation program in Bintan (Riau island, Sumatra) in 1991 and described complaints registered after a round of IRS [313]. 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 insectide on their furniture.

2.4.5. Malaria surveillance

According to the Indonesian Malaria Control Program guidelines [70], malaria surveillance is needed to support three activities: early warning, outbreak management and post-oubreak 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 analyzing of data is conducted at primary health center level. An increase in the number of malaria cases, which is more than two-fold 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 analyze these data [373,374].

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 on-going malaria surveillance used by Indonesia's Malaria Control Program 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 1,300 hospitals across the archipelago. There is no adjustment of API in the Malaria Control Program 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) [15,45]. As can be seen by the work of many presented in this review, the risk and mechanics of infection sharply varies across the 5,000 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 here what we consider to be seven conspicuously useful and practical areas of research endeavor 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.

2.6. Acknowledgements

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CHAPTER 3

The distribution and bionomics of *Anopheles* malaria vector mosquitoes in Indonesia

3.1. Introduction

An integrated approach to interventions against mosquito vectors of malaria has become increasingly important for those nations aiming for elimination of malaria transmission or a significant reduction of infection risk [375]. Such evidence-based strategies for vector control require detailed knowledge of the identity, distribution and bionomics of the primary malaria vectors within the target area [376]. Recent work by the Malaria Atlas Project (www.map.ox.ac.uk), defining the spatial distributions of the dominant vector species (DVS) of human malaria worldwide [41], have begun to address the need for geographical species-specific information, including a detailed review of the bionomics of these primary vectors in the Asia-Pacific region [41,43]. On a national scale, however, and despite a long history of study of the important *Anopheles*, no contemporary systematic review of this mosquito genus has been undertaken in Indonesia. This paper, therefore, closely examines both the past and current state of knowledge of many of the anopheline malaria vectors present in this environmentally diverse archipelago.

The main arsenal for adult mosquito control consists of applying long-lasting, residual insecticides, either on bednets or applied/sprayed directly onto the walls within human dwellings [377]. Unfortunately, the continuous exposure of mosquitoes to these chemicals has resulted in measurable physiological resistance, and in some instances

significant behavioural avoidance amongst a number of studied malaria vectors species [248]. Physiological resistance refers to the ability of a mosquito to tolerate doses of insecticide which would normally prove lethal to the majority (> 98%) of individuals in a local population of the same species, whilst behavioural avoidance relates to the tendency of mosquitoes to avoid contact with the insecticide-treated surface, either as a result of contact 'irritancy', spatially active repellency, or a combination of both [378]. Monitoring the insecticide resistance profile of a population of medically important *Anopheles* species is essential for better design and implementation of an evidence-based vector control policy [379]. Until now, no contemporary review of the insecticide resistance patterns among Indonesian anophelines vectors has been published.

3.2. Assembling a national database of *Anopheles* mosquitoes susceptible to *Plasmodium* spp. infections, host preference, bionomics, and insecticide susceptibility in Indonesia

A systematic search and review of published and unpublished entomological literature from online and library sources was used to assemble a database of the distribution of Indonesian *Anopheles,* their natural infection with human malaria parasites, bionomics and frequency of insecticide resistance. Visits were made to university and Ministry of Health library resources to search for more obscure or offline/unpublished information. Searches were completed on 31 December 2011. Once a relevant data source was identified, information was extracted into an Excel worksheet including an unique identification record of each source, year of source, location (region, island, province, district, sub-district, and specific locality such as village), species and species identification method used (morphological and molecular-based), physiological measures (mating status, parity, age-grading, blood feeding preference, etc), the

sporozoite and oocyst rate (using midgut and salivary gland dissections, circumsporozite immunological assays and molecular-based tests). Based on the presence of oocysts and/or sporozoites, each record was classified into two 'susceptibility' categories: infected (midgut oocysts) or infective (presence of salivary gland sporozoites). When a mosquito was found to be infected but not necessarily infectious, it was classified as a 'suspect' vector, whereas those identified as infectious were classified as an incriminated or 'confirmed' malaria vector [380,381]. Additional data recorded for the number found positive for the presence of human blood (i.e., human blood index; HBI) were also searched. Larval and adult bionomic data was included focusing on blood feeding behaviour and activity patterns, predominant resting sites of adults and aquatic habitats for immature stages. These data were stratified into western and eastern sectors of the Indonesian archipelago for descriptive purposes. Western and eastern sectors of Indonesia are biogeographically distinct regions of the archipelago, demarked by a series of different transecting lines including Wallace's and Weber's Lines near the center of the nation (surrounding the island of Sulawesi; shown in Figures 5.1 – 5.21) [382,383].

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Finally, a database of the vector insecticide susceptibility status was assembled identifying those sources that reported an insecticide susceptibility test, including the method (bioassay, biochemical, molecular), the insecticide (active ingredient) tested, doses (percent concentrations) used, number of mosquitoes assayed and the mosquito mortality following exposure. The insecticides in the database included the six currently recommended for indoor residual spraying by the Indonesian Vector Control Program (VCP), primarily pyrethroid and carbamate class chemicals [332], plus other insecticide classes used historically such as organophosphates and organochlorine compounds.

3.3. Infectivity of *Anopheles* mosquitoes to *Plasmodium* in Indonesia

From the reviewed and compiled literature, a total of 74 sources were used to extract 1,266 records reporting *Plasmodium* spp. infections (sporozoites or oocyst stages) for 29 *Anopheles* species found in Indonesia between 1919 and 2010 (Table 3.1). The data indicates the presence of 20 *Anopheles* species confirmed as primary or secondary (incidental) malaria vectors in the country. No records of naturally occurring infectious stages (sporozoites) were found for the remaining nine species, despite four species, including *An. annularis*, *An. hyrcanus*, *An. indefinitus* and *An. umbrosus* being reported as suspected vectors in Indonesia (Table 3.2).

The confirmed malaria vectors are not uniformly distributed across the archipelago. Twelve species are located in the western portion of the country and 13 species in the eastern region of Indonesia with some overlap across both areas: *An. balabacensis, An. flavirostris*, *An. nigerrimus*, *An. subpictus* and *An. sundaicus* were reported as natural vectors in both regions. The distribution of malaria vectors among the main islands is also not uniform (Figure 3.1), with Java and Sulawesi appearing to contain the greatest number of reported malaria vectors (eight species), followed by Sumatra (six species), Papua (at least five species) and the Lesser Sundas archipelago (five species). Only two species were confirmed as malaria vectors in Kalimantan. No data on the infectivity of *Anopheles* species on Maluku were identified but at least two species present in the island chain (*An. farauti* and *An. punctulatus*) are known to be efficient vectors elsewhere (Papua).

A map of the distribution of the *Anopheles* malaria vectors in Indonesia is provided (Figure 3.1) which illustrates species by principal islands or island groups from Sumatra in the west to Papua in the east. Sulawesi and the Lesser Sundas archipelago lie in the

center of Indonesia and are between two major zoogeographical lines (Wallace's and Weber's lines drawn to demark the Oriental and Australasia Regions) based on unique and overlapping fauna distributions in the region.

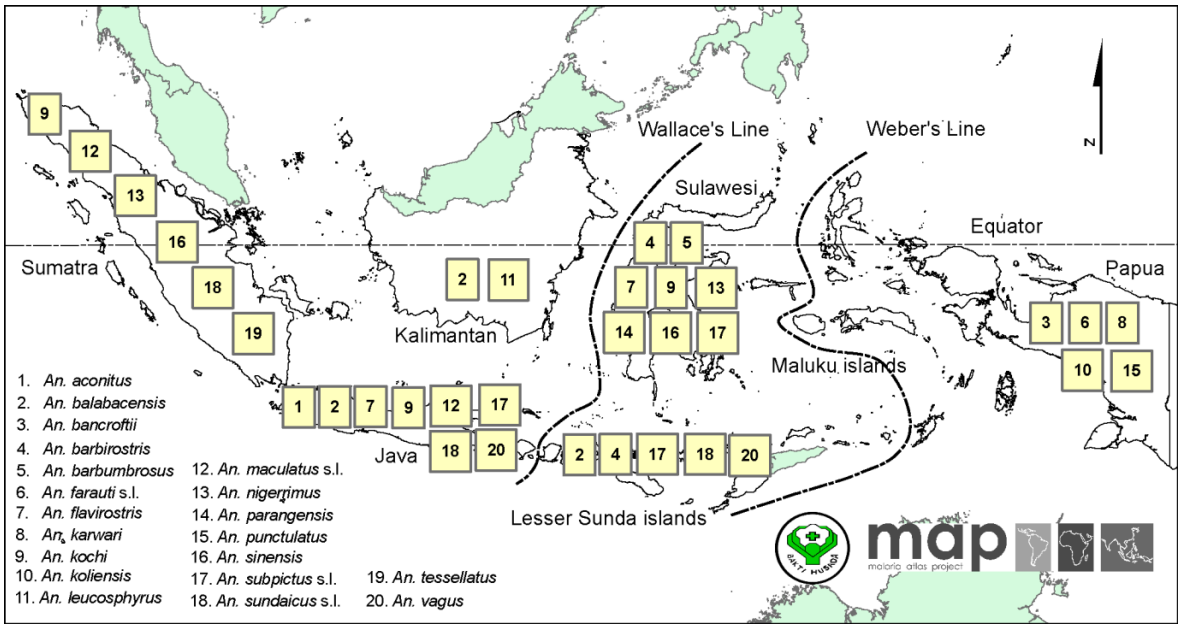


Figure 3.1. A map of the distribution of primary *Anopheles* malaria vectors in Indonesia.

Table 3.1. Natural *Plasmodium species* infections of *Anopheles* mosquitoes in Indonesia. The "?" mark denotes where the *Plasmodium* species infecting the mosquitoes is unknown. In some instances, the observed oocysts and sporozoites upon dissection might have been derived from non-human primate or rodent hosts; "Yes" indicate parasite species was identified using CSP-ELISA.

Species	Year of samples	Oocyst detection			Sporozoite detection			*Plasmodium* infection			
		Number of mosquitoes examined	Number of mosquitoes with oocysts	Oocyst rate (%)	Number of mosquitoes examined	Number of mosquitoes with sporozoites	Sporozoite rate (%)	*P. falciparum*	*P. vivax*	*P. malariae*	*P. ovale*
An. aconitus	1917-2007	8,827	115	1.30	17,554	15	0.09	Yes	Yes	?	?
An. aitkenii	1919	2	0	0.00	-	-	-				
An. albotaeniatus	1918-1931	48	0	0.00	6	0	0.00				
An. annularis	1917-2007	1,229	2	0.16	489	0	0.00				
An. balabacensis	1982-2005	-	-	-	2,348	111	4.73	Yes	Yes	?	?
An. bancroftii	1928-2002	1,119	29	2.59	983	2	0.20	?	?	?	?
An. barbirostris	1917-2007	6,750	314	4.65	9,568	91	0.95	Yes	Yes	?	?
An. barbumbrosus	1940-2002	19	1	5.26	22	1	4.55	?	?	?	?

Species	Year of samples	Oocyst detection			Sporozoite detection			*Plasmodium* infection			
		Number of mosquitoes examined	Number of mosquitoes with oocysts	Oocyst rate (%)	Number of mosquitoes examined	Number of mosquitoes with sporozoites	Sporozoite rate (%)	*P. falciparum*	*P. vivax*	*P. malariae*	*P. ovale*
An. crawfordi	1994-2002	-	-	-	773	0	0.00				
An. farauti	1922-1979	1,093	57	5.22	1,199	12	1.00	Yes	Yes	?	?
An. flavirostris	1938-2007	53	5	9.43	2,175	2	0.09	Yes	?	?	?
An. hyrcanus	1918-1929	30,055	682	2.27	-	-	-				
An. indefinitus	1917-2007	2,413	1	0.04	173	0	0.00				
An. karwari	1919-1955	65	0	0.00	685	6	0.88	?	?	?	?
An. kochi	1917-2007	7,223	89	1.23	2,967	1	0.03	Yes	Yes	?	?
An. koliensis	1947-1994	-	-	-	2,616	24	0.92	?	Yes	?	?
An. leucosphyrus	1918-1986	3,757	324	8.62	89	1	1.12	Yes	?	?	?
An. longirostris	1953-1964	-	-	-	7	0	0.00				
An. maculatus	1918-2007	1,289	26	2.02	3,504	6	0.17	Yes	Yes	?	?
An. nigerrimus	1932-1995	5,074	483	9.52	3,443	11	0.32	?	?	?	?
An. parangensis	1939-2002	2	0	0.00	688	6	0.87	Yes	?	?	?

Species	Year of samples	Oocyst detection			Sporozoite detection			*Plasmodium* infection			
		Number of mosquitoes examined	Number of mosquitoes with oocysts	Oocyst rate (%)	Number of mosquitoes examined	Number of mosquitoes with sporozoites	Sporozoite rate (%)	*P. falciparum*	*P. vivax*	*P. malariae*	*P. ovale*
An. peditaeniatus	1934-2007	-	-	-	594	0	0.00				
An. punctulatus	1917-1992	1,614	1	0.06	10,501	117	1.11	Yes	Yes	Yes	?
An. sinensis	1917-1998	29,489	612	2.08	2,733	1	0.04	?	?	?	?
An. subpictus	1918-2007	32,698	130	0.40	88,784	160	0.18	Yes	Yes	?	?
An. sundaicus	1917-2007	49,649	1,469	2.96	56,624	169	0.30	Yes	Yes	?	?
An. tessellatus	1919-2007	2,266	4	0.18	838	10	1.18	Yes	?	?	?
An. umbrosus	1918-1921	257	16	6.23	25	0	0.00				
An. vagus	1919-2007	10,303	2	0.02	6,844	7	0.10	Yes	?	?	?

Table 3.2. Natural sporozoite infections of *Anopheles* mosquitoes from the main islands in Indonesia. Sporozoite infections based on dissections only are presumed to be of human origin, but in some instances (e.g., forest/forst-fringe dwelling vectors) might have been derived from non-human primate or rodent hosts.

Species	Year of samples	Western Indonesia			Eastern Indonesia			
		Sumatra	Java/Bali	Kalimantan	Sulawesi	Maluku	Lesser Sundas	Papua
An. aconitus	1918-2007	0/15	**15/17,463 (0.08)**	-	-	-	0/76	-
An. albotaeniatus	1918	-	0/6	-	-	-	-	-
An. annularis	1934-2007	0/107	0/283	-	-	-	0/99	-
An. balabacensis	1982-2005	-	**4/138 (2.9)**	**60/1,449 (4.14)**	-	-	**47/761 (6.18)**	-
An. bancroftii	1954-2002	-	-	-	-	-	-	**2/983 (0.2)**
An. barbirostris	1918-2007	0/119	0/3,263	-	**82/6,063 (1.35)**	-	**9/123 (7.32)**	-
An. barbumbrosus	1940-2002	-	-	-	**1/22 (4.55)**	-	-	-
An. crawfordi	1994-2002	0/773	-	-	-	-	-	-
An. farauti	1953-1979	-	-	-	-	-	-	**12/1,199 (1.0)**
An. flavirostris	1941-2007	-	**1/1,452 (0.07)**	-	**1/60 (1.67)**	-	0/663	-
An. indefinitus	1982-2007	-	0/133	-	-	-	0/40	-
An. karwari	1953-1955	-	-	-	-	-	-	**6/685 (0.88)**
An. kochi	1934-2007	**1/1,025 (0.1)**	0/1,864	-	0/1	0/75	0/2	-

Species	Year of samples	Western Indonesia			Eastern Indonesia			
		Sumatra	Java/Bali	Kalimantan	Sulawesi	Maluku	Lesser Sundas	Papua
An. koliensis	1947-1994	-	-	-	-	-	-	**24/2,616 (0.92)**
An. leucosphyrus	1938-1986	-	-	**1/85 (1.18)**	0/4	-	-	-
An. longirostris	1953-1964	-	-	-	-	-	-	0/7
An. maculatus	1941-2007	0/13	**6/3,270 (0.18)**	-	-	-	0/213	-
An. nigerrimus	1939-1995	**3/555 (0.54)**	0/1,343	-	**8/1,545 (0.52)**	-	-	-
An. parangensis	1939-2002	-	-	-	**6/688 (0.87)**	-	-	-
An. peditaeniatus	1934-2007	0/258	0/336	-	-	-	-	-
An. punctulatus	1953-1992	-	-	-	-	-	-	**117/10,501 (1.11)**
An. sinensis	1919-1998	**1/1,660 (0.06)**	0/1,072	-	0/1	-	-	-
An. subpictus	1918-2007	0/678	**52/69,702 (0.07)**	-	**19/12,996 (0.15)**	0/219	**89/5,189 (1.72)**	-
An. sundaicus	1918-2007	**6/1,480 (0.41)**	**128/51,701 (0.25)**	-	**16/1,635 (0.98)**	-	**19/1,808 (1.05)**	-
An. tessellatus	1934-2007	**10/455 (2.2)**	0/283	-	0/1	0/39	0/60	-
An. umbrosus	1918-1991	0/23	0/2	-	-	-	-	-
An. vagus	1934-2007	0/92	**7/6,562 (0.11)**	-	-	0/104	0/86	-

3.4. The distribution of *Anopheles* malaria vectors in Indonesia

A total of 259 sources, published from 1917 to 2011, have documented the presence of 20 *Anopheles* malaria vector species in Indonesia representing 755 independent sites. A greater number of sites in western Indonesia reported vectors present than in eastern Indonesia (66% vs. 34%), no doubt reflecting the relatively higher number of investigations in the far more densely populated western sector. Over the seven main islands in Indonesia, the greatest number of sites where vectors have been found were on Java (41%, 311 sites) with the least found on Papua (4%; 32 sites). *Anopheles vagus* was reported from the greatest number of independent sites (46%, 349 sites) across Indonesia, while *An. bancroftii* was the most restricted (1%; 7 sites in Papua, 1 Maluku).

For each species, an individual map has also been generated indicating geo-referenced locations of occurrence and where malaria infectious mosquitoes have been recorded (Figures 3.2 – 3.21). These records were then overlaid to the *Plasmodium falciparum* malaria endemicity map in Indonesia that was produced in an earlier publication [384]. The endemicity maps defined five land categories with areas color shaded accordingly: no malaria risk area (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission risk area (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk area (light red, $Pf\text{PR}_{2\text{-}10}$ <5%), intermediate risk area (medium red, 5% < $Pf\text{PR}_{2\text{-}10}$ < 40%) and high risk area (dark red, $Pf\text{PR}_{2\text{-}10}$ > 40%). Using these georeferenced records and endemicity map, distribution maps were produced for each species or species complex. The presentation of species is alphabetical rather than geographical or by taxonomic affinities.

3.5. Malaria vectors in Indonesia: *Plasmodium* spp. infections, host preferences, larval and adult bionomics, and insecticide susceptibility

3.5.1. *Anopheles (Cellia) aconitus* Donitz

Anopheles aconitus is a member of the Funestus Group [385]. This species is broadly distributed throughout the Indonesian archipelago although relative densities and frequency vary dramatically. A total of 132 sources reported the presence of *An. aconitus* at 325 independent sites (Figure 3.2). The species has been most commonly reported from Java (197 sites) and extends across the archipelago as far east as Timor-Leste and the Maluku islands, but it seems absent from Papua (the Indonesian half of New Guinea Island). Using an enzyme-linked immunosorbent assay (ELISA) to detect the parasite circumsporozoite protein, Barodji *et al.* found only one specimen among 1,432 tested in Central Java having malaria (*P. falciparum*) sporozoites [386]. Over a 20-year period, the US. Naval Medical Research Unit No. 2 (NAMRU-2) in Jakarta detected sporozoite (*P. falciparum* and *P. vivax*) positive *An. aconitus* only from Central Java Province [387]. No other infective specimens have been reported from the other main islands. This species is reputed to be a major vector on Java, but generally only when present in high human-biting densities [388].

The adult females are predominantly zoophilic, with a greater presence in cattle and other outdoor animal shelters than human habitations [389-394]. The combined proportion of mosquitoes that contained human blood resting in cattle shelters was 2.9% (94/3,185) [389,390,395,396], while those captured in human settlements was only slightly higher at 6.7% (1004/14,811) [39,389,390,395,397,398] (Table 3.3). A stronger exophagic (outdoor biting/blood feeding) habit is commonly reported in Java [389-391,394,399-404], whereas a stronger endophagic (indoor biting) behaviour has

been shown along the southern coastal zone of western Java [405] and West Sumatra Province [406]. Females typically reach their peak blood feeding activity in the second quarter of the night [386,390,402,405], after which blood-fed females are generally found resting outdoors [327,386,389-391,394,399,401,402,407,408] in shaded animal shelters [327,389,390,399,401], rock crevices [407], earthen pits [407] and river banks [402] to complete their gonotrophic cycle.

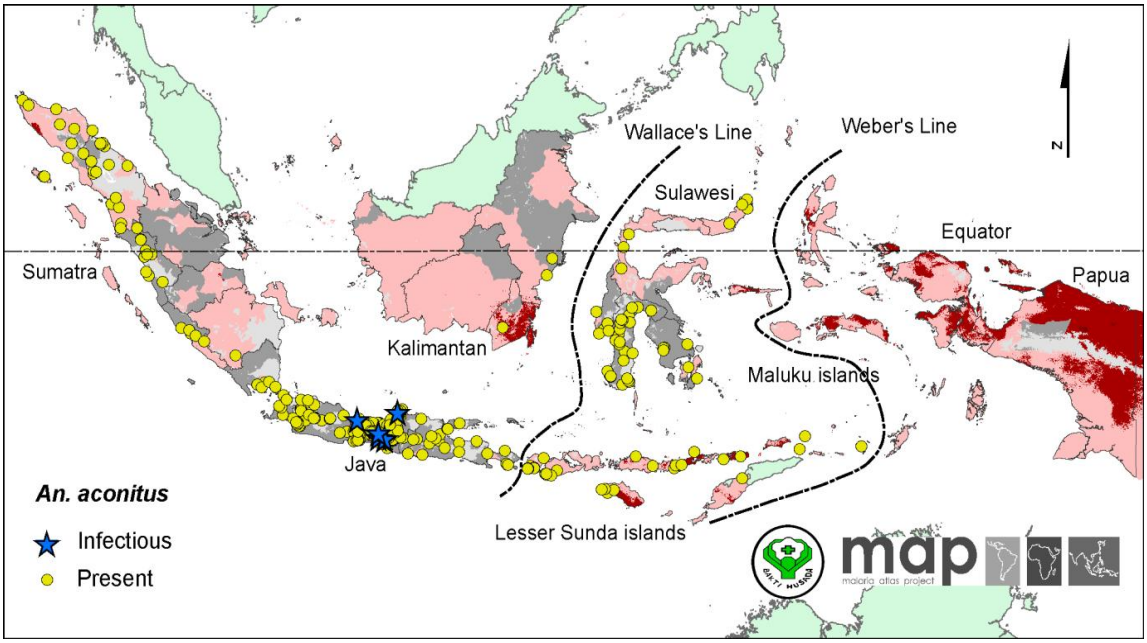


Figure 3.2. *Anopheles aconitus* distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles aconitus* mosquitoes found. The yellow dots show 325 records of occurrence for this species between 1917 and 2011. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2-10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2-10} < 40\%$) and high risk (dark red, $PfPR_{2-10} \geq 40\%$) [384].

The characteristic larval habitats of *An. aconitus* have been comprehensively described in Indonesia. Larvae are most commonly found in sunlit, exclusively fresh water, often clear in appearance, stagnant or slow flowing [32] and either natural or man-made

habitats (Supplementary Table S5). Natural water collections include marshes [409,410], streams [38,409,411] and river beds [33,38,402,408], and man-made sources most commonly include rice fields [38,39,390,399,402,406,409,411-415], fish ponds [409,412] and irrigation ditches [38,390,399,402]. A positive correlation between *An. aconitus* larval densities and phase of rice production has been observed with larval peak abundance occurring early in the growing season, around six weeks after rice planting [388,399]. This species is widely dispersed in the environment and can be found from the coastal plain [411,415] to hilly areas [38,39,170,390,411,415] up to altitudes of 1,000 meters above sea level (asl) wherever suitable larval habitats exist [39].

3.5.2. *Anopheles (Cellia) balabacensis* Baisas

Anopheles balabacensis is a member of the Leucosphyrus Subgroup, within the Leucosphyrus Complex, [81], a subgroup which includes several very important vectors of human malaria in forest fringe areas of Southeast Asia, including the Southeast Asian mainland, Philippine Islands, Brunei, Malaysian Borneo and Indonesia [43]. Thirty-four sources reported the presence of *An. balabacensis* from 43 independent sites on Java, Kalimantan, Sulawesi and Lesser Sundas with this species was most commonly reported from Java (30 sites) (Figure 3.3). *Anopheles balabacensis* has been found infected with *P. falciparum* sporozoites in Kalimantan [416]. Both *P. falciparum* and *P. vivax* infections were also detected in East (Kenangan) and South Kalimantan (Salaman) and Central Java (Magelang and Purworejo [Menoreh Hills]) [387]. The presence of *P. vivax* sporozoites has also been reported from Central Java [417].

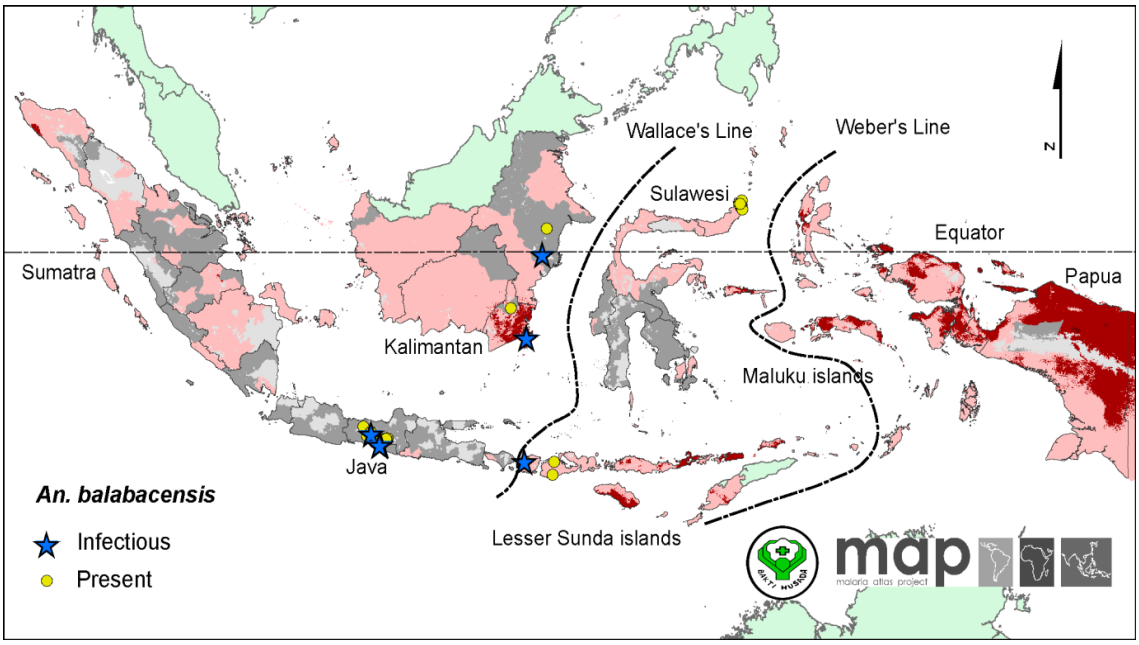


Figure 3.3. *Anopheles balabacensis* distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles balabacensis* mosquitoes found. The yellow dots show 43 records of occurrence for this species between 1987 and 2010. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2\text{-}10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2\text{-}10} < 40\%$) and high risk (dark red, $PfPR_{2\text{-}10} \geq 40\%$) [384].

The degree of anthropophily amongst female *An. balabacensis* appears to depend on location. Low levels of anthropophilic behaviour have been observed in hilly areas of Central Java [407], while in the mountainous areas of Lombok Island in the Lesser Sundas a high degree of anthropophily was noted [418] (Table 3.3). Females have been reported to mostly bite outdoors in Central Java [403,408,419-421] and Lesser Sundas [418], and mostly feeding indoors in eastern Kalimantan [422]. The feeding activity also varies by location with peak biting normally occurring during the second quarter of the night in Java and Lesser Sundas [388,403,416-421,423-428] and in the third quarter of the night in Kalimantan [388,408,422]. After blood feeding, *An. balabacensis* generally exits houses soon afterwards to rest outdoors [407,423,426] in

shaded locations such as cattle shelters [402,408,419,423,429], under trees [403,407,408,416,421,428-430], on enbankments at heights up to one meter above ground level [407,408,423] and inside ground pits [407].

Anopheles balabacensis larvae are found almost exclusively in shaded habitats containing fresh, often clear water [32] in both natural or man-made habitats (Supplementary Table S5) including stream-side rock pools [388,422,431,432], pools found under shrubs or low trees [388,403,408,422,423,425,432], river banks [421,423], puddles, muddy (turbid) animal wallows, hoof prints and tyre tracks. This species is usually found associated with hilly, forested terrain [420-423,432] up to 700 meters asl [420].

3.5.3. *Anopheles (Anopheles) bancroftii* Giles

Anopheles bancroftii was reported from only seven sources and at only eight independent sites from eastern Indonesia (Figure 3.4),: one site in Seram Island, Maluku and seven sites in Papua (New Guinea Island). Five of the six references were published before the 1960s. The single contemporary source documented its presence in Jayapura, Papua in 2008 [433] and *An. bancroftii* has also been encountered, but infrequently, in human-landing collections in Timika, southern Papua [434]. *Anopheles bancroftii* was found in unusually high abundance during a one-year study in the late 1920s in Tanah Merah, in a remote jungle environment in southern Papua. Seventy percent of approximately 10,100 collected *Anopheles* mosquitoes were morphologically identified as *An. bancroftii*. In this high vector density area, this species was found infected with malaria oocycts (3%, 29/1,199) [435]. The role of *An. bancroftii* in malaria transmission has been confirmed in Papua with the identification of two mosquitoes harboring malaria sporozoites among 982 dissected in Merauke in 1957 [436]. Likewise

it has been confirmed a malaria vector in the neighboring country of Papua New Guinea (PNG) that shares a border with Papua, Indonesia [437]. No infective *An. bancroftii* have been reported from Maluku (Table 2). This species has not been considered a very important malaria vector [36] despite reports of high human blood indices from specimens captured on a bednet [397] (Table 3.3). It also appears to be partially endophilic, with Van den Assem reporting the presence of many blood-fed females resting inside huts in southern Papua yet none having advanced ovarian development [438], suggesting that females likely leave their daytime indoor resting site the following evening post blood meal.

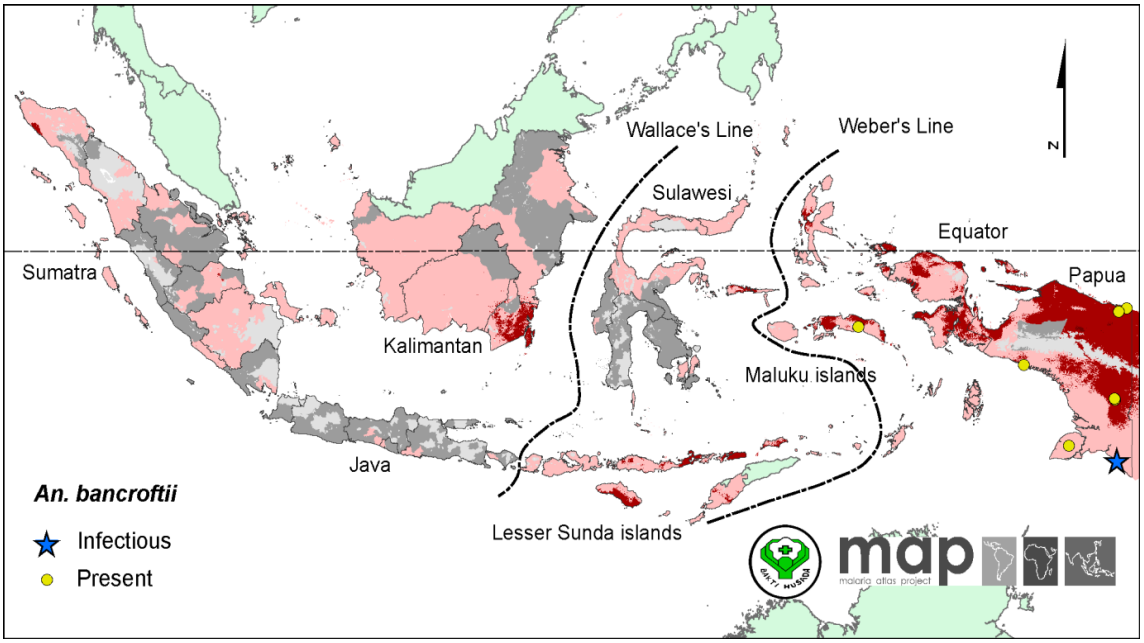


Figure 3.4. *Anopheles bancroftii* distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles bancroftii* mosquitoes found. The yellow dots show eight records of occurrence for this species between 1929 and 2008. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2-10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2-10} < 40\%$) and high risk (dark red, $PfPR_{2-10} \geq 40\%$) [384].

Supplementary Table S5 shows gravid females and immature stages of *An. bancroftii* prefer shaded habitats with fresh, clear and still to slow running water [439]. Larvae are typically found in natural habitats, such as marshes [37], pools associated with creeks and rivers [440], ground pools [440] or man-made habitats including heavily shaded irrigation ditches [37].

3.5.4. *Anopheles (Anopheles) barbirostris* van der Wulp

Anopheles barbirostris is a member of the Barbirostris Group [43], made up of at least 12 species. It is a taxonomically complex assemblage that is broadly distributed throughout the Indonesian archipelago and much of south and Southeast Asia. *Anopheles barbirostris* is currently regarded as a complex of three to five sibling species with unclear distributions and vector status in Southeast Asia [441]. In Indonesia, 119 sources have reported the presence of *An. barbirostris* at 330 independent sites and it was commonly reported from Java (140 sites), Sumatra (74 sites) and Sulawesi (55 sites) (Figure 3.5). The species complex has a wide distribution, extending from Sumatra, Java, Bali, Kalimantan, Sulawesi and throughout the Lesser Sunda island chain to Timor [442]. *Anopheles barbirostris* has been documented in Maluku (Buru Island) but no reliable/confirmed records of its presence in Papua (New Guinea) have been found.

Anopheles barbirostris is medically important (malaria and filariasis) in the eastern part of Indonesia and Sulawesi. The role of *An. barbirostris* as a malaria vector was first reported in 1939 by Machsoes who examined 1,041 mosquitoes in South Sulawesi and found 30 (2.9%) with sporozoites [443]. In the early 1990s, Marwoto *et al.* [444,445] and Sukowati *et al.* [446] confirmed the infection of *An. barbirostris* with both *P. falciparum* and *P. vivax* from specimens collected in the Lesser Sunda Island group

(Lombok and Flores) and northern Sulawesi. Both *P. falciparum* and *P. vivax* infections were also detected in northern Sulawesi (Meras and Tomohon), Flores (Korowuru and Tilang) and Adonara Island in the eastern Lesser Sundas [387]. Cooper *et al*. also detected sporozoite infective mosquitoes in neighboring Timor-Leste (Timor Island) [447]. This species complex has not been incriminated as a malaria vector outside of Sulawesi and Lesser Sunda island chain. In addition, this species is an important vector of lymphatic filariasis in Sulawesi (*Brugia malayi*) and eastern Lesser Sundas (*Brugia timori*) [448]. Although *An. barbirostis* is commonly found in Sumatra and Java, the most plausible reason it is not important as a malaria vector is due to its strong zoophilic behavior.

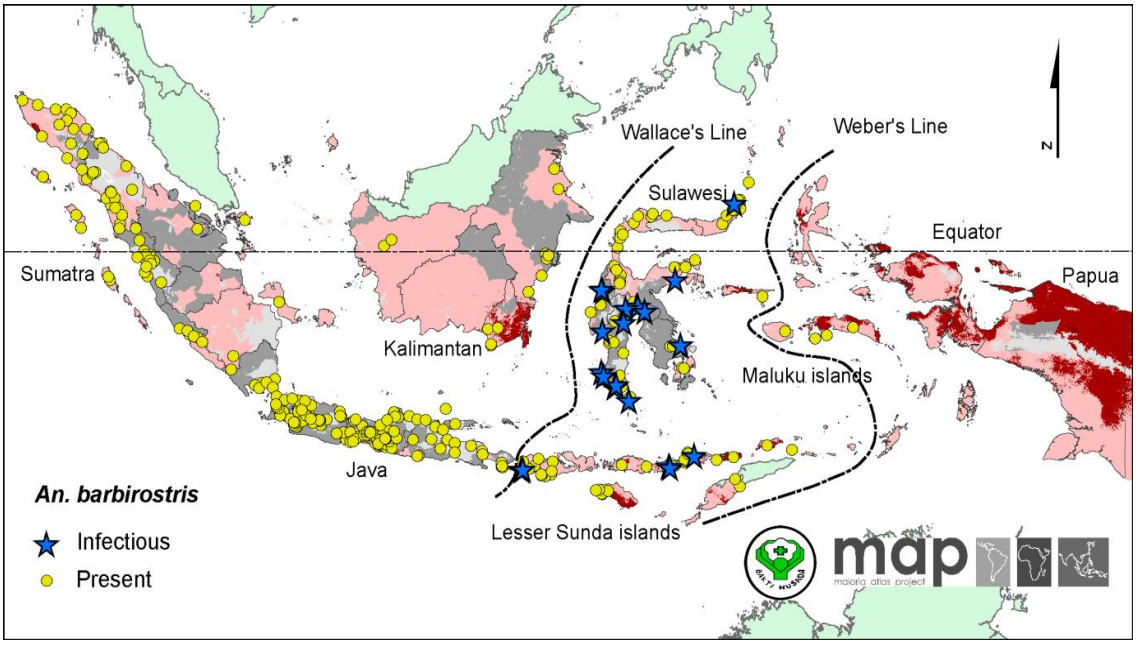


Figure 3.5. *Anopheles barbirostris* distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles barbirostris* mosquitoes found. The yellow dots show 330 records of occurrence for this species between 1918 and 2011. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2\text{-}10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2\text{-}10} < 40\%$) and high risk (dark red, $PfPR_{2\text{-}10} \geq 40\%$) [384].

The first evidence that *An. barbirostris* in Indonesia is a complex of species was based on analysis of mtDNA Cytochrome Oxidease I gene (COI) in which three putative species were formally designated W, X, and Z (form Y was identified from Thailand) [449]. More recently, the molecular phylogeny of *An. barbirostris* in Indonesia (COI and ITS2 data) has revealed several sympatric but distinct species clades exist in Java and Sumatra, the precise distribution, biology and vector status of each and control implications have yet to be determined [441].

Zoophilic and anthropophilic from of *An. barbirostris* have been reported in Indonesia [450], behavioral traits which can greatly influence their capacity to transmit pathogens (Table 3.3). *Anopheles barbirostris* females are often found resting outdoors [224,394,399,412,451] and are more common amongst cattle shelters than human settlements, especially in Java [32,386,392,394,397,399,418,419,452,453]. The HBI varies depending on the source location of the mosquitoes with 12.6% (42/332) from animal shelter resting collections containing human blood [389,396] and 20% (2/10) from indoor collections [397]. When biting humans, *An. barbirostris* typically feeds outdoors [399,405,412,418,419,453-458] but the biting behavior and activity of this species will vary depending on geographic location. For example, in western Java and central Sulawesi, females are more frequently found biting during the first half of the night [405,457,459], but elsewhere these mosquitoes will typically reach biting peaks during the third quarter of the night (24:00 – 03:00) [399,454,455,457,458].

The preferred larval habitat of *An. barbirostris* is sunlit water bodies containing exclusively fresh, often clear water, with varying amounts of emergent aquatic vegetation to (Supplementary Table S5) [32] include lagoons, [460-462], marshes [40,410,412,455,457,463], pools [224,408,458-461,464,465], slow running streams [40,412,431,453,454,461,466], along river banks [408,462,465], springs [399] and

various man-made habitats, such as rice fields [40,399,408,412,415,451-455,457-459,462,464,466,467], fish ponds [464,467], drainage ditches [40,386,399,451,453, 464] and wells [40]. *Anopheles barbirostris* is broadly dispersed from the coastal plain [415,444,454,459] to hilly terrain [415,454,459] at altitudes up to 2,000 meters asl [468].

3.5.5. *Anopheles (Anopheles) barbumbrosus* Strickland & Chowdhury

Anopheles barbumbrosus was documented by 13 sources at 63 independent sites in Indonesia (Figure 3.6). This species has been reported from almost all of the main islands, excluding Papua, and most commonly from Sulawesi (45 sites). This species can often be mistaken for *An. barbirostris*. Reid considers its distribution to be limited to western part of Indonesia (Sumatra and Java) and peninsular Malaysia, Thailand, India and Sri Lanka [469]. It has been suggested that this species is replaced by a very similar and closely related species, *An. vanus,* in Kalimantan, Sulawesi, Maluku and possibly the western tip of Papua. Nevertheless, Van Hell reported a single *An. barbumbrosus* female containing sporozoites among 21 specimens collected from South Sulawesi in 1952 (unknown if the infection was a human malaria parasite or other primate plasmodia) [470]. No other reports are known describing the presence of sporozoites in this species [465,471]. To date, this species is only regarded as a secondary malaria vector in Sulawesi (Tabel 3.2) and is typically found in low abundance regard human blood feeding [445,464,472,473].

Like the majority of species in the subgenera *Anopheles*, *An. barbumbrosus* shows a marked zoophilic tendency. Sulaeman reported greater numbers of females resting in cattle shelters than human settlements (54% vs. 46%; n = 83) and a ratio of indoor to outdoor human biting of 1:6 [472], indicating much greater exophagy. There are no

known reports on the HBI or any evidence of preferential resting habits in Sulawesi or elsewhere.

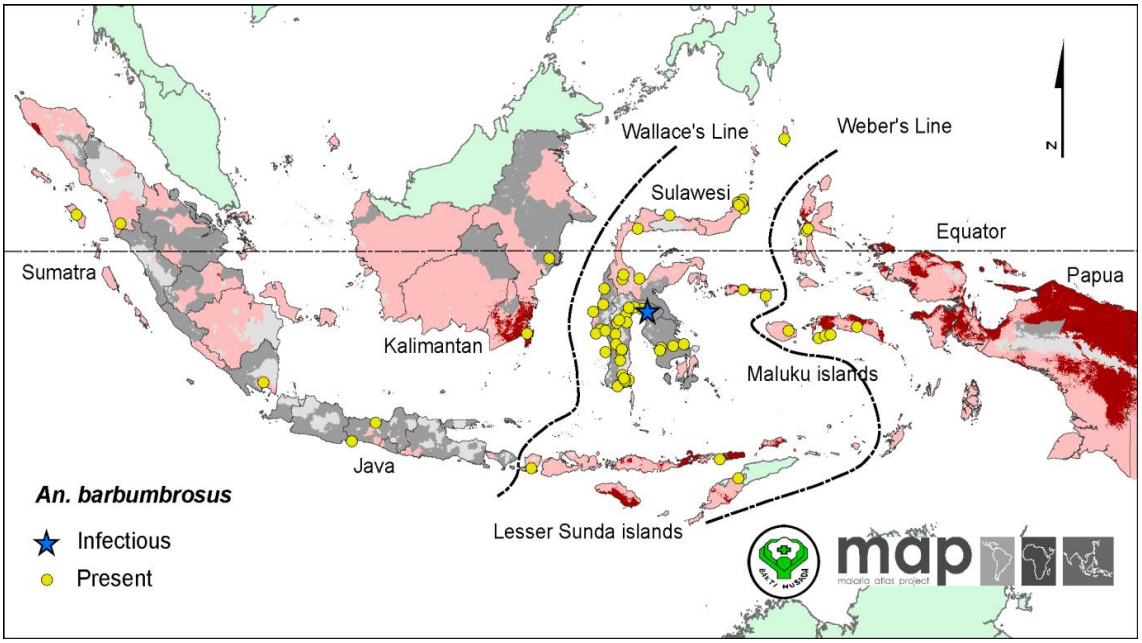


Figure 3.6. *Anopheles barbumbrosus* distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles barbumbrosus* mosquitoes found. The yellow dots show 63 records of occurrence for this species between 1932 and 2010. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2\text{-}10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2\text{-}10} < 40\%$) and high risk (dark red, $PfPR_{2\text{-}10} \geq 40\%$) [384].

The immature stages of *An. barbumbrosus* prefer a variety of habitats including both partially shaded and sunlit fresh and slowly running water, grass-fringed streams to stagnant water pools (Supplementary Table S5) [32]. These include natural water collections along river banks [465], clear streams emerging from jungle areas [37,474] open grassy ravines [37,475], and man-made water collections, such as rice fields [37,475].

3.5.6. *Anopheles (Cellia) farauti* Laveran species complex

The *An. farauti* complex comprises the largest complex of sibling species (8 members) within the Punctulatus Group [43,437], seven of which have been identified on the island of New Guinea [437]. *Anopheles farauti* s.s. has the widest geographic distribution of any member in the group but is restricted to the coastal areas. Papua has been shown to contain at least five of the sibling species based on molecular analysis [434], including *An. hinesorum* (= *An. farauti* 2), a confirmed malaria vector in Papua New Guinea [437]. Unfortunately, the vast majority of studies on *An. farauti* s.l. occurred before the advent of molecular (DNA) analysis techniques that provide the ability to differentiate isomorphic (morphological identical) species in the complex [476]. Fifteen sources were found reporting the presence of *Anopheles farauti* s.l. at 31 independent sites in Indonesia (Figure 3.7). Of these, 19 sites were located in Papua, where the role of this complex in malaria transmission has been well known since the mid 1950s when Metselaar reported a sporozoite rate of 0.8% (8/1,023) near Jayapura [171]. This species sporozoite positive (*P. falciparum* and two *P. vivax* variants) was found in both southern (Mapurujaya, Tipuka, Timika, Atuka) and northern (Arso, Armopa) areas of mainland Papua from 1987 through 1999 [387]. Evidence of sporozoite infection in *An. farauti* s.s. (*P. falciparum* and *P. vivax*) has also been reported from Gag Island, the western-most locality in Papua (east of Halmahera Island, northern Maluku Island chain where it is also present and regarded a malaria vector). The complex appears to exist at relative low densities in southern Papua (< 5% of collections) compared to other members in the Punctulatus Group [438,477], but it can be found in high abundance in northern Papua (> 50% of collections) [478,479].

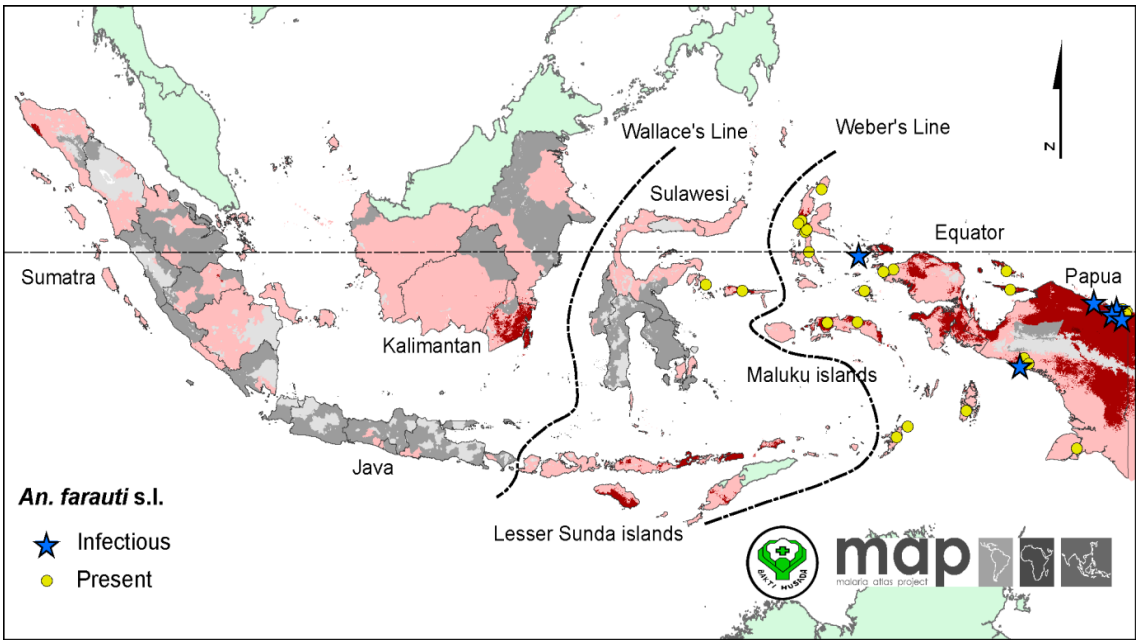


Figure 3.7. *Anopheles farauti* s.l. distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles farauti* s.l. mosquitoes found. The yellow dots show 31 records of occurrence for this species between 1945 and 2010. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2-10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2-10} < 40\%$) and high risk (dark red, $PfPR_{2-10} \geq 40\%$) [384].

The behaviour of *An. farauti* s.l. appears to vary by geographical location and presumably by sibling species (note that most work on this species was conducted before it was known to be a complex of sibling species). For example, a study conducted in the coastal areas of northwestern Papua (Sorong) [480] found the human biting ratio between indoor and outdoor collections was 1:8, suggesting a strong exophagic tendency in that location; whereas a longitudinal study in northeastern Papua (near Jayapura) reported an indoor: outdoor human biting ratio of 1:3 and hence moderate or little preference in biting location [479]. On the coast of northwest Papua [480] and on the northeast side of the island (Entrop near Jayapura), biting activity peaked early in the evening hours whereas at a site 35 km away (Arso), biting was

more commonly observed between the second or third quarter of the night [479]. Resting behaviour may also vary by both location and sibling species, with females from the coastal northwest of Papua showing a preference to rest indoors immediately after feeding but leaving the the house before dawn [480]. Conversely, those in the northeast, showed a strong exophilic behaviour, with high numbers of newly blood fed females collected in exit traps during the evening compared to those remaining indoors [479].

Anopheles farauti s.l. larvae prefer sunlit habitats with fresh or brackish water [32], depending on the sibling species (Supplementary Table S5). The primary vector species in the complex, *An. farauti* sensu stricto, is restricted to the coastal zones and generally prefers brackish habitats, often tolerating high salinity levels. The larval stages of this species complex have been found in a variety of natural habitats, including marshes, ponds and lagoons with emergent vegetation [37,468,477,479-481], large and small streams with grassy margins and floating wood and other natural debris [40], along river banks [468] or temporary man- and animal-made habitats, such as borrow pits, pig-gardens, garden pools and pools along river and stream margins [480-483], fishponds [480], and ditches [40,480]. *Anopheles farauti* has also been observed in container habitats such as discarded cans, drums, coconut shells and open canoes, as well as holes in coral pits, wells and carb holes [483]. This species complex is found from the coastal plain [40,477,481] to hilly and mountainous terrain [481,484] to altitudes up to 2,250 meters asl [32,437,484].

3.5.7. *Anopheles (Cellia) flavirostris* (Ludlow)

Anopheles flavirostris is a member of the Minimus Subgroup [485] and was previously considered a subspecies of the Minimus Complex, however, molecular investigations have confirmed *An. flavirostris* as a valid species. Moreover, Sinka *et al*. now regard all previous records of *An. minimus* reported from Indonesia, the Philippines and Sabah, Malaysia as invalid and misidentifications of *An*. *flavirostris* [43], therefore data presented here includes *An. minimus* records. *Anopheles flavirostris* was reported from 46 sources at 119 independent sites across Indonesia, most commonly from central and southern Sulawesi (39 sites) and Java (30 sites) (Figure 3.8), followed but also Sumatra, Kalimantan and the Lesser Sunda Islands extending to Timor-Leste [447]. *Anopheles flavirostris* has been found infected with *P. falciparum* sporozoites on Sulawesi [470] and Java [486]. In many locations in Java [415,452,487-489], Lesser Sundas [431,444,490] and Sulawesi [445], it has generally been reported in low abundance (< 5% of all *Anopheles* species collected).

Anopheles flavirostris is typically zoophilic [43] (Table 3.3). Greater relative numbers of *An. flavirostris* mosquitoes were captured at cattle shelters than human settlements (inside homes) in Central Java [426,491]. Another study in Java reported 9% of mosquitoes contained human blood and suggested low anthropophily [407], but as only a small number of mosquitoes (n = 33) were examined and the data presented did not differentiate between indoor and outdoor collections such a conclusion is potentially questionable. There are some apparent, albeit minor, variations in the biting habits of *An. flavirostris* depending on location. For example, Barbara *et al.* reported a ratio of indoor/outdoor human biting in western Sumba Island of 1:1.2 [490], indicating no clear preference for feeding location, whereas an indoor/outdoor ratio of between 1:1.5 to 2.9 was reported from Flores Island [492]. In all cases, the general tendency appears to be

towards exophagy, although this preference appears weak indicating a more 'opportunistic' biting habit. In coastal Flores, biting activity has been shown to peak in the second quarter of the night, yet in the interior of the island activity can peak during the third quarter of the night [492]. In Flores, *An. flavirostris* appears endophilic, preferring to rest indoors after feeding [492].

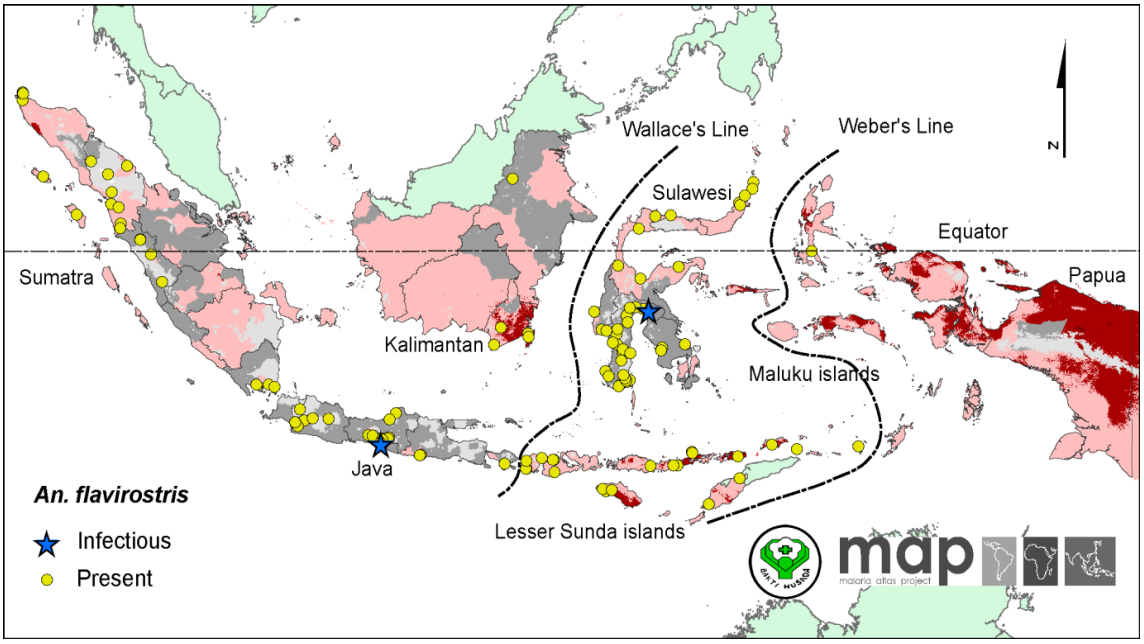


Figure 3.8. *Anopheles flavirostris* distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles flavirostris* mosquitoes found. The yellow dots show 119 records of occurrence for this species between 1932 and 2011. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2\text{-}10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2\text{-}10} < 40\%$) and high risk (dark red, $PfPR_{2\text{-}10} \geq 40\%$) [384].

The immature stages of *An. flavirostris* are often found in shaded habitats containing fresh and clear water (Supplementary Table S5) [32] that can include springs [423,459,493], shaded grassy edges of clear, slow-flowing small streams [37,386,423, 431,459,461,468,492,493], pools [423,459,461,493], rice fields [414,415] and irrigation

ditches [470]. This species can be found from the coastal plains [411] to the hill areas [415,431,490] up to 600 meters asl [475,494].

3.5.8. *Anopheles (Cellia) karwari* James

Anopheles karwari is a member of the Maculatus Group and the second scarcest species reported here from Indonesia, present at only 36 independent sites and identified by only seven sources (Figure 3.9), four of which were published prior to 1985. Sumatra had the highest number of sites, with others reported from Java, Kalimantan, Sulawesi and Papua. *Anopheles karwari* is apparently absent from the Lesser Sundas and Maluku island chains and infective females have only been reported from Papua (near Jayapura) [171]. Very little is known about the bionomics of this species in Indonesia because of its infrequent and patchy occurrence in collections. It is presumed to be primarily zoophilic.

Anopheles karwari larvae are found in natural and man-made shaded habitats containing fresh water (Supplementary Table S5), such as marshes [37,440], small, slow moving streams [35,37,40], seepages [40,440], ground and rock pools [440,481], springs [37,40] and irrigation canals associated with rice cultivation [35,37,40,440].

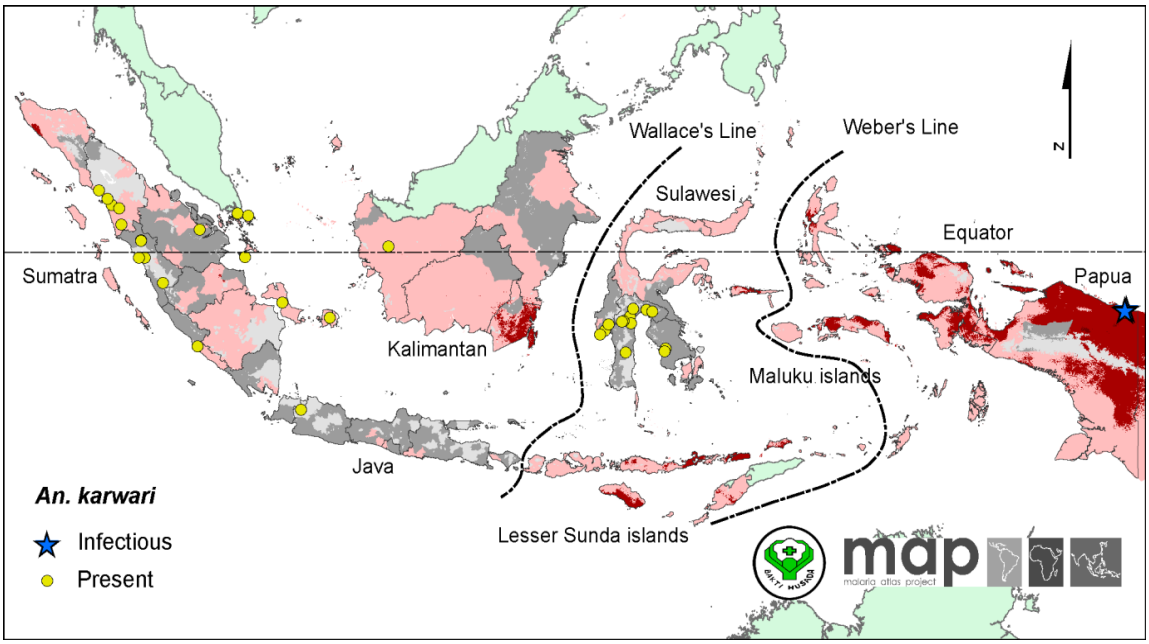


Figure 3.9. *Anopheles karwari* distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles karwari* mosquitoes found. The yellow dots show 36 records of occurrence for this species between 1932 and 2005. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2-10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2-10} < 40\%$) and high risk (dark red, $PfPR_{2-10} \geq 40\%$) [384].

3.5.9. *Anopheles (Cellia) kochi* Dönitz

Anopheles kochi is widely dispersed across Indonesia and is found on nearly all of the main islands except for New Guinea (Papua). Foley *et al*. reported the apparent introduction (likely by aircraft) to southern Papua [495] but there have been no evidence this species has established itself on the island. It has been documented from 88 sources and 253 independent sites (Figure 3.10). Published accounts of its role in malaria transmission has only been confirmed in Nias Island off the western coast of northern Sumatra [496]. Studies in Java [386,405,408,423] and Sulawesi [471] have been unable to detect the presence of sporozoites in *An. kochi*. However, this species

positive CSP-ELISA for *P. falciparum* and *P. vivax* was found in northern Sulawesi and for *P. vivax* in Central Java [387].

Anopheles kochi generally appears in low densities in human-landing collections [386,391,405-407,415,416,445,451,457,490,497-504], possibly reflecting a zoophilic feeding behavior throughout much of its range (Table 3.3). Indeed, females appear more common in cattle shelters than human habitation [386,394,399,406,457,472]. In western and eastern Java from 554 females captured resting in cattles shelters, 15% contained human blood [389,396] and only 2.8% of 287 mosquitoes contained human blood from indoor collections in homes [407,505]. Human landing catches in northern Sumatra recorded an indoor/outdoor ratio of 1:6 [506], whereas a near equal distribution (1:1.2) was reported in Java [405] and 1:8 ratio in central Sulawesi [472], indicating a general tendency for exophagy. *Anopheles kochi* reach their peak blood feeding activity during the first half (second quarter) of the night [389]. Their resting habits depend on location for example, they appear more exophilic in Central Java [394] and endophilic in southern Java [389,491].

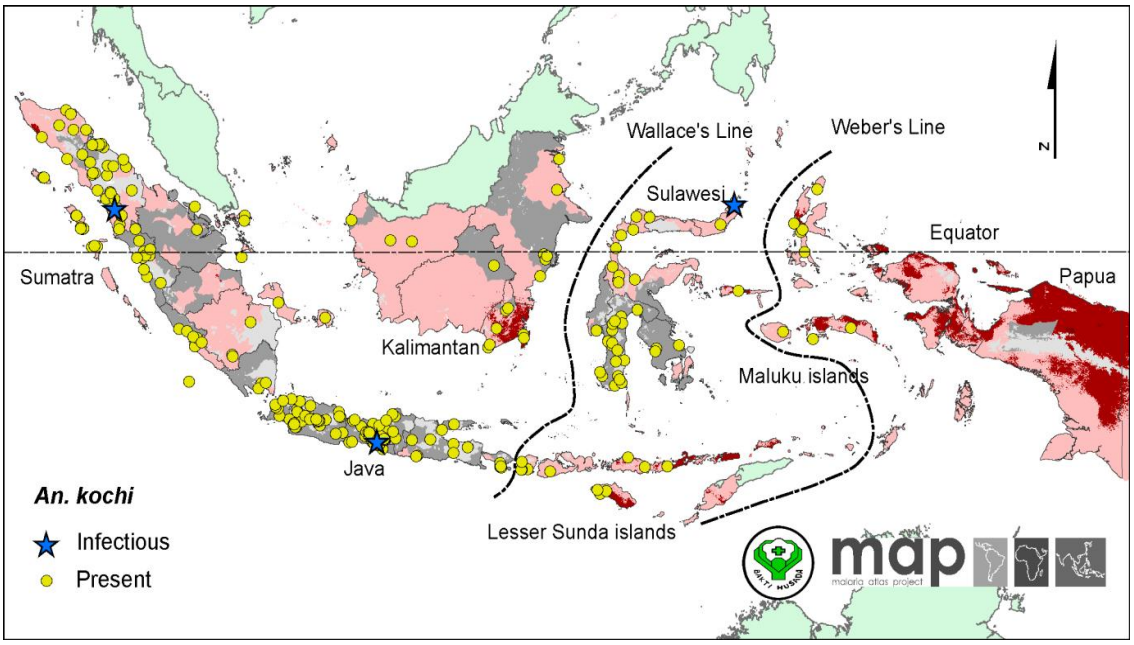


Figure 3.10. *Anopheles kochi* distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles kochi* mosquitoes found. The yellow dots show 253 records of occurrence for this species between 1918 and 2011. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2-10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2-10} < 40\%$) and high risk (dark red, $PfPR_{2-10} \geq 40\%$) [384].

Anopheles kochi larvae prefer sunlit habitats with either fresh or brackish running or stagnant, often muddy (turbid) water (Supplementary Table S5) [32]. Swellengrebel and Swellengrebel-de Graaf specifically noted this species as " [a] true dirty water breeder" because of its apparent preference for muddy habitats [409]. Larval habitats also include natural and man-made sites such as marshes [406,409,440], springs [34,37,396,423,475], rice fields [37,396,408,409,475,506-508], ponds [37,38,406,409,410,475,506], pools [34], buffalo wallows [409,475], wells [440] and ditches [37,38,409,451,509]. This species can be found from the coastal plain [38,405,411] to hilly locations [38,411,415] at altitudes up to 1,100 meters asl [510]. In western Java, more *An. kochi* mosquitoes were found nearer coastal locations than upland areas (99% vs. 1%, n = 88) [405].

3.5.10. *Anopheles (Cellia) koliensis* Owen

Anopheles koliensis is a member of the diverse Punctulatus Group [43] which also includes the primary malaria vectors, *An. punctulatus* and *An. farauti* complexes [437,511]. *Anopheles koliensis* occurrence has been reported from 12 sources covering 15 independent sites which were all located in Papua (Figure 3.11). Unfortunately, the vast majority of these studes took place before the advent of molecular (DNA) analysis techniques provide the ability to differentiate species

accurately within the group because of the occurrence of overlapping and variable (polymorphic) morphological characters between species [476]. Metselaar dissected 1,748 mosquitoes collected in Jayapura, and found 11 containing malaria sporozoites (0.63 %) [171]. Pribadi *et al*. [512] reported a *P. vivax* sporozoite rate of 0.3% by CSP-ELISA in the Mimika area, southern Papua and an entomological inoculation rate (EIR) of 0.17 infective bites/person/night. *Anopheles koliensis* appears particularly abundant in settlement areas near sago palm and swamp forests [477,479]. This species has been found infected in many locations in northern and southern Papua [387].

Lee *et al*. observed that due to a lack of abundance of large animals such as cattle, buffaloes or horses in Papua, the human population is the primary host for this vector [477]. Indeed, a high proportion of mosquitoes containing human blood (74%; 126/170) have been reported from outdoor collections [479]. However, before this species can be designated as anthropophilic a well-designed host-choice experiment should be undertaken. The feeding behaviour of *An. koliensis* varies depending on location. A human indoor/outdoor biting ratio of 1: 1.1 was reported from Arso, Papua, whereas a ratio of 1:4 was found in Entrop, Papua, suggesting a exophagic habit in some areas. In Arso, *An. koliensis* was the most common vector species found biting indoors between the second and third quarters of the night with biting occurring mainly in the first quarter of the night outdoors. In contrast, early-biting was seen both indoors and outdoors in Entrop. After indoor blood feeding, this species usually leaves the house very soon afterwards to rest outdoors [479].

The larval stages of *An. koliensis* can be found in mostly sunlit temporary and semi-permanent sunlit habitats such as ground pools in grassland and along the edge of jungles [40,477,481], ditches [477,479,513], riverside ponds [477] and occasionally in pig ruts and wallows [513,514] (Supplementary Table S5). In some locations it is often

closely associated with *An. farauti* [479,483]. This species can also be found in temporary pools such as shallow earth drains, footprints and wheel ruts, the typical habitat of *An. punctulatus*. This species can be found from lowland areas [40,515] to the highlands, up to 1,700 meters asl [484].

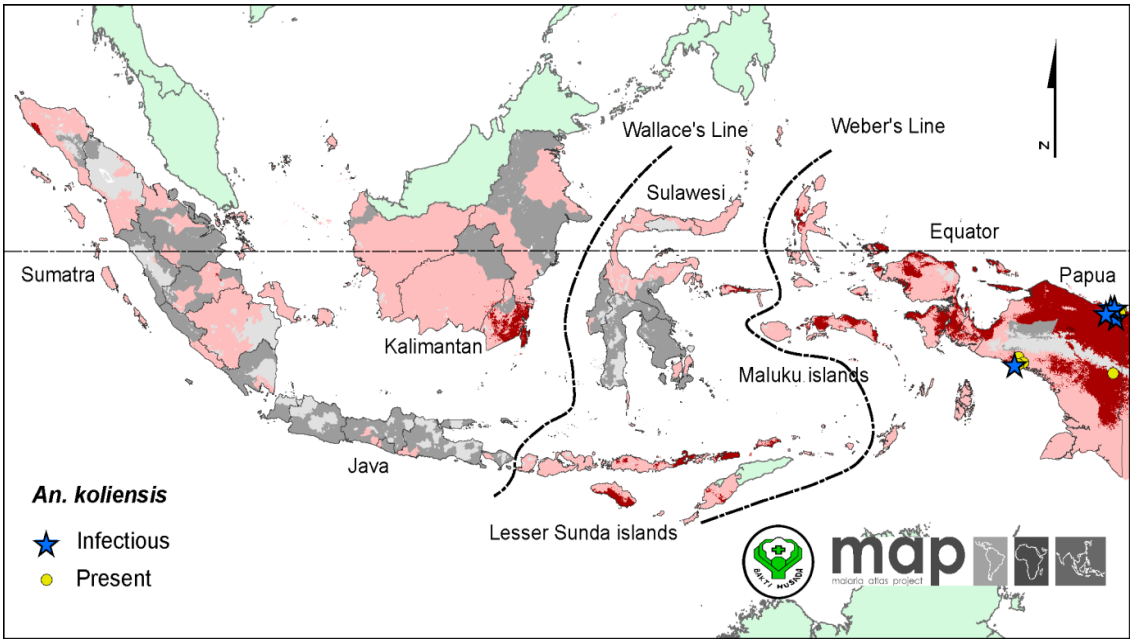


Figure 3.11. *Anopheles koliensis* distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles koliensis* mosquitoes found. The yellow dots show 15 records of occurrence for this species between 1946 and 2008. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2-10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2-10} < 40\%$) and high risk (dark red, $PfPR_{2-10} \geq 40\%$) [384].

3.5.11. *Anopheles (Cellia) leucosphyrus* Dönitz

Anopheles leucosphyrus is a member of the Leucosphyrus Subgroup [516]. It is considered to be of epidemiological importance for malaria transmission in forested areas of Sumatra [517], reflecting its preferred habitat. Within the Leucosphyrus

complex, *Anopheles leucosphyrus* is a sister species to *An. balabacensis* and more recently *An. latens* [518], the primary vector of zoonotic *Plasmodium knowlesi* between monkeys and humans in Sarawak, Malaysia (northern Borneo) and possibly elsewhere in Kalimantan (Indonesian Borneo). The separation of these two species was derived from earlier cytogenetic evidence [519] and eventually DNA analysis [81]. *Anopheles latens* appears to be restricted to the island of Borneo. Due to confusion and potential misidentification, Sinka *et al*. suggested that much of the published literature on "*An. leucosphyrus"* should be treated with caution, specifically where referring to *An. leucosphyrus* in locations other than Sumatra [43].

In this current study, *An. leucosphyrus* was reported from eight sources at 47 independent sites including Sumatra (25 sites) and Kalimantan (16 sites) (Figure 3.12). However, in light of the issues raised by Sinka *et al*. [43] and the clear genetic differentiation between *An. latens* and *An. leucosphyrus*, occupying very similar environmental conditions and the existance of *An. latens* in Malaysian Borneo, these latter data cannot be confirmed. However, we suggest molecular identification should be conducted on *An. leucosphyrus* specimens collected from Indonesian Kalimantan to confirm the presence of absence of these species beyond the State of Sarawak, Malaysia.

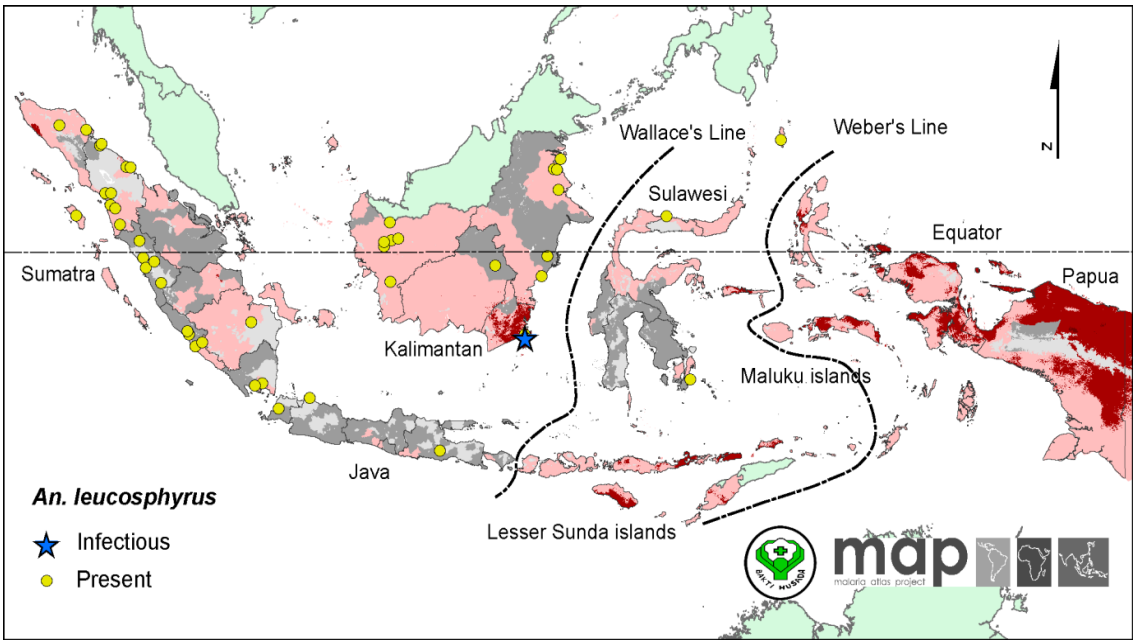


Figure 3.12. *Anopheles leucosphyrus* distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles leucosphyrus* mosquitoes found. The yellow dots show 47 records of occurrence for this species between 1932 and 2004. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2\text{-}10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2\text{-}10} < 40\%$) and high risk (dark red, $PfPR_{2\text{-}10} \geq 40\%$) [384].

The bionomic information for *An. leucosphyrus* remains limited. Walch found that in areas where cattle are scarce, 101 of 102 *An. leucosphyrus* mosquitoes collected indoors contained human blood [505]. However, this finding may be bias sampling as the same experimental design was not repeated in areas where cattle or other alternative blood sources were abundant. Therefore, the conclusion of human host preference may not be valid for all localities. Limited information exists on the vector status of *An. leucosphyrus* (via detection of natural malaria sporozoite infections). Harbach *et al*. in the 1980s did report a single sporozoite positive *An. leucosphyrus* (tested by NAMRU-2) collected from southern Kalimantan [416] but the species identification is now in question and would need to be confirmed.

Similar to all members of the complex, *Anopheles leucosphyrus* prefers shaded larval habitats within or very near forested environments and containing fresh water (Supplementary Table S5) [422,475]. Larval sites include marshes [34], small streams [34,440], seepage springs [34], jungle pools [34,38,440], ground depressions [34], fishponds [34,440], wheel ruts [34] and hoof prints [34].

3.5.12. *Anopheles (Cellia) maculatus* Theobald species subgroup

Anopheles maculatus s.l. belongs to the larger Maculatus Group comprised of several subgroups in the Southeast Asian region [520]. The precise relationship of the Indonesian populations remains to be clarified and may represent as an yet undescribed species in the subgroup. Occurrence data has been reported by 93 sources from 188 independent sites (Figure 3.13) throughout much of western and central Indonesia. The most common sites were located on Java (86 sites) where this species group is encountered relatively often in collections; elsewhere in Indonesia its biting densities are typically very low. There is no evidence of this species being present in Maluku or Papua. *Plasmodium* spp. infections of *An. maculatus* have been reported in Indonesia, particularly from eastern [521] and Central Java [486]. Likewise, CSP-ELISA positive *P. falciparum* and *P. vivax* specimens were also observed in three localities near Jogyakarta (Kokap, Purworejo and Banjarmangu), in Central Java and one locality in southern Sumatra (Tenang) [387]. This species is considered a major malaria vector in the Menoreh Hills of Central Java [100,486,489].

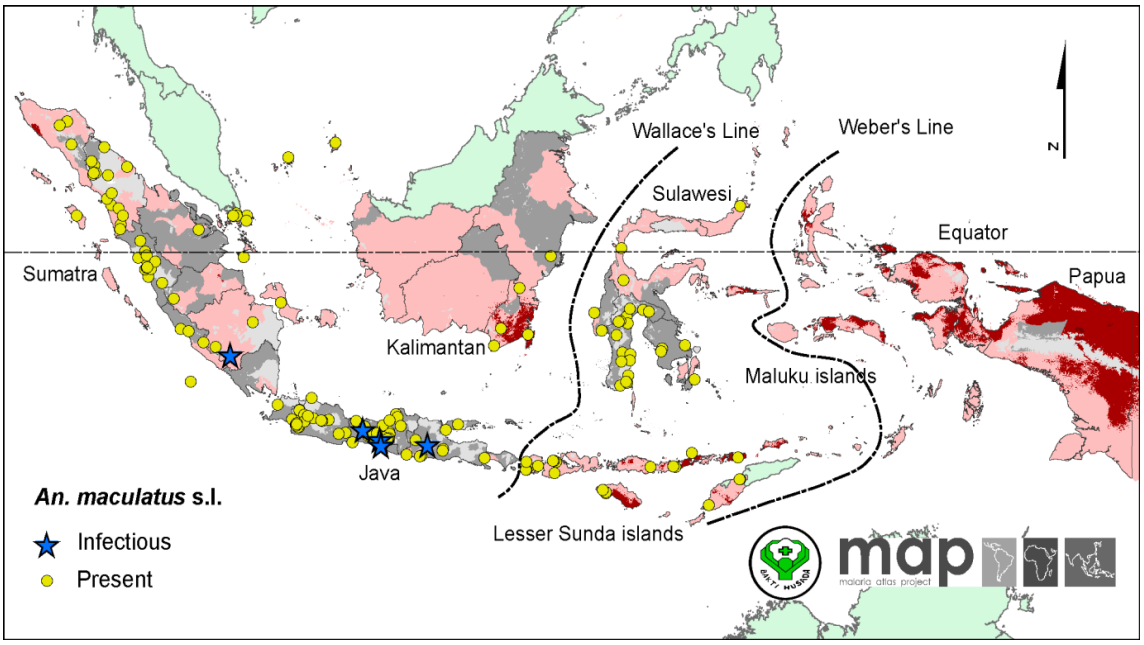


Figure 3.13. *Anopheles maculatus* s.l. distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles maculatus* s.l. mosquitoes found. The yellow dots show 188 records of occurrence for this species between 1918 and 2011. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2\text{-}10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2\text{-}10} < 40\%$) and high risk (dark red, $PfPR_{2\text{-}10} \geq 40\%$) [384].

Female *An. maculatus* are considered primarily zoophilic throughout most of their range and are regularly reported as more prevalent in cattle shelters than in human habitation [386,396,402,408,412,425,426,432,452,456,458,489,499,521,522]. It has been found biting humans both indoors [412] and outdoors [386,399,405,408,412,419, 420,426,432,489,499]. Blood feeding activity varies by location but in most areas *An. maculatus* generally tends to bite during the first half of night [402,405,408,412,419, 420,425,426,489], however an increased biting density has been observed to occur near the early morning (dawn) hours in Central Java [402,403,420]. After feeding indoors, *An. maculatus* typically leaves the house to rest outdoors [389,399] in or near cattle shelters [402,425,426,432,488,489], natural ground pits and among bushes/low

vegetation [488], under shaded plants [389,408,489], under moist banks of small streams [39] and in earthen overhangs in cliff sides [489].

The larvae of *An. maculatus* prefer habitats that are sunlit, containing fresh and clear water (Supplementary Table S5) [32]. Larval habitats include stream-side rock pools [412,432,475,489], along margins of small, slow-moving streams [32,402,403,408,431, 453,461,521], drying river beds [474], ground seepages [39,440,475], small pools and puddles containing turbid water [34], natural springs [34,39,396,399,402,403,425,475, 489], rice fields [34,38,39,396,412,453,461,523], ponds [34,440,489] and ditches [32,34,432,453]. This species can be found from the coastal plain [34,415,452,456] to hilly areas [34,38,39,389,409,415,489] at altitudes up to 1,100 meters asl [510].

3.5.13. *Anopheles (Anopheles) nigerrimus* Giles

Anopheles nigerrimus is a member of the Hyrcanus Group. The presence of this species has been reported in Indonesia by 32 sources at 91 independent sites (Figure 3.14). It appears more common on Sulawesi (43 sites) followed by Sumatra, Java and Kalimantan. No evidence was found of *An. nigerrimus* occurrence on the eastern islands of the Lesser Sundas or Papua and only one report from Maluku that is likely a misidentification [442]. *Anopheles nigerrimus* is a confirmed malaria vector in Indonesia with the first evidence of *Plasmodium* infection reported by Overbeek from Palembang, South Sumatra in 1940 [524]. This species has been found infected in Sihepeng, northern Sumatra [387].

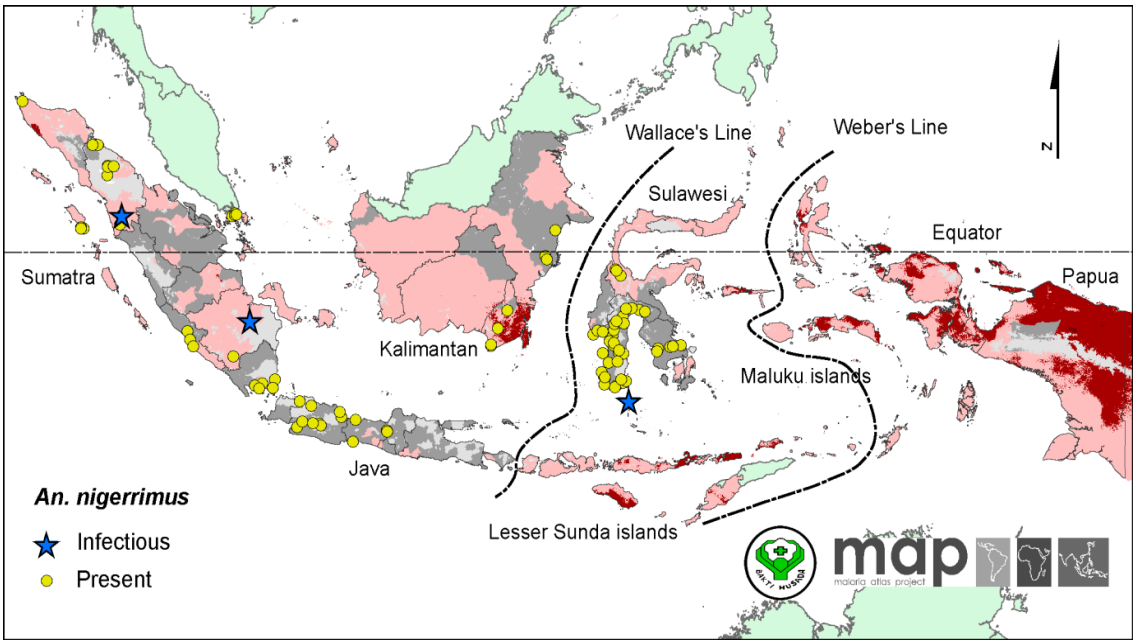


Figure 3.14. *Anopheles nigerrimus* distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles nigerrimus* mosquitoes found. The yellow dots show 91 records of occurrence for this species between 1932 and 2008. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2\text{-}10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2\text{-}10} < 40\%$) and high risk (dark red, $PfPR_{2\text{-}10} \geq 40\%$) [384].

The host preference for this species is unclear. Only one study was found to report HBI and they found only a low proportion of females (7%) contained human blood among 236 examined from animal shelter collections in eastern Java [389], however this could be the result of sampling bias. *Anopheles nigerrimus* appears to rest in cattle shelters in preference to human habitations [464,525]. Where human biting occurs, it tends to be exophagic [451,463,464,506,525,526]. *Anopheles nigerrimus* has been found to bite unusually early in the evening compared to most other malaria vectors, peaking during first quarter of the night in Sulawesi [464]. When it is found biting indoors (northern Sumatra), *An. nigerrimus* usually exits immediately after feeding to rest outdoors [506].

Anopheles nigerrimus larvae prefer sunlit habitats containing fresh and clear still or slow running water (Supplementary Table S5) [32]. Their larval sites include lake margins [389], marshes [37], pools [451], rice fields [37,467,506], irrigation channels [37] and fishponds [506]. This species has been found along the coastal plain to hilly enviroments at altitudes up to 700 meters asl [411].

3.5.14. *Anopheles (Cellia) parangensis* (Ludlow)

Anopheles parangensis is a member of the Pyretophorus Series, an assemblage of mosquitoes that represent important vectors in both Asia and Africa. The presence of this species was reported by 12 sources at 42 independent sites (Figure 3.15), most commonly from Sulawesi (40 sites). One record, published in the early 1930s, indicated its presence on Ternate, Maluku [36]. The first record of *An. parangensis* from Sumatra was reported by O'Connor and Sopa in 1981 but with no details on location [442]. In 2005, this species was found in concrete pools on Simeulue Island, Aceh, northern Sumatra [410]. Where present, the density of this species was lower than other biting *Anopheles* species in central and southeast Sulawesi (<1%) [455,457,473] but higher in northern Sulawesi (~60%) [445]. *Plasmodium* falciparum sporozoites have been detected by NAMRU-2 in *An. parangensis* from Sulawesi, near Manado [527] and an EIR of 0.1 infective bites/person/night was reported from the same locality during the epidemiological investigation [445].

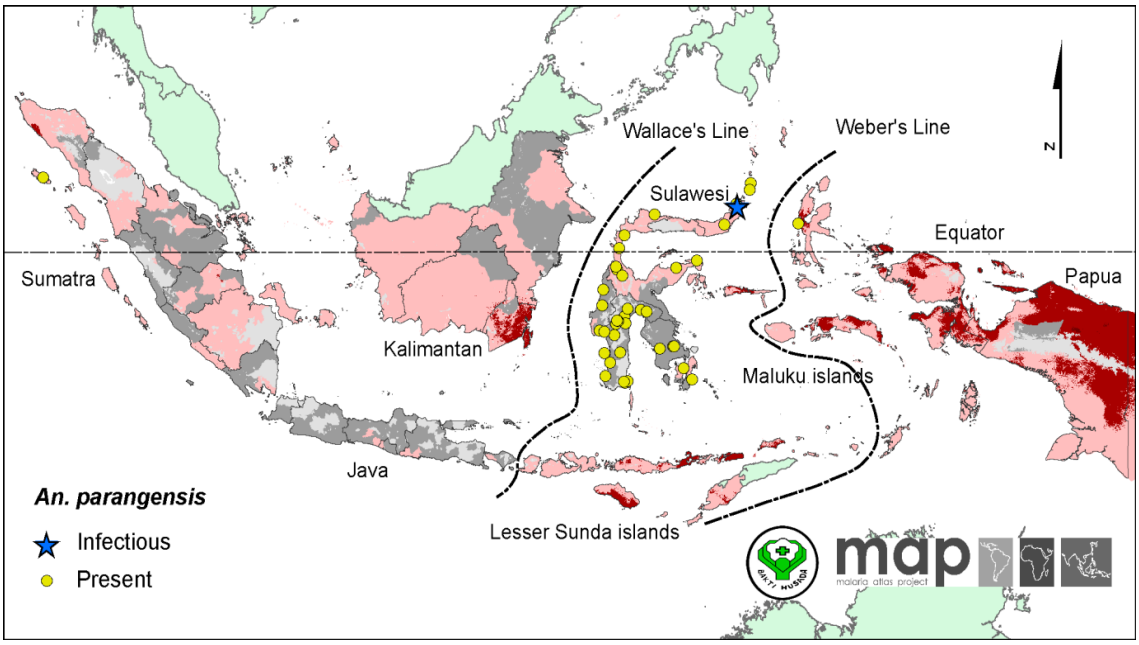


Figure 3.15. *Anopheles parangensis* distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles parangensis* mosquitoes found. The yellow dots show 42 records of occurrence for this species between 1932 and 2011. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2\text{-}10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2\text{-}10} < 40\%$) and high risk (dark red, $PfPR_{2\text{-}10} \geq 40\%$) [384].

The host preference of this species is poorly known in Indonesia and there is no known study examining the presence of human blood in this species. Widjaja *et al*. observed greater numbers of *An. parangensis* females resting in cattle shelters than in houses (95% vs. 5%; n = 78) in central Sulawesi [455]. However, in northern Sulawesi, only 41% (n = 7,594) of resting *An. parangensis* were collected from cattle shelters, together with ratio of 1:1.6 indoor to outdoor human landing captures [445], indicating a stronger tendency for exophagic behaviour. The larval stages are found in sunlit habitats containing either fresh or coastal brackish water (Supplementary Table S5) [37] including marshes [37,465], pools [475,528] or man-made habitats, such as fish ponds [459,465,528] and ground puddles [475].

3.5.15. *Anopheles (Cellia) punctulatus* Dönitz

Anopheles punctulatus is one of 12 members of the Punctulatus Group [43] which also includes the malaria vectors *An. farauti* s.l. and *An. koliensis* [511]. *Anopheles punctulatus* occurrence data were extracted from 18 sources and 46 independent sites in Indonesia (Figure 3.16). The two reported locations were Papua (23 sites) and Maluku (21 sites). In Papua, this species is a proven malaria vector of *P. falciparum, P. vivax* and *P. malariae* [171,513,514] and is an important vector in neighbouring Papua New Guinea [437]. This species has been found infected with *P. falciparum* and *P. vivax* in both southern and northern Papua, from coastal and lowland inland areas (Armopa, Timika, Arso, Mapurujaya and Tipuka) and highland (Obio, near Wamena and Oksibil Valley) locations [387].

Anopheles punctulatus was reported responsible for a malaria outbreak in the highlands of Papua in 1989 at an elevation of 1,260 m asl [514] where it was the predominant species (98%; n = 2,577) biting humans. This species has also been implicated in transmission in the central highlands of Papua during a period of extreme drought period [99]. *Anopheles punctulatus* usually bites humans outdoors [515] but when indoor feeding does occur, peak activity is normally before midnight (second quarter) [477,514]. After feeding, this species will typically rest outdoors, including the exterior surfaces of house walls and amongst surrounding vegetation [477,479].

Anopheles punctulatus larval sites are routinely sunlit containing fresh, clear or turbid water (Supplementary Table S5) [32]. Larvae have been sampled from freshwater coastal marshes [32], low-lying riverine areas [32], riverside pools [477], grasslands [32], along jungle edges [32], pools [32,436,474,477,481,515], ground depressions and shallow drainage around houses [513], rock pools in drying stream beds [40,475],

earthen drains [435], footprints [32,479], ditches [477,513], pig ruts [513], pits with grey turbid water [409,435] and wheel prints [32,479]. Lee *et al*. [483] found the most commonly recorded habitats are man-made depressions (wheel ruts, roadsite ditches, footprints) holding water temporarily and exposed to direct sunlight. The water is commonly without vegetation and may be clear to muddy. Larvae have been found in water of nearly 42^{o}C, indicating a tolerance to high temperatures [481,515]. This species is found in the lowlands [477,515] and in hilly and mountainous terrain [436,479,513] at 1,500 asl or higher [513].

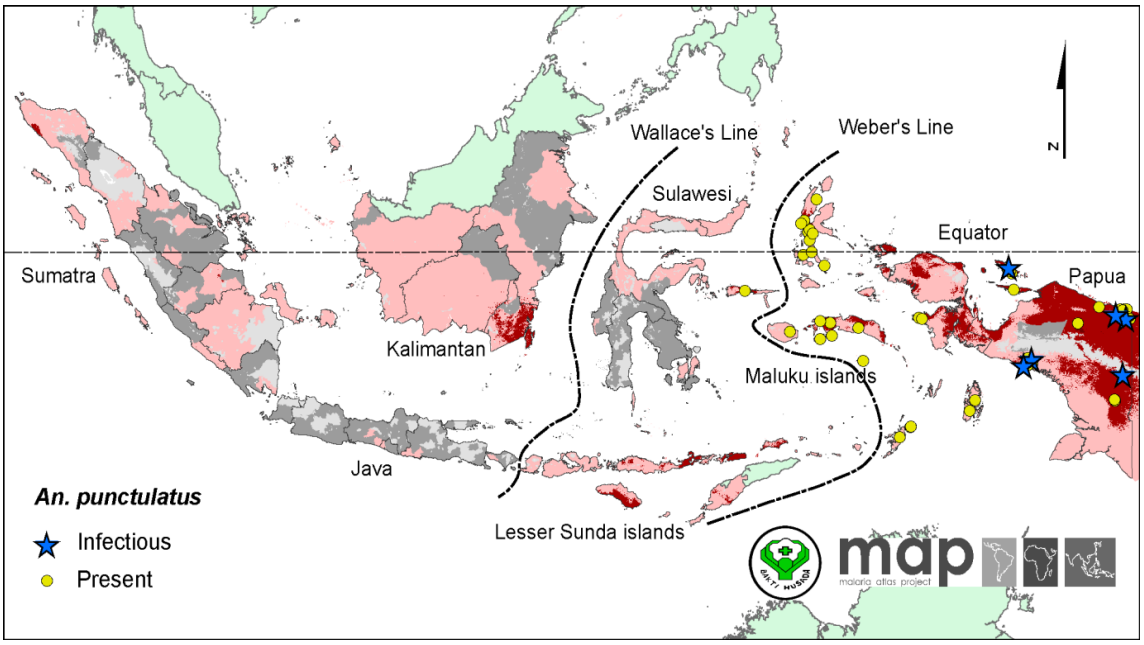


Figure 3.16. *Anopheles punctulatus* distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles punctulatus* mosquitoes found. The yellow dots show 46 records of occurrence for this species between 1929 and 2011. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2\text{-}10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2\text{-}10} < 40\%$) and high risk (dark red, $PfPR_{2\text{-}10} \geq 40\%$) [384].

3.5.16. *Anopheles (Anopheles) sinensis* Wiedemann

Anopheles sinensis is a member of the Hyrcanus group of mosquitoes [520] and is the second member (*An. nigerrimus*) of the group that is a confirmed malaria vector in Indonesia. A total of 13 sources reported the presence of this species from 32 independent sites across Sumatra, Kalimantan and Sulawesi (Figure 3.17). *Anopheles sinensis* was most commonly reported from Sumatra (30 sites). Boewono *et al.* first documented the mosquito, including specimens with *Plasmodium* sporozoites, among 1,614 examined by head-thorax dissections in Nias, northern Sumatra [496]. *Anopheles sinensis* normally appears in low densities compared to other *Anopheles* mosquito populations (< 1%) in both northern Sumatra [506,529] and eastern Kalimantan [530]. Although this species appears to play a relatively minor role in malaria transmission in Indonesia, it is still recognized as a primary vector in Korea and central/northern China [531].

The host preferences of *Anopheles sinensis* in Indonesia is poorly known but is assumed to be mostly zoophilic. However, studies examining the impact of cattle presence on human feeding found that in areas with cattle, 83% of females (n = 381) contained human blood, whereas 90% (n = 102) contained human blood in areas where cattle were scarce [505]. The author concluded that this species remained anthropophilic even in the the presence of abundant alternative hosts. However, those mosquitoes examined were collected from indoor collections only therefore likely providing a bias sampling. *Anopheles sinensis* shows exophagic human biting behaviour in northern Sumatra (Nias Island) where a 1: 1.3-3.5 indoor to outdoor ratio was reported [526]. The feeding activity has been shown to peak in the first quarter of night [532] and with a flight range of up to 1,500 meters [532]. We found no information

reporting the specific resting habits of *An. sinensis* in Indonesia, however, elsewhere this species appears to mostly rest outdoors in animal shelters after feeding [533].

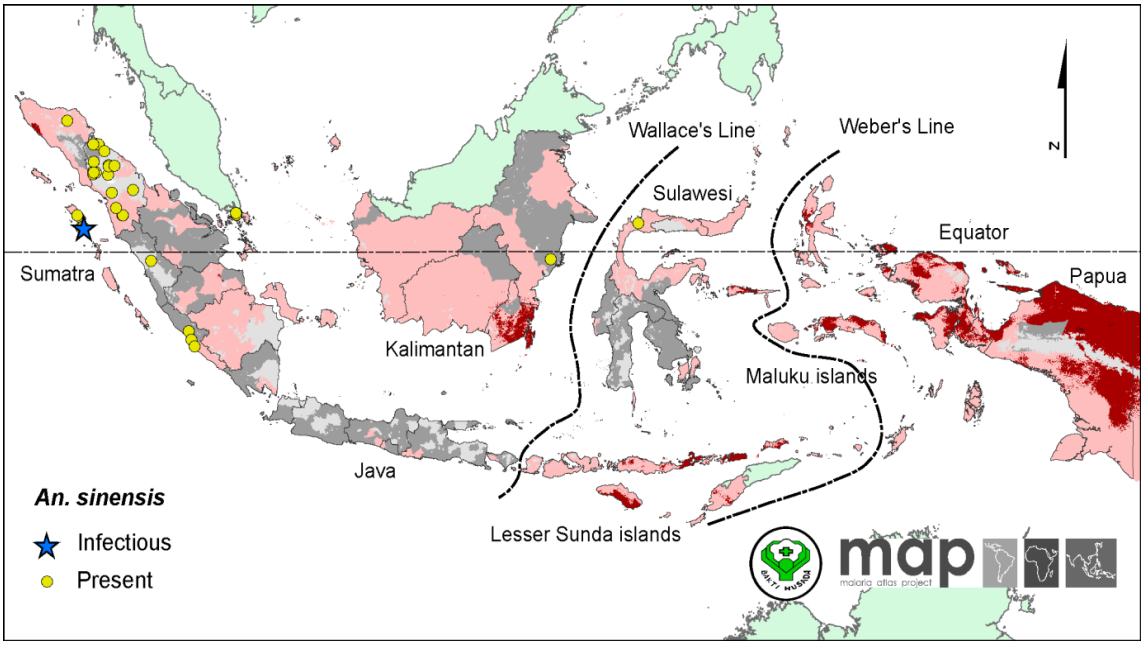


Figure 3.17. *Anopheles sinensis* distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles sinensis* mosquitoes found. The yellow dots show 32 records of occurrence for this species between 1931 and 2005. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2-10} \leq 5\%$), intermediate risk (medium red, 5% < $PfPR_{2-10}$ < 40%) and high risk (dark red, $PfPR_{2-10} \geq 40\%$) [384].

The larval stages of *An. sinensis* are typically found in sunlit habitats containing fresh clear or stagnant water (Supplementary Table S5) [32]. There is some evidence of larvae being found in saline or brackish water [34,409] and it has also been reported from rice fields where the water temperature exceeded 41°C, indicating a tolerance to high temperatures [533]. Larvae have been found along lake margins [32,38,475], marshes [32,34,37,38,409,440,475], pools [34,38,440,534], small streams [32,34,409, 440,475,534], borrow-pits [32,475], fish ponds [34,440], rice fields [32-

34,37,409,507,510,523,535,536], wells [440] and irrigation ditches [32,34,37,38,409, 475]. *Anopheles sinensis* has been recorded in the lowlands [34] and in hilly terrain [537] at altitudes up to 1,100 meters asl [510].

3.5.17. *Anopheles (Cellia) subpictus* Grassi species complex

Subpictus Complex is a member of Pyretophorus Series [520] and is by far the most widely distributed species in Indonesia, being found from Sumatra to Papua. The Subpictus Complex has been described as consisting of at least four sibling species in India: A, B, C and D [538]. Species A, B and D are generally found in fresh water habitats, while species B appears restricted to coastal brackish-water [43]. The presence of this species complex in Indonesia was documented by 72 sources at 204 independent sites and was more commonly reported from Java (74 sites) than any other island (Figure 3.18). The role of *An. subpictus* as a malaria vector in Indonesia [539] was first confirmed in the late 1920s when Soesilo found 32 mosquitoes with sporozoite infections among 164 collected [540]. Sporozoite positive females have also been reported from the Sikka area (Flores Island) in the eastern Lesser Sundas [444], Sulawesi [445,470,527] and western Lombok [541]. Results from sporozoite CSP-ELISA have found this species infected in northern [542] and southern Sulawesi (Selayar Island) and the Lesser Sundas (Lombok, Flores, and Adonara) [387].

Anopheles subpictus s.l. are generally zoophilic throughout most of their range [43]. The proportion of mosquitoes collected from indoor and outdoor sampling on Java and Sulawesi revealed only 15% (of 2,093) containing human blood [39,389,396,397,505, 543,544]. Overall, females tend to be captured more often from cattle shelters than human houses [406,412,452,457,522,541,545] also suggesting stronger zoophilic tendencies. Where *An. subpictus* are recorded feeding on humans, they are generally

found feeding outdoors but this can vary depending on geographic location [39,199,412,451,454,457,458,493,522,545] for example, in western Java and northern Sulawesi where indoor biting has been recorded [405,445,543]. *Anopheles subpictus* has been shown to bite primarily during the second half of the night [412,457,503,545] although in the Lesser Sundas and Sulawesi, this species is reported to be active during the first half of the night [199,454,458,493,544].

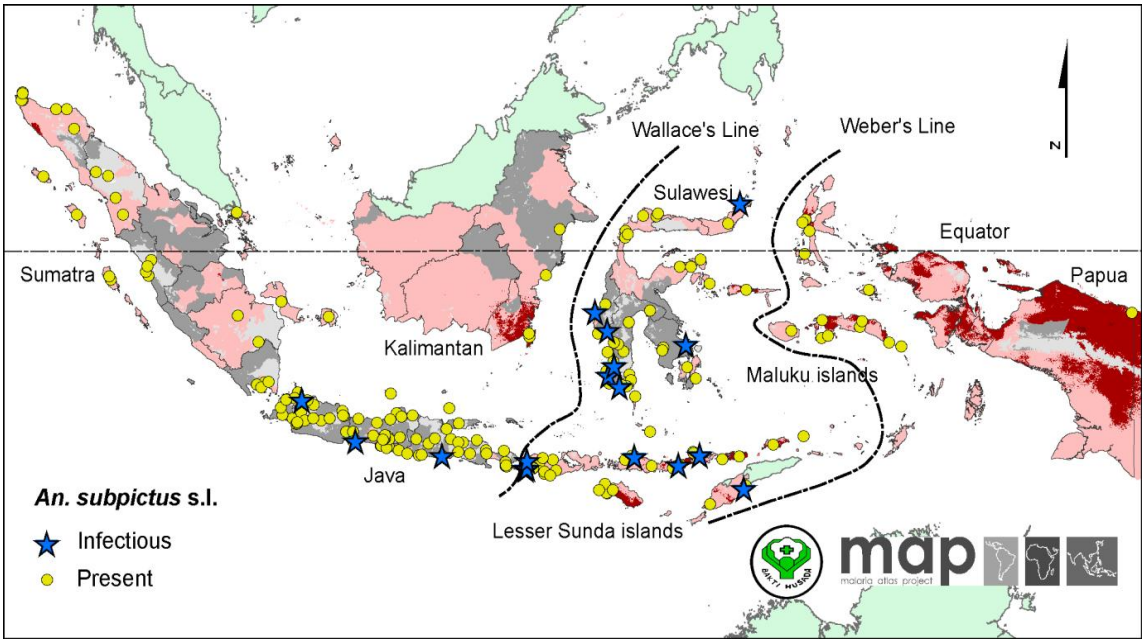


Figure 3.18. *Anopheles subpictus* s.l. distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles subpictus* s.l. mosquitoes found. The yellow dots show 204 records of occurrence for this species between 1932 and 2011. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2\text{-}10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2\text{-}10} < 40\%$) and high risk (dark red, $PfPR_{2\text{-}10} \geq 40\%$) [384].

A number of studies have reported *An. subpictus* females as endophilic [406,451,493,541,544,545]. Resting sites include bed nets [406,545], hanging clothes [406,545], interior wall surfaces [406,543,545] and ceiling [543]. However, in western

Sumatra, this species has been found resting outdoors [412], in bushes and under shaded trees.

Anopheles subpictus larvae are common in sunlit aquatic habitats containing either fresh or brackish water (Supplementary Table S5) [32], including tidal lagoons and coastal blocked freshwater rivers and streams [32,39,406,454,457,458,461,462, 467,491,493,503,545], marshes [32,406,459,545], pools [40,410,451,467,475,546], rocky streams [412,461], mangrove forests [32], springs [460,492], rice fields [32,39,154,451,491,547], fish ponds [32,199,406,431,451,459,548], borrow pits [40], drains [40], furrows in gardens [40], water tanks [40,412,452,492,545], buffalo wallows [406,545], brackish ponds [515], seaweed ponds [32,548,549] and irrigation ditches [32,414,451,466]. This species can be found primarily across coastal plains [405,415,445,459,461,466,491,544,548,550] and much less so in hilly terrain [411,415,550] up to 700 meters asl [550].

3.5.18. *Anopheles (Cellia) sundaicus* Rodenwaldt species complex

The Sundaicus Complex belongs to the Pyretophorus Series [43] and represents one of the most important malaria vectors in Indonesia. Sukowati *et al*. [551,552] first described the cytotypes (forms) A, B and C of the *An. sundaicus* complex using both cytogenetics and enzymatic analysis. Form A was collected from coastal areas in Sumatra and Java, while form B was mainly collected in the freshwater habitats at South Tapanuli in northern Sumatra (> 87% of samples) with fewer found in the brackish water habitats near Purworejo in Central Java (only 10% of samples). Form C was only found at a coastal location in Asahan, northeastern Sumatra, where all three forms were sympatric (A 48%, B 15%, C 37%) [553]. *Anopheles sundaicus* form D has been identified only from the Nicobar Islands in the Indian Ocean [554]. Dusfour *et al*.

reported no genetic distinction between the brackish and fresh water forms using mitochondrial DNA markers (cytochrome oxidase I and cytochrome-*b* genes) [555], suggesting they were the same species. Their ecological differences were regarded as adaptations to the prevailing ecology of the area ranging from strongly brackish to fresh water [556]. Using the same markers validated by PCR, Dusfour *et al*. analyzed specimens collected from Sumatra and Java [555,557] and found no similarity to sympatric forms A, B, and C of Sukowati [552] and proposed the presence of a new sibling species of the Sundaicus Complex in Indonesia, designated *An. sundaicus* E.

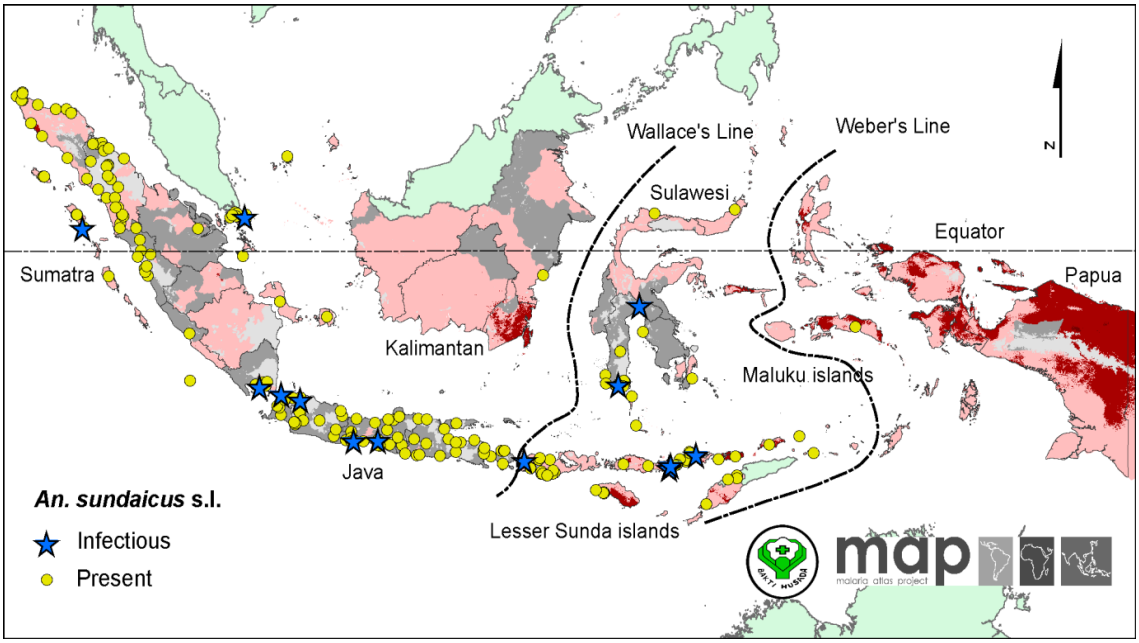


Figure 3.19. *Anopheles sundaicus* s.l. distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles sundaicus* s.l. mosquitoes found. The yellow dots show 205 records of occurrence for this species. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2-10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2-10} < 40\%$) and high risk (dark red, $PfPR_{2-10} \geq 40\%$) [384].

The distribution of *An. sundaicus* s.l. has been reported throughout the main islands of the archipelago, except Papua, from 79 sources representing 205 independent sites (Figure 3.19). More sites reported the presence of *An. sundaicus* in western Indonesia than the eastern part of the country (73% vs. 27%). Based on these reports, the complex appears most common in Sumatra (81 sites), followed by Java (67 sites) although this is likely influenced by sampling frequency. It has been primarily reported from coastal lowlands but can extend inland to slightly higher elevations, up to altitudes of 300 meters asl in western Java [411].

The *Anopheles sundaicus* complex is mainly responsible for malaria transmission in coastal areas of Indonesia. Mangkoewinoto first identified sporozoites among 31 dissected *An. sundaicus* s.l. in western Java in 1918 [38]. Nalim *et al.* identified both *P. falciparum* and *P. vivax* sporozoites in specimens collected from Lampung, southern Sumatra [558]. Other authors have also confirmed this species as an important malaria vector in Java [38,39,540,543], Sulawesi [470,544] and the Lesser Sundas [444] (Table 2), and most recently in western Sumba (*An. sundaicus* E) [559]. Results from CSP-ELISA have found this species infected more often than any other species tested over a 30 year period across Sumatra (Nias, Sihepeng, Riau/Bintan Island, Lampung), Java (Pari Island, near Jakarta) and the Lesser Sunda Islands (Sumbawa, Flores, and Adonara Islands) [387].

The females of *An. sundaicus* have a slightly greater tendency to bite humans compared to domesticated animals. The compiled human blood tests for this species revealed 54% of 5,928 mosquitoes collected indoors and outdoors from Sumatra and Java contained human blood [39,397,505,543,544] (Table 3.3). The Sundaicus Complex appears to have no clear preferential biting location, exhibiting both endophagic and exophagic behaviours. However, a stronger exophagic habit (> 60%)

has been reported from Sumatra [545,560], Java [39,405] and western Lesser Sundas (Lombok) [561], with a slightly more endophagic habit (54%) seen in the eastern Lesser Sundas [490]. In western Java, biting activity has been seen to be high during both the first and last quarters of the night [405], while in Central Java, feeding activity begins more slowly, peaking during the second and third quarters of the evening [39,544]. After feeding, females may be found resting indoors on clothes, curtains and walls or outdoors, under shaded tress, rock crevices and bushes [39,545,562]. Age grading of nearly 1,130 *An. sundaicus* s.l. mosquitoes captured in early morning resting collections indoors in Sulawesi, identified 96% as fed or gravid, suggesting most had remained indoors after blood feeding [544].

Larvae of the Sundaicus Complex are primarily found in sunlit sites containing either brackish or fresh water (Supplementary Table S5) [170,553]. Sites are also generally of low acidity, varying water depth and with the presence of vegetation [411,563], in particular floating filamentous algae. Examples include: lagoons [410,460,545], marshes [410,508,560], pools [508,545], seasonally blocked streams [564] and man-made water collections, especially abandoned fish ponds [410,508,545,560], rice fields [414,506,508] and irrigation ditches [414].

3.5.19. *Anopheles (Cellia) tessellatus* Theobald

Anopheles tessellatus is within its own group within the Neomyzomyia Series [516]. The presence of *An. tessellatus* were documented by 56 sources at 121 independent sites (Figure 3.20). The most common sites were located on Java (39 sites). This species is found throughout the archipelago, including isolated reports from western Papua (Sorong, Manokwari) [442]. *Anopheles tessellatus* has been confirmed as a malaria vector in Sumatra with *P. falciparum* infected females identified in Nias,

northern Sumatra [496]. No other reports were found incriminating *An. tessellatus* as a malaria vector on any other of Indonesia's main islands.

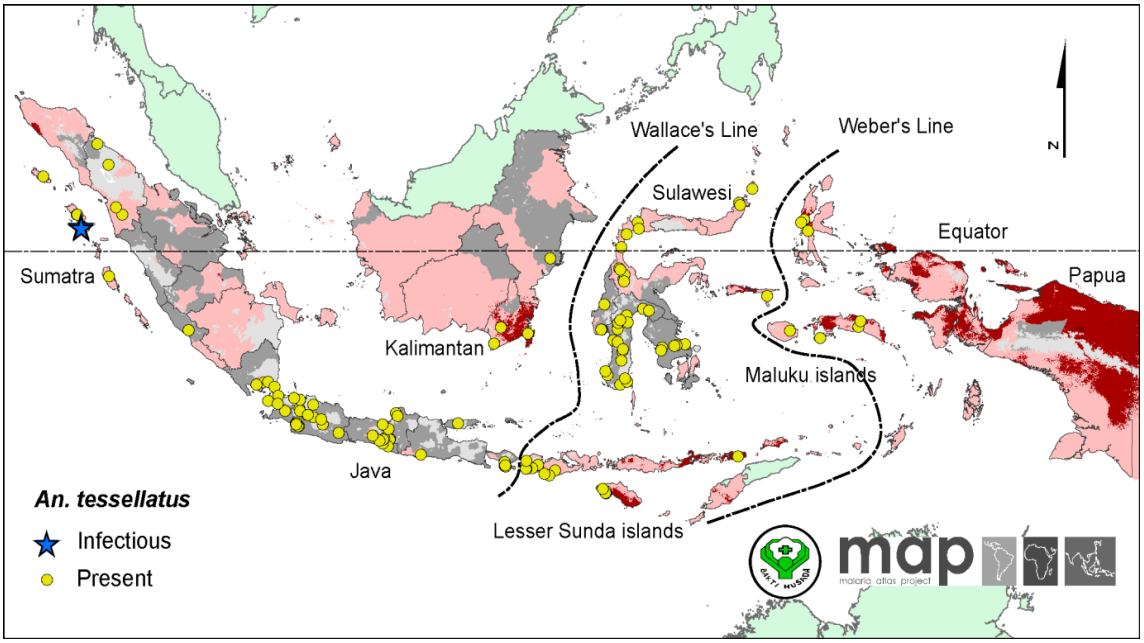


Figure 3.20. *Anopheles tessellatus* distribution in Indonesia. The blue stars indicate the records of infectious *Anopheles tessellatus* mosquitoes found. The yellow dots show 121 records of occurrence for this species between 1947 and 2011. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2\text{-}10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2\text{-}10} < 40\%$) and high risk (dark red, $PfPR_{2\text{-}10} \geq 40\%$) [384].

Anopheles tessellatus is primarily zoophilic, with the assembled records showing that only 10% of 182 mosquitoes examined from Sumatra and Java contained human blood [389,396,397,505]. In western Lesser Sundas, where cattle are prevalent, higher numbers of *An. tessellatus* were collected from cattle shelters compared to inside houses (>90%), also suggesting stronger zoophilic tendencies. Feeding behaviour varies by location with more female *An. tessellatus* found biting indoors (> 60%) in western Java [405], whereas exophagic biting appears more common in eastern

Indonesia (Sulawesi and Lombok) [418,455-457,472]. Blood feeding activity was also seen to peak during the second quarter of the evening in Sukabumi, western Java [405]. In Java, females also prefer to rest outdoors after feeding [394,399]. *Anopheles tessellatus* has been reported in greater densities in coastal compared to upland areas [405,418].

The larval stages of *An. tessellatus* can be found in shaded habitats, typically associated with slow moving water (Supplementary Table S5) [32]. This species is usually found in fresh water, but can also tolerate relatively high salinity [565]. They are also found in ground pools [410], rice fields and fish ponds [453].

3.5.20. *Anopheles (Cellia) vagus* Dönitz

Anopheles vagus is the third species in the Indonesia list of important malaria vectors belonging to the Pyretophorus Series. Similar to *An. subpictus*, it is broadly distributed throughout the main islands of the Indonesian archipelago, excluding Papua [442]. The species is also broadly distributed acroos much of Asia and it would come as no surprise if it was also a species complex. The presence of this species was reported by 107 sources from 349 independent sites (Figure 3.21), 138 of which were found on Java, followed by 83 sites on Sumatra. This species has been confirmed as a malaria vector (*P. falciparum*) in Central Java (Purworejo, Kokap) [486] and western Timor Island (Kupang) [387]. A morphologically similar but genetically different (putative) species (*An. vagus* genotype B) has been found infected in neighboring Timor-Leste on Timor Island [447]. The taxonomic status of this genotype remains unclear. Numerous attempts to find *Plasmodium* infected *An. vagus* from Sumatra, Sulawesi, Maluku and other Lesser Sunda locations has as yet failed to detect the presence of malaria parasites [387,444,447,463,465,503,504,529,546,566].

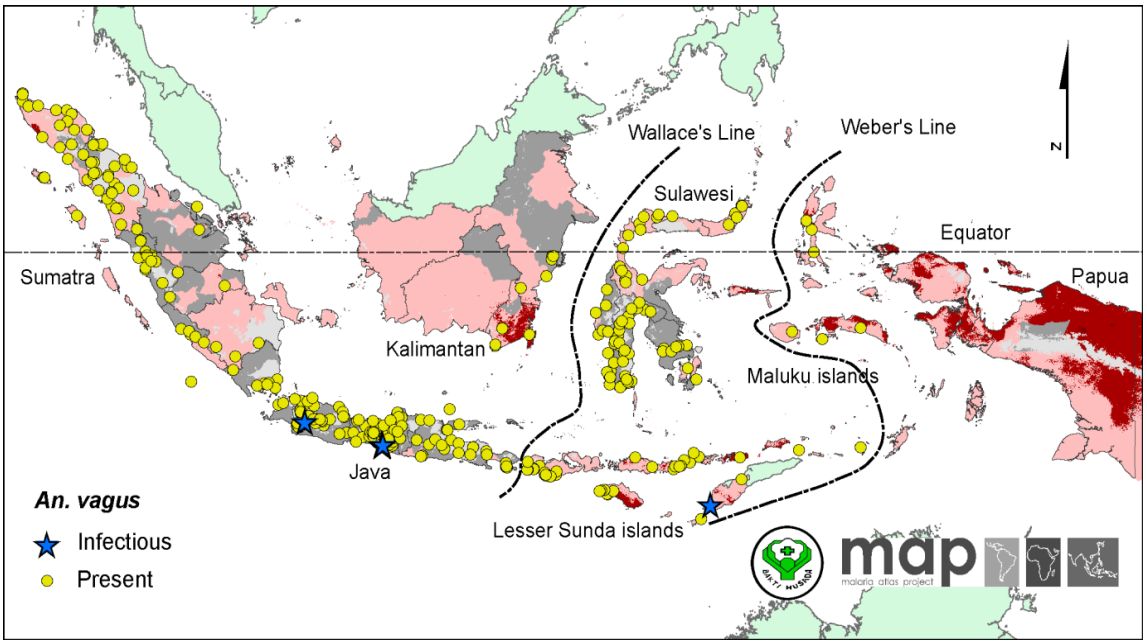


Figure 3.21. *Anopheles vagus* distribution in Indonesia. The blue stars show the records of infectious *Anopheles vagus* mosquitoes found. The yellow dots show 349 records of occurrence for this species between 1931 and 2011. Sources from which the database of distribution was acquired are listed in the Appendix to Chapter 3. Areas were defined as no risk (light grey, where *Pf*API = 0 per 1,000 pa), unstable transmission (medium grey, where *Pf*API < 0.1 per 1,000 pa), low risk (light red, $PfPR_{2-10} \leq 5\%$), intermediate risk (medium red, $5\% < PfPR_{2-10} < 40\%$) and high risk (dark red, $PfPR_{2-10} \geq 40\%$) [384].

Anopheles vagus is predominately a zoophilic, exophagic and exophilic species. It is often found in very high densities compared to other local anophelines. The combined proportion of mosquitoes having human blood was reported at 45% (820/1,806) from studies in Sumatra and Java [389,396,407,505]. In areas where cattle are readily available hosts, *An. vagus* is typically found in much higher proportions resting in cattle shelters rather than human structures; for example, in Central Java (95%) [394], Central Sulawesi (87%) [456,457] and Lesser Sundas (99%) [418]. More *An. vagus* were captured at outdoor than indoor locations in Java (85% of 5,212 mosquitoes), Sulawesi (71% of 477) [394,405,498] and Lesser Sundas (78% of 419) [418]. In western Java [405], *An vagus* females blood fed throughout the night, whereas in

eastern Java [389], a clear peak was seen in the second quarter of night. Significantly more mosquitoes were found resting outdoors than indoors in Central Java (64% vs. 36%, n = 6,982) [394], in ground pits and tree poles in “salak” (*Salacca zallaca*) plantations [407], low bushes [488], cattle shelters [488] and grassy ditches [451].

Anopheles vagus larval habitats are typically sunlit, containing fresh, stagnant, shallow water (Supplementary Table S5). Natural habitats include still margins of streams [440], river edges [431,534], small pools near beaches [410,423] and springs [396,425,460]. Larvae also can be found in many man-made habitats, such as rice fields [154,408,451,453,462,466,467,510], irrigation ditches [386,451,453] wheel ruts [451,474] and a variety of artificial containers such as tyres, drums and upturned small boats. A 12-month longitudinal survey in Sukabumi, West Java recorded the presence of larvae in 464 aquatic habitats, mostly in the lowlands, close to human habitation, and containing water of low salinity and warm temperatures [411]. This species can often be found in great abundance from the coastal plain to low hilly areas, but predominantly associated with hillside rice fields (< 140 meter elevation) than coastal areas (95% vs. 5%) [415]. *Anopheles vagus* had been found at altitudes up to 1,100 m asl in eastern Java [510].

Table 3.3. Blood feeding preference/ human blood index of *Anopheles* malaria vectors in Indonesia.

Species or species complex *	Year of samples	Total sample giving positive reaction to blood present	Total sample contains human blood	Human Blood Index (%)
An. aconitus	1932-2003	17,762	1,551	8.7
An. balabacensis	2003	82	8	9.8
An. bancroftii	1928	51	46	90.0
An. barbirostris	1932-2003	510	60	11.8
An. farauti s.l.	1962	20	18	90.0
An. flavirostris	2003	33	3	9.1
An. kochi	1932-2003	841	89	10.6
An. koliensis	1962	170	126	74.1
An. leucosphyrus	1932	204	202	99.0
An. maculatus s.l.	1932-2003	425	134	31.5
An. nigerrimus	1958	236	10	7.2
An. punctulatus	1954-1962	84	67	79.8
An. sinensis	1932-1954	1,157	903	78.0
An. subpictus s.l.	1932-1976	2,093	309	14.8
An. sundaicus	1932-1976	5,928	3,188	53.8
An. tessellatus	1932-1960	182	19	10.4
An. vagus	1932-2003	1,806	820	45.4

* No human blood index data was found for *An. barbumbrosus, An. karwari* and *An. parangensis*.

3.6. *Anopheles* susceptibility to insecticides

Seventy-four sources of *Anopheles* insecticide susceptibility data from Indonesia were reviewed. Table 3.4 summarizes insecticide resistance amongst *Anopheles* mosquitoes in Indonesia including the six insecticides that are currently recommended by the Vector Control Program (VCP), Indonesian Ministry of Health, for indoor residual spraying: five pyrethroids: alpha-cypermethrin, bifenthrin, deltamethrin, etofenprox, lambda-cyhalothrin and one carbamate: bendiocarb [331]. The assembled data of insecticide susceptibility tests reveals that resistance to four chemicals (alpha-cypermethrin, bifenthrin, deltamethrin, and bendiocarb) has been detected in Indonesian anophelines, specifically *An. aconitus*, *An. barbirostris*, *An. kochi* and *An. sundaicus*. Resistance to two other insecticides that were used prior to 2003, fenithrothion and DDT were also found in five *Anopheles* species: *An. aconitus*, *An. koliensis*, *An. maculatus*, *An. subpictus* and *An. sundaicus*.

3.6.1. *Anopheles aconitus*

Insecticide resistance in *An. aconitus* has been known since the early 1960s. In Indonesia, it was first noted against DDT in Central Java in 1962 [176]. Over 275 sentinel sites were subsequently established to monitor the status of DDT resistance on Java between 1960s and 1970s. These activities confirmed that DDT resistance in *An. aconitus* had developed across the island over time [362,390,567,568]. The long history of DDT use in the rice fields of Java may have been partially (or primarily) responsible for the swift development of resistance [567,569]. Molecular analysis conducted to assess the presence of the insecticide-resistant allele (1014F *kdr* mutation) [569] associated with the resistant phenotype (to organochlorine and pyrethroid class insecticides) yet the analysis did not detect the allele, albeit only a

small sample of six *An. aconitus* were tested. In contrast, in southern Sumatra, two of three *An. aconitus* examined indicated the existence of the *kdr* gene, but again, only a small sample size was tested preventing any definitive conclusions being made regarding the distribution of this allele in Indonesia and its significance in control operations.

Anopheles aconitus has shown resistance against both fenitrothion and deltamethrin in Indonesia. Fenithrothion resistance was first reported in Central Java in 1976 [390] and reconfirmed over two decades later, via molecular analysis of specimens collected in the same region [570]. The proportions of *An. aconitus* larvae exhibiting evidence of resistance were 23% (n = 208) in high malaria endemic areas, 19% (n = 210) with medium endemicity, and only 3% (n = 199) in low endemic localities, presumably a reflection of degree of previous exposure in each respective population. Resistence to deltamethrin was first reported in Indonesia within *An. aconitus* populations from the northern coast of Central Java in 2003 [571]. A mortality rate of only 66% was detected among 125 *An. aconitus* mosquitoes following exposure with 0.05% deltamethrin for one hour.

The Indonesian Vector Control Program routinely currently conducts insecticide susceptibility tests (standard WHO contact tube tests), mostly in Java, to bifenthrin, bendiocarb and lambda-cyhalothrin [572]. Resistance to 0.1% concentration of bifenthrin has been documented among less than 50% of tested *An. aconitus* mosquitoes in Central Java. Exposure to 0.05% lambda-cyhalothrin also showed evidence of resistance in western Java with a mortality rate of 80%. Resistance has not yet been detected to 0.2% bendiocarb in Java. At the time of writing, we have found no published evidence of resistance to alpha-cypermethrin and etofenprox.

Table 3.4. Insecticide susceptibility of *Anopheles* malaria vectors in Indonesia. The resistance of insecticide was determined based on physiological toxicity response tests or presence of *kdr* (knock-down resistance) gene mutation. Presence of this gene mutation in those species marked with †.

Insecticide	Class	IMCP		Insecticide Resistance	*Anopheles* malaria vector species
		1993	2003		
Alpha-cypermethrin	Pyrethroid	No	Yes	Yes	*An. barbirostris*, *An. sundaicus* †
Bifentrin	Pyrethroid	No	Yes	Yes	*An. aconitus* †
Cyflutrin	Pyrethroid	No	No	No	
Deltamethrin	Pyrethroid	No	Yes	Yes	*An. aconitus* †, *An. sundaicus* †
Etofenprox	Pyrethroid	No	Yes	No	
Lambda-cyhalothrin	Pyrethroid	Yes	Yes	No	
Bendiocarb	Carbamate	Yes	Yes	Yes	*An. kochi*
Propoxur	Carbamate	No	No	No	
Fenithrothion	Organophosphate	Yes	No	Yes	*An. aconitus* †, *An. maculatus*, *An. subpictus* †, *An. sundaicus* †
Malathion	Organophosphate	Yes	No	No	
Pirimiphos-methyl	Organophosphate	Yes	No	No	
DDT	Organochlorine	Yes	No	Yes	*An. aconitus* †, *An. koliensis, An. sundaicus* †

3.6.2. *Anopheles barbirostris*

WHO bioassay tests by the Indonesian VCP reported 72-79% mortality rates after one-hour exposure to 0.05% alpha-cypermethrin from *Anopheles barbirostris* collected in Central Java and southern Sumatra [572]. Tests exposing *An. barbirostris* from western Java, eastern Lesser Sundas and northern Sulawesi to 0.2% bendiocarb, 0.05% deltamethrin and 0.05% lambda-cyhalothrin showed no evidence of resistance [572]. To date, there are no published accounts of resistance to etofenprox.

3.6.3. *Anopheles farauti* s.l.

No records were found on susceptibility status of this species complex to residual chemicals. However, use of methoprene (an insect growth regulator) for control of immature stages was found effective for the control of this species [573].

3.6.4. *Anopheles kochi*

The Indonesian VCP have tested of *An. kochi* for resistance to 0.75% alpha-cypermethrin, 0.05% lambda-cyhalotrin and 0.1% bendiocarb [572] of which only specimens from western Sumatra have appeared to show low levels of resistance (mortality rate slightly above 70% after one hour exposure) to 0.1% bendiocarb. No resistance was found to alpha-cypermethrin in Maluku and lambda-cyhalothrin in eastern Kalimantan.

3.6.5. *Anopheles koliensis*

DDT resistance has been reported in *An. koliensis* populations from Papua since the late 1980s [366]. Bioassay tests involving 404 *An. koliensis* resulted in a mortality rate of over 70% after one-hour exposure to 4% DDT. Further tests using two-hour 4% DDT exposure produced only a 67% mortality rate within the 24 hours holding period. Tests using 1% fenithrothion and *An. koliensis* from same locality indicated no resistance to this chemical [574]. Very little is known about the current insecticide susceptibility profile of this species in Papua.

3.6.6. *Anopheles maculatus*

Anopheles maculatus has been found to be resistant to fenitrothion with biochemical assays indicating resistance in 6% of mosquitoes from Central Java and 27% of mosquitoes near Yogyakarta [575]. In contrast, no resistance was observed after one-hour exposure with 0.05% deltamethrin [571] in six districts in Central Java Province and to 0.1% bendiocarb [351] in Yogyakarta, central-south Java. The VCP conducted bioassay tests for susceptibility to 0.75% alpha-cypermethrin, 0.05% lambda-cyhalotrin, 0.2% bendiocarb and 4% DDT [572] and reported no resistance among specimens tested from all locations in southern Sumatra and both West and Central Java. At the time of writing, no published resistance to bifenthrin and etofenprox has been found.

3.6.7. *Anopheles subpictus* s.l.

Susceptibility tests to fenitrothion at nine sites in high malaria endemic areas in Central Java and Yogyakarta revealed that approximately two percent of *An. subpictus* larvae showed resistance to organophosphate and carbamate active ingredients [575].

Molecular analysis of *An. subpictus* from Lampung, southern Sumatra, also documented the existence of the *kdr* mutation to organochlorine and pyrethroid class chemicals [569]. Tests for suceptibility to 0.75% alpha-cypermethrin, 0.2% bifenthrin, 0.05% lambda-cyhalothrin, and 0.1% bendiocarb found no evidence of resistance in northern Sumatra, southern Sulawesi, Maluku and Lesser Sundas [572]. No other published information on resistance against other insecticides has been reported for this species.

3.6.8. *Anopheles sundaicus* s.l.

Anopheles sundaicus s.l. was the first species in Indonesia to be reported as having developed resistance to insecticides and the first evidence of DDT resistance in Central Java [169,176,362]. Bioassay tests among 1,070 *An. sundaicus* mosquitoes within DDT indoor residual spray zones showed only 0.5-2.2% mortality rates after exposure to 0.2-5% DDT [169]. The widespread use of DDT in agriculture is believed partially responsible for the rapid appearance of DDT resistance in this area including the broad scale use of both aerial and ground-based spraying of DDT as a larvicide between 1945 and 1949 [169]. After the last application of DDT in Indonesia in 1992 [367], nearly 30% of 77 tested mosquitoes continued to demonstrate resistance after one-hour exposure with 4% DDT in southern Sumatra in 2008 [572]. Furthermore, molecular analysis of *An. sundaicus* adult mosquitoes from South Lampung District in southern Sumatra found the *kdr* mutation among 72.5% (29/40) mosquitoes examined [569]. Resistant to alpha-cypermethin and fenithrothion insecticides have been detected in this species from the same area. Susceptibility tests documented 18% resistance among 78 mosquitoes after exposure of 0.005% alpha-cypermethrin [572] and biochemical tests to fenithrothion revealed 6-33% of tested mosquitoes from eight

sentinel sites in Central Java were resistant in 2002 [575]. To date, no published evidence of resistance bifenthrin and etofenprox is available.

3.6.9. *Anopheles vagus*

Molecular analysis found five out of six mosquitoes of *An. vagus* examined from southern Sumatra had the insecticide-resistance allele (*kdr*) against pyrethroid and organochlorine class insecticides [569]. The VCP conducted susceptibility tests for 0.75% alpha-cypermethrin and 0.05% lambda-cyhalothrin [572] and found no resistance among *An. vagus* specimens collected from sites in Lampung, Kalimantan, and Maluku.

3.7. Outlook for Indonesian challenges to malaria vector control

This paper presents an updated overview of the known geographical distribution and bionomics of twenty species or species complexes known or suspected to transmit malaria in Indonesia. A review of the status of insecticide susceptibility of eight malaria vector species also provided to illustrate what is known in Indonesia and the general paucity of information on this important topic.

We list here what we consider to be three challenges aimed at better equipping vector control strategy in Indonesia.

(1). *Species identification*: An updated keys to the anopheline fauna of Indonesia is crucial to help in understanding the complicated nature of malaria in Indonesia. The current keys used in much of the reviewed literature were based on entomological/taxonomical work of decades ago before the use of molecular species

identification was available or widely used. The variability of morphological characteristics within and between species, the practical limitations of local keys and the presence of cryptic species within many of the *Anopheles* taxa clearly undermines the effectiveness of relying on morphological identification techniques alone. Differences in the biological characteristics of members of the complexes have also an important bearing on malaria transmission dynamics. It is, therefore, imperative to determine sibling species composition and their bionomics as well as their roles in the transmission of malaria [576]. The advancement of molecular entomology tools are able to support better understanding of anopheline species identification and the genetic structure of anopheline populations [577]. Additionally, these molecular tools are also able to detect and distinguish the four human *Plasmodium* species in individual mosquitoes or in pools of up to one hundred mosquitoes in populations with low level parasite infections [578].

(2). *Vector bionomics*: Knowing the local *Anopheles* species and adjusting the control program to their particular behaviour is essential if malaria control and elimination activities in Indonesia are to be successful. In Indonesia, relatively scant information on vector bionomics and response to chemical measures is available, often either dated, geographically patchly or completely lacking. Understanding the feeding behaviour, host preference and peak feeding periods may have significant implications for selecting the most appropriate adult vector control strategies. For example, long-lasting insecticide-treated bed nets might be a poor investment if the vectors are feeding in the early part of the night or predominantly outdoors where most of the local human population are unprotected during the peak transmission period. Consequently, there is a need for implementing complementary vector control tools that can target exophagic and early biting vectors [579], such as control of larval production and habitats, house screening, and personal protection [580]. Other novel methods of control should be

explored such as zooprophylaxis (host diversion) or use of spatial repellents to prevent attack via a behavioural avoidance mechanism in the vector. Integrated vector control approaches, tailor-made and site-specific to the local ecology will therefore strengthen efforts to suppress malaria transmitting mosquitoes [5].

(3) *Insecticide susceptibility monitoring*: The evolving resistance patterns of mosquito vectors to insecticides is one of the main challenges facing insecticide-based malaria vector control programmes in Asia and Indonesia [569,581,582]. Resistance to four of the six recommended insecticides has been reported in four primary malaria vectors in the country. Therefore, comprehensive monitoring of insecticide susceptibility using standardised tests against the local main vectors species is needed to ensure the continued viability and proper use of the chemicals currently available in the malaria control arsenal [569,581,582].

3.8. Conclusions

Vector control interventions require evidence-based strategies using accurate and current knowledge of the identity, distribution, and bionomics of the key malaria vectors in different localities in the country. This contemporary review of the primary anopheline malaria vectors of the Indonesian archipelago is aimed at providing the Indonesian health authorities and other organizations responsible for malaria control with the background and means of better focusing their resources where vector control interventions will be most effectively applied.

3.9. Acknowledgements

Since this thesis was submitted for examination, a modified version of this chapter has been submitted in *Advances in Parasitology* (2013; 83). The co-authors are Marianne E. Sinka [1], Peter W. Gething [1], Siti N. Tarmidzi [2], Asik Surya [2], Rita Kusriastuti [2], Winarno [2], J. Kevin Baird [3,4], Simon I. Hay [1], Michael J. Bangs [5]:

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CHAPTER 4

Plasmodium falciparum malaria endemicity in Indonesia in 2010

4.1. Introduction

The Indonesian archipelago of some 17,000 islands straddles the equator and stretches 5,200 km from western Malaysia to Papua New Guinea and covers a land area of 1.9 million km^2 (Figure 3.1) [583]. Seven main islands or island groups comprise the nation: Sumatra, Java, Kalimantan, Sulawesi, Maluku, the Lesser Sundas, and Papua (Figure 4.1). Indonesia was home to over 230 million people in 2010 [31] . These islands also harbour 20 known anopheline vectors of malaria transmitting all four of the species of *Plasmodium* that routinely infect humans [32]. By a narrow margin over *Plasmodium vivax*, *P. falciparum* is the most common cause of human malaria in Indonesia [580] with an estimated 12 million (6-21 million) clinical cases of *P. falciparum* cases each year [93]. Elyazar *et al*. detail this complex geography and mosaic of infection risk which seriously complicates efforts to control malaria on the archipelago [580].

On 28 April 2009, the Indonesian Ministry of Health announced its plan [584] to reach the pre-elimination stage by 2020 and to be free of malaria transmission by 2030 [585]. The plan states that these objectives would be reached in four distinct stages (Figure 4.1) [584]: (stage 1) the Thousand Islands group just north of Jakarta, 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. These efforts require detailed maps of malaria risk to guide the strategic distribution of limited fiscal resources, expertise, and, importantly, social and political capital in meeting declared objectives [2,5,74,584-586]. Updates of the baseline map described here will be essential as control progresses, thus identifying the main foci of active transmission and bringing focus to efforts to interrupt sources of residual transmission and in limiting importation risk in areas that have been cleared of malaria.

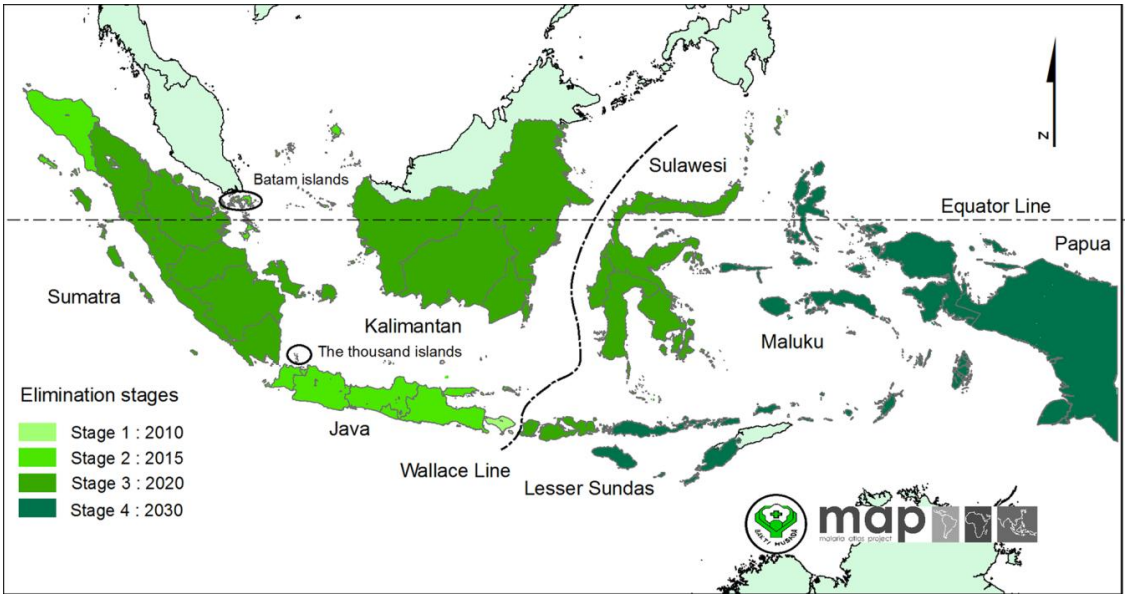


Figure 4.1. The map of Indonesian provincial administrative boundaries and their elimination objectives. The Indonesian archipelago consists of 33 provinces and comprises seven main islands: Sumatra, Java, Kalimantan, Sulawesi, Maluku, the Lesser Sundas and Papua. The dashed lines, Wallace Line, separate the Western Indonesia (to left from the line) and Eastern Indonesia regions (to right from the line). The Indonesian elimination objectives are to be implemented in four stages: (stage 1) The thousand islands [91], 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.

There have been many recent efforts to establish national contemporary malaria distributions to help optimize malaria intervention strategies in Africa, Asia and the Western Pacific. In Africa, Kazembe *et al*. derived malaria risk maps in Malawi using data from 73 survey sites across that country between 1977 and 2002 [23]. Noor *et al*. presented *P. falciparum* malaria prevalence maps in Somalia in 2008 at 5 × 5 km resolution using 452 community-based parasite prevalence surveys conducted data between 2005 and 2007 [24]. Noor *et al*. also defined Kenya *P. falciparum* risk maps at 1 × 1 km resolution in 2009 using 2,095 malaria surveys sites between 1975 and 2009 [25]. Gosoniu *et al.* have produced Angolan malaria prevalence maps for 2010 at a spatial resolution of 1 × 1 km resolution using malaria data from 92 survey locations [26]. In Asia, Brooker *et al*. developed *P. vivax* maps in Afghanistan for 2006 at spatial resolution 8 x 8 km using logistic regression models and malaria survey data from 269 endemic villages [27]. Reid *et al*. constructed *P. falciparum* risk maps for Bangladesh for 2007 at 1 × 1 km resolution using Bayesian geostatistical logistic regression models and 345 malaria prevalence surveys in 2007 [28]. Manh *et al*. produced malaria distribution maps in Vietnam for 2010 using zero-inflated Poisson regression models in a Bayesian framework from 12 months of *P. falciparum* and *P. vivax* malaria reported cases from 670 districts [587]. In the Western Pacific, Reid *et al*. established the baseline of malaria distribution maps prior to an elimination programme on the most malarious province in Vanuatu for 2010 using 220 geo-referenced villages [22]. This work reflects increasing demand for national level malaria risk maps to help guide malaria control operations, as well as growing confidence and sophistication of the methodologies used to derive useful and operationally relevant maps.

This report describes the use of a Bayesian model-based geostatistics (MBG) approach [15,588] to predict the risk of *P. falciparum* malaria in Indonesia in 2010 at a spatial resolution of 1 × 1 km using the largest assembled contemporary empirical

evidence for any country in Asia. This collaborative effort between the Ministry of Health of the Republic of Indonesia and the Malaria Atlas Project (MAP, www.map.ox.ac.uk) aims to improve national planning for the implementation of malaria control and elimination strategies. This work currently addresses only *P. falciparum* malaria as work on the important *P. vivax* problem is in progress.

4.2. Methods

4.2.1. Assembling a national database of *Plasmodium falciparum* Annual Parasite Incidence data

The collation of Annual Parasite Incidence (API) at the highest spatial resolution available between 2006 and 2008 was routinely conducted by the Sub-Directorate of Malaria Control at the Directorate of Vector-borne Diseases in Jakarta. The reported cases of confirmed *P. falciparum* malaria per 1,000 population were computed for each year by district level and averaged over the number of reporting years. Each *Pf*API summary estimate was mapped by matching it to its corresponding first and second level administrative unit in a geographic information system (GIS; ArcView GIS 9.3, ESRI, 2008).

4.2.2. Assembling a national database of *Plasmodium falciparum* malariometric prevalence

The process of assembling community-based survey estimates of parasite prevalence undertaken since 1985 has been described previously [75]. Searches for *Pf*PR data are an on-going activity of the Malaria Atlas Project (MAP, http://www.map.ox.ac.uk) and

were completed for the current study on 1 June 2010. The completed database was subjected to various levels of exclusion in order to obtain the final input data set for modelling as follows: removing surveys located only to large (>100 km^2) and small polygons (>25 km^2), removing those surveys that could not be precisely geo-positioned, removing those that could not be temporally disaggregated into independent surveys or for which the date was unknown. The dataset was then stratified into two regions for descriptive purposes (Figure 4.1), since western and eastern Indonesia are biogeographically distinct regions of the archipelago, typically demarked by the Wallace Line [382].

4.2.3. Assembling Indonesia human population data

The Global Rural Urban Mapping Project (GRUMP) *beta* version provides gridded population counts and population density estimates at 1 × 1 km spatial resolution for the years 1990, 1995 and 2000, both adjusted and unadjusted to the United Nations' national population estimates [589,590]. The adjusted population counts for the year 2000 were projected to 2010 by applying the relevant national urban and rural growth rates by country [591] using methods described previously [592]. The urban growth rates were applied to populations residing within the GRUMP-defined urban extents [589], and the rural rates were applied elsewhere. National 2010 totals were then adjusted to match those estimated by the United Nations [593]. These population counts were then stratified nationally by age group using United Nations-defined [593] population age structures for the year 2010 to obtain population count surfaces for the 0-5 years, 5-14 years and ≥15 years age groups. This population surface was extracted for Indonesia and aligned to all other spatial data grids used in the analysis.

4.2.4. Defining the limits of *Plasmodium falciparum* transmission

Following previously defined protocols [15,45,594], *Pf*API data were mapped to the lowest available administrative unit and used to classify areas as either no risk (zero cases over three years), and either unstable or stable risk if the mean annual number of confirmed cases over three years was lower or higher than 0.1 per 1,000 people per annum respectively. These polygon-based data were then rasterised to 1 × 1 km spatial grids. A biological model that identified areas where low temperatures were likely to preclude transmission [595] was used to identify further risk-free areas, and merged onto the same 1 × 1 km grid to create a single surface defining areas of no risk, unstable, and stable transmission at high spatial resolution.

4.2.5. Assembling environmental covariates

The MAP maintains a large library of globally mapped environmental data that represent potentially useful covariates of malaria prevalence. This grid library has recently been described in detail [42] and includes suites of temporal Fourier analysis (TFA) [596] products deriving from time-series of remotely sensed land-surface temperature, normalized difference vegetation index (NDVI), and middle infra-red (MIR) data from the Advanced Very High Resolution Radiometer (AVHRR) platform [597]; equivalent TFA-processed precipitation products derived from the WorldClim gridded climatology resource [598]; land cover classifications from the GlobCover project [599]; delineations of rural and urban areas based on the GRUMP [589] product with additional stratification of the latter into urban/peri-urban using approaches described previously [600]; and finally a bespoke temperature suitability index that captures the dynamic suitability of local ambient temperature regimes to support malaria parasite development within anopheline vectors [598]. All grids were clipped to a standard

regional extent that incorporated Indonesia and that matched the grids defined for the spatial limits of transmission, and subject to an automated pre-processing algorithm that used per-pixel resampling and/or nearest neighbour interpolation to ensure identical spatial resolution and definition of land versus sea pixels.

4.2.6. Defining an optimum suite of environmental covariates

The environmental data library described above consists of around 90 potential covariates. A variable selection procedure was implemented to identify an optimum subset of 20 covariates, a number chosen to representing an appropriate trade-off between gaining maximum informative power from the covariates whilst retaining computational feasibility and avoiding over-fitting. The Bayesian Information Criteria [599,601] is a model comparison metric which provides an objective means of quantifying the trade-off described above: predictive accuracy (which tends to increase with more covariates) is scored against model parsimony (which decreases with more covariates) and an optimum compromise is suggested. A total set-analysis was undertaken whereby models were built using all possible combinations of 20 covariate sets, and the BIC statistic calculated for each. The set with the optimum (i.e. lowest) BIC value was then identified. Because of their very large computational expense, this preliminary analysis could not be conducted using full geostatistical models and, in line with previous studies [601], was instead based on comparison of simpler non-spatial generalised linear regression models. The final selected suite consisted of the two indicator grids defining areas that were urban or peri-urban; the bespoke temperature suitability index; six products from the TFA processed WorldClim precipitation data; and five, four, and two from the TFA processed AVHRR NDVI, land surface temperature, and MIR data sets, respectively.

4.2.7. Bayesian space-time geostatistical modelling

Building on approaches described previously for global prevalence mapping [15]. The underlying value of *Pf*PR$_{2\text{-}10}$ in 2010, $Pf\mathrm{PR}_{2-10}(x_i)$, at each location x_i was modelled as a transformation $g(\cdot)$ of a spatiotemporally structured field superimposed with unstructured (random) variation $\in (x_i)$. The number of *P. falciparum* positive responses ${N_i}^+$ from a total sample of N_i individuals at each survey location was modelled as a conditionally independent binomial variate given the unobserved underlying age-standardized *Pf*PR$_{2\text{-}10}$ value [602]. An age-standardisation procedure [15,603] was implemented to allow surveys conducted in participants of any age range to be converted to the epidemiologically informative two-up-to-ten-year age range using an algorithm based on catalytic conversion models first adapted for malaria by Pull and Grab [211]. Each survey was referenced temporally using the mid-point (in decimal years) between the recorded start and end months. The spatiotemporal component was represented by a stationary Gaussian process $f(x_i, t_i)$ with mean μ and covariance defined by a spatially anisotropic version of the space-time covariance function proposed by Stein [604]. A modification was made to the Stein covariance function to allow the time-marginal model to include a periodic component of wavelength 12 months, providing the capability to model seasonal effects in the observed temporal covariance structure. These effects arise when studies performed in different years but during similar calendar months have a tendency to be more similar to each other than would be expected in the absence of seasonality. The mean component μ was modelled as a linear function of a vector of the final selected suite of twenty environmental covariates, $k{:}\,\mu = \beta_x + \beta k(x)$. The unstructured component $\in (x_i)$ was represented as Gaussian with zero mean and variance V. Bayesian inference was implemented using Markov Chain Monte Carlo to generate 100,000 samples from the posterior distribution of: the Gaussian field $f(x_i, t_i)$ at each data

location: the unobserved parameters β_x, β, and V as stated above and further unobserved parameters defining the structure and anisotropy of the exponential space-time covariance function. Distances between locations were computed in great-circle distance to incorporate the effect of the curvature of the Earth, which becomes important for a nation as large as Indonesia. Samples were generated from the 2010 annual mean of the posterior distribution of $f(x_i, t_i)$ at each prediction location. For each sample of the joint posterior, predictions were made using space-time conditional simulation over the 12 months of 2010 {t = 2010_{Jan}, ..., 2010_{Dec}}. These predictions were made at points on a regular 1×1 km spatial grid. Model output therefore consisted of samples from the predicted posterior distribution of the 2010 annual mean *Pf*PR_{2-10} at each grid location, which were used to generate point estimates and uncertainty metrics (computed as the mean and standard deviation, respectively, of the set of posterior samples at each pixel). Additionally each pixel was also classified into one of three endemicity classes defined previously [15] as of particular relevance for control: *Pf*PR_{2-10} ≤ 5%; 5% < *Pf*PR_{2-10} < 40%; *Pf*PR_{2-10} ≥ 40%. Classification was based on the class with the highest posterior probability of membership.

4.2.8. Evaluating model performance

An empirical model assessment exercise was carried out by first selecting 10% (252) of the full data set using a spatially de-clustered stratified random sampling algorithm, described previously [15], and then re-running the model in full using the remaining 90% (2,264) of data to make predictions at the space-time locations of these held-out data. Model performance was then evaluated using three criteria: the ability of the model to (1) predict point-values of *Pf*PR_{2-10} at un-sampled locations, (2) predict the correct endemicity class at un-sampled locations and to generate credible intervals that capture appropriately the uncertainty associated with predictions at each location.

The ability of model to predict point-values of *Pf*PR_{2-10} at un-sampled locations was then evaluated by comparing observed values to those predicted (using the posterior mean) by the model at the equivalent locations. Assessment was made using three summary statistics: (a) the mean prediction error (ME), (b) the mean prediction absolute error (MAE) and (c) the linear correlation coefficient. The ME measures the bias of prediction and the MAE measures the accuracy of predictions. The correlation coefficient indicates the linear association between predicted and observed values, which was also visualised using a scatter plot.

The ability of the model to predict the correct endemicity class at un-sampled locations was assessed by (1) using the area of under curve [605] of a receiver-operating characteristics (ROC) curve and (2) calculating the overall percentage of validation points predicted to the correct class and those grossly mis-assigned (with a low endemicity point being classed as high, and *vice-versa*). These assessments indicated the reliability of endemicity class assignment [15,606-608]. The interpretation of AUC was defined by established cut-off values, whereby an AUC of one indicates the model is perfect in differentiating a given endemicity class, values above 0.9 regarded as excellent discrimination and between 0.7 and 0.9 as fair to good discrimination. An AUC value of 0.5 represents a model with no ability to differentiate endemicity classes above a random allocation.

The ability of the model to generate appropriate credible intervals was tested via a coverage plot. Working through 100 progressively narrower credible intervals [609], from the 99% CI to the 1% CI, each was tested by computing the actual proportion of held-out prevalence observations that fell within the predicted CI. Plotting these actual proportions against each predicted CI level allows the overall fidelity of the posterior probability distributions predicted at the held-out data locations to be assessed.

4.2.9. Measuring area and population at risk

The modelled surface defining the limits of stable transmission was combined with that defining the binned endemicity classes within this limit to produce a single five-category map delineating areas within Indonesia: those at zero risk; at risk of unstable transmission; and those at risk of stable transmission experiencing infection prevalence of between 0% and 5%; 5% and 40%, and 40% to 100% *Pf*PR_{2-10}. The quantification of areas within each category was undertaken by first projecting the predicted class map from geographic to Mollweide equal area projection in ArcGIS 9.3. The areas covered by each category were then calculated in km^2. To derive population at risk within each zone, this categorical map was overlaid with the GRUMP-*beta* 2010 gridded population surface using an exact bespoke algorithm written in Fortran90, and the total population living in each risk category was calculated. These totals were further disaggregated by provincial level.

4.3. Results

4.3.1. Summaries of *Plasmodium falciparum* malaria prevalence survey data

A total of 2,581 temporally independent community *Pf*PR were identified nationally from 27 of the 33 *P. falciparum* malaria endemic provinces from a total of 79 different sources between 1985 and 2009 (Figure 4.2). The three data richest provinces were Papua (n=643), East Nusa Tenggara (n=516) and Aceh (n=288). A total of 65 survey locations were excluded from analysis because they were polygon data (n=6), could not be geo-positioned (n=6), were longitudinal surveys that could not be disaggregated temporally (n=39) or were missing information on the month of survey (n=14).

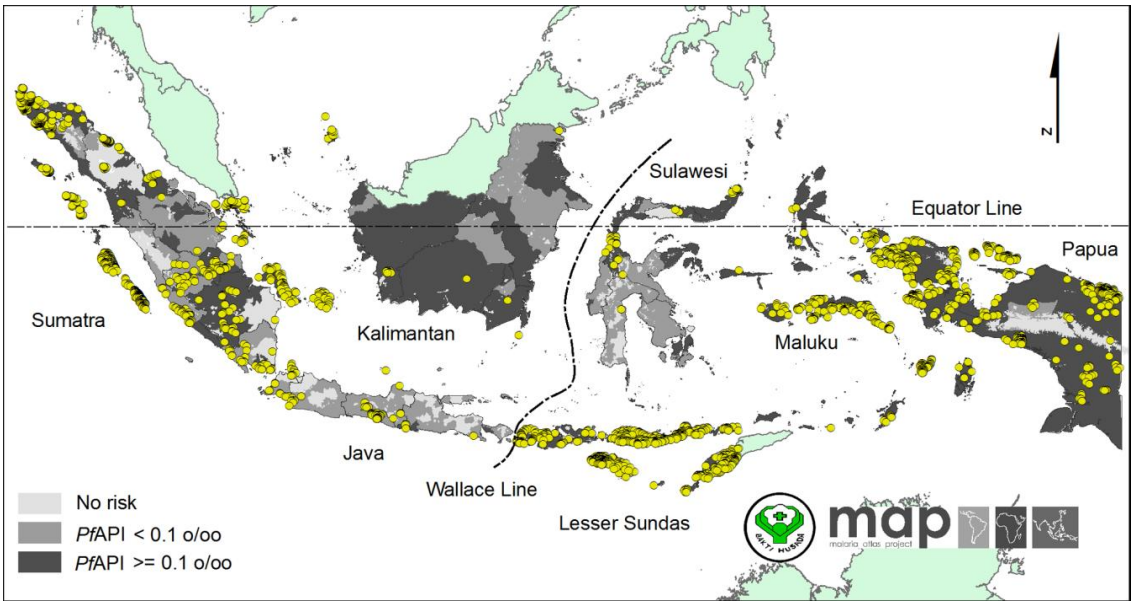


Figure 4.2. The spatial limits of *Plasmodium falciparum* defined by Annual Parasite Incidence and the temperature mask. Areas were defined as stable (dark grey areas, where *Pf*API $\geq$ 0.1 per 1,000 pa), unstable (medium grey areas, where *Pf*API < 0.1 per 1,000 pa), or no risk (light grey, where *Pf*API = 0 per 1,000 pa). The 2,516 community surveys of *P. falciparum* prevalence conducted between 01 January 1985 and 31 May 2010 are plotted.

Of the remaining 2,516 data points, Table 4.1 shows the summaries of *Pf*PR by region. The presence of *P. falciparum* was observed in 75% of total data points. *Pf*PR was generally higher in surveys in the eastern than the western region. The majority of the *Pf*PR data incorporated resulted from surveys conducted in 2008 (57%). Most surveys included the upper age > 20 years (89%). A total of 85% of the total number of records resulted from direct communication with malaria specialists across Indonesia and with the Indonesian National Malaria Control Program. Twelve percent of surveys were geo-positioned by Global Positioning Systems (GPS). Surveys with small sample sizes (n<50) represented 12% of the total data archived whilst 38% had sample sizes between 100 and 500. The median sample size was 187. Microscopy was the most commonly recorded diagnostic technique (66% of all surveys).

Overall, more malaria surveys were conducted in Eastern regions compared to Western regions (60% vs. 40%). The distribution of *P. falciparum* malaria surveys was not uniform among main islands in the archipelago (Figure 4.2). The islands of Sumatra (Western), Papua (Eastern) and Lesser Sundas (Eastern) were reported as the three richest *Pf*PR data islands with proportion of 34.7%, 25.4% and 24.6%, respectively. Kalimantan was reported as the island with the sparsest *Pf*PR data (0.8%) followed by Sulawesi (1.2%). In Java where more districts reported no-risk of malaria, only 4.8% of *Pf*PR data were collected between 1985 and 2009.

4.3.2. The spatial limits of *Plasmodium falciparum* transmission

The *Plasmodium falciparum* malaria risk defined by API and the temperature mask is shown in Figure 4.2. The clear demarcation of no *P. falciparum* risk in the Papuan highland is the most striking feature; the aridity mask [15] was not used as it did not modify risk in any areas of Indonesia. Of a total land area of 1.9 million km^2, 0.2 million km^2 (11.4%) was classified at no risk of malaria transmission, 0.5 million km^2 (26.4%) as unstable transmission and 1.2 million km^2 (62.2%) as stable transmission (Table 4.2). Further regional stratifications of areas at risk are provided in the Appendix to Chapter 4 (Supplementary Table S6).

Table 4.1. Summary of the important aspects of the *Pf*PR data by main region.

Total records of input data set	Western (n = 1,013)	Eastern (n = 1,503)	Total (n = 2,516)	Percentage (100%)
Number selected for model				
Population sample size	264,304	674,753	939,057	
Number of *Pf*PR > 0	520	1,355	1,875	74.5
Mean (standar deviation) *Pf*PR (%)	3.06 (6.64)	8.14 (9.57)	6.09 (8.87)	
Median [610] *Pf*PR (%)	0.16 (0 – 61.3)	5.02 (0 – 81.7)	2.63 (0 – 81.7)	
Primary source of *Pf*PR data				
Peer reviewed sources	95	150	245	9.7
Unpublished work	819	1,343	2,162	85.9
Reports (MoH, theses)	99	10	109	4.4
Source of spatial coordinates				
Personal communication	35	39	74	2.9
GPS	129	165	294	11.7
Encarta	106	142	248	9.9
Combination	661	1,070	1,731	68.8
Other digital gazetteers	36	29	65	2.6
Paper source	4	1	5	0.2
Map	42	57	99	3.9
Time period				
1985-1989	104	12	116	4.6
1990-1994	58	64	122	4.9
1995-1999	35	60	95	3.8
2000-2004	81	115	196	7.8
2005-2009	735	1,252	1,987	78.9
Upper age sampled				
<=10	18	42	60	2.4
>10 and <=15	70	10	80	3.2
>15 and <=20	-	117	117	4.6
>20	925	1,334	2,259	89.8
Diagnostic method				
Microscopy	806	866	1,672	66.5
RDT	207	637	844	33.5
Denominator				
1-49	216	72	288	11.5
50-100	282	252	534	21.2
101-500	305	662	967	38.4
>500	210	517	727	29.9
Median (IQR)	104 (53 - 424)	245 (108 - 725)	187 (84 - 581)	

Table 4.2. Area and population at risk of *Plasmodium falciparum* malaria in 2010 throughout of the Indonesian archipelago.

Area and population at risk	Region				Total	
	Western		Eastern			
	Value	%	Value	%	Value	%
Area (km^2)	*1,153,945*	*100.0*	*748,886*	*100.0*	*1,902,831*	*100.0*
No-risk	145,516	12.6	71,373	9.5	216,889	11.4
At-risk	1,008,429	87.4	677,513	90.5	1,685,942	88.6
Unstable	402,204	34.9	99,427	13.3	501,631	26.4
Stable	606,225	52.5	578,086	77.2	1,184,311	62.2
Pf$PR_{2-10} \leq 5\%$	588,510	51.0	378,317	50.5	966,827	50.8
$5\% < $ *Pf*$PR_{2-10} < 40\%$	17,715	1.5	198,905	26.6	216,620	11.4
Pf$PR_{2-10} \geq 40\%$	0	0	864	0.1	864	0.05
Population	*204,915,987*	*100.0*	*27,628,308*	*100.0*	*232,544,295*	*100.0*
No-risk	92,753,767	45.3	6,912,056	25.0	99,665,823	42.9
At-risk	112,162,220	54.7	20,716,252	75.0	132,878,472	57.1
Unstable	87,994,775	42.9	5,538,611	20.0	93,533,386	40.2
Stable	24,167,445	11.8	15,177,641	54.9	39,345,086	16.9
Pf$PR_{2-10} \leq 5\%$	23,517,672	11.5	13,225,290	47.9	36,742,962	15.8
$5\% < $ *Pf*$PR_{2-10} < 40\%$	649,773	0.3	1,946,790	7.0	2,596,563	1.1
Pf$PR_{2-10} \geq 40\%$	0	0	5,561	0.02	5,561	0.02

Free, unstable and stable risk areas were corresponded to *Pf*API = 0 per 1,000 pa, 0 < *Pf*API < 0.1 per 1,000 pa and *Pf*API $\geq$ 0.1 per 1,000 pa.

4.3.3. The spatial distribution of *Plasmodium falciparum* malaria endemicity

The continuous predicted surface of *P. falciparum* is presented in Figure 4.3. In stable transmission areas, the distribution of *P. falciparum* shows a high degree of heterogeneity ranging from 0.3% to about 41%. The frequency distribution of both input data and predicted *Pf*PR_{2-10} in 2010 for Indonesia were visualised using violin plots (Figure 4.4). These plots display a smoothed distribution of *Pf*PR_{2-10} overlaid on a central bar showing median and inter-quartile range values. The median of predicted *Pf*PR_{2-10} was 11.9% (range 0.4% – 39.5%).

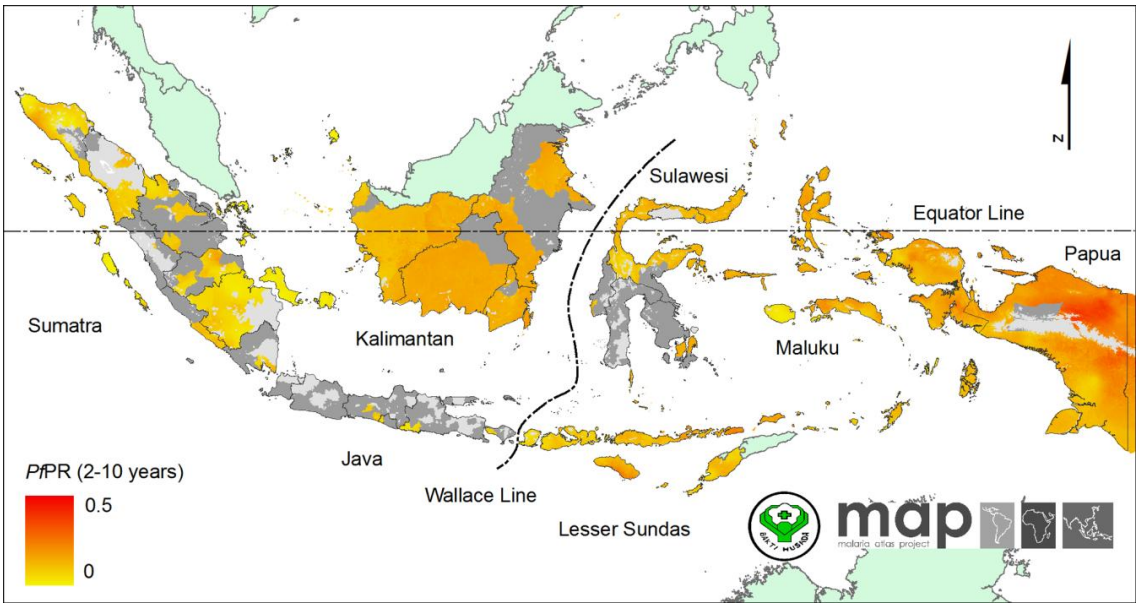


Figure 4.3. The *Plasmodium falciparum* malaria *Pf*PR_{2-10} endemicity map. Model-based geostatistical point estimates of the annual mean *Pf*PR_{2-10} for 2010 within the stable spatial limits of *P. falciparum* malaria transmission, displayed as a continuum of yellow to red from 0%–50% (see map legend). The rest of the land area was defined as unstable risk (medium grey areas, where *Pf*API < 0.1 per 1,000 pa) or no risk (light grey, where *Pf*API = 0 per 1,000 pa).

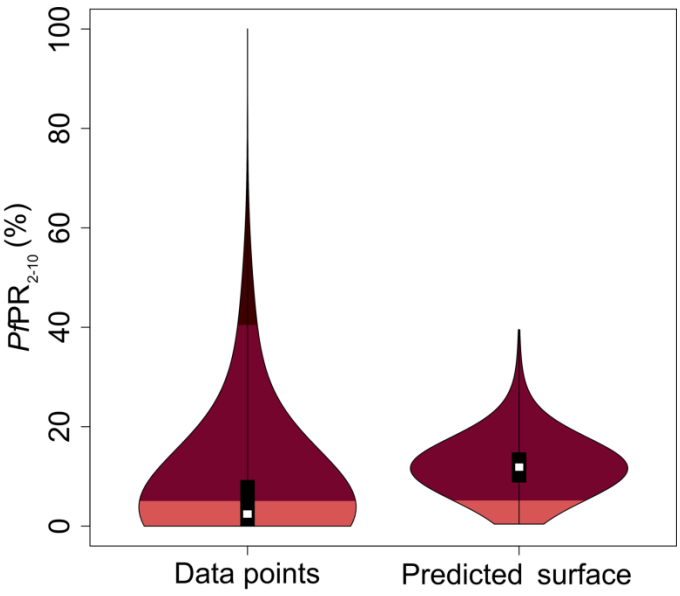


Figure 4.4. Violin plots showing for each region frequency distributions of *Pf*PR$_{2-10}$ data. The width of each polygon illustrates the relative frequency of different *Pf*PR$_{2-10}$ values. The background is coloured to match the endemicity classes shown in Figure 4.5. The black central bar indicates the inter-quartile range and white circles indicate the median values.

The map of the predicted malaria endemicity class of *Pf*PR$_{2-10}$ is presented in Figure 4.5. Each pixel was also classified into one of three endemicity classes defined previously [15,611] as of particular relevance for control: *Pf*PR$_{2-10}$ ≤ 5%; 5% < *Pf*PR$_{2-10}$ <40%; *Pf*PR$_{2-10}$ ≥ 40%. We refer to these as low, intermediate and high stable risk. Of those exposed to stable *P. falciparum* risk, the largest area was at low risk (0.967 million km^2, 50.8% of total area at risk), followed by intermediate risk (0.216 million km^2, 11.4%) and high risk (864 km^2, 0.05%). Further regional stratifications of areas at risk are provided in Table 4.2 and provincial level estimates in the Appendix to Chapter 4 (Supplementary Table S6).

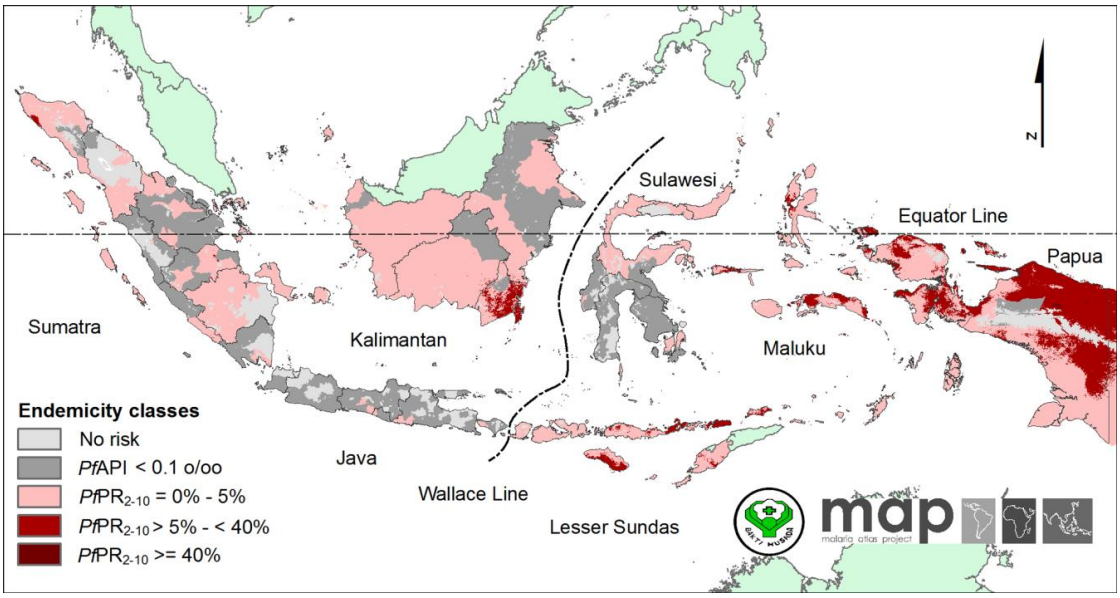


Figure 4.5. The *Plasmodium falciparum* malaria $Pf\text{PR}_{2\text{-}10}$ predictions stratified by endemicity class. They are categorized as low risk ($Pf\text{PR}_{2\text{-}10} \leq 5\%$), intermediate risk ($5\% < Pf\text{PR}_{2\text{-}10} < 40\%$) and high risk ($Pf\text{PR}_{2\text{-}10} \geq 40\%$). The rest of the land area was defined as unstable risk (medium grey areas, where *Pf*API < 0.1 per 1,000 pa) or no risk (light grey).

4.3.4. The estimation of population at risk of *Plasmodium falciparum* malaria

Table 4.2 shows the estimated population at risk of *P. falciparum* malaria in Indonesia in 2010. We have estimated 132.8 million people (57.1%) lived at any risk of *P. falciparum* transmission in Indonesia in 2010. Of these, 93.5 million (70.3%) inhabited areas of unstable and 39.3 million (29.7%) in stable transmission. Among those exposed to stable *P. falciparum* risk the vast majority were at low risk (36.7 million, 93.3%) with the reminder at intermediate (2.6 million, 6.6%) and high risk (0.006 million, 0.01%). Further provincial level estimates of population at risk are provided in the Appendix to Chapter 4 (Supplementary Table S7).

In the Western region, 112.1 million people (54.7%) live at any risk of *P. falciparum* transmission. Of these, 87.9 million (78.5%) inhabited areas of unstable and 24.2 million (21.5%) in stable transmission. Within the area of stable *P. falciparum* risk, 23.5 million lived in low risk (97.3%) and 0.65 million in intermediate risk (2.7%). Alternatively, more people in western Indonesia lived in unstable transmission zone than those of stable transmission zone (78% vs 22%). The distribution of the population at risk was not uniform across the islands of the western region: 80.4 million in Java, 23.3 million in Sumatra and 8.5 million in Kalimantan. The proportion of unstable to stable risk was 96% vs. 4% in Java, 38% vs. 62% in Sumatra and 23% vs. 77% in Kalimantan. In the stable transmission zone, 100% of people in Java lived in low endemicity risk, 98.8% in Sumatra and 92.7% in Kalimantan.

In the Eastern region, 20.7 million (75%) people live at any risk of *P. falciparum* transmission. Of these, 5.5 million (26.7%) inhabited unstable transmission areas and 15.2 million (73.3%) stable. Within areas stable *P. falciparum* risk, 13.2 million (87.1%) lived in low risk, 1.9 million (12.8%) in intermediate risk and 0.005 million (0.04%) in high endemicity risk. In other words, less people lived in unstable transmission areas than those of stable transmission areas (27% vs 73%). All of 10.2 million people lived at any risk of *P. falciparum* transmission in Sulawesi, followed by 6.6 million in Lesser Sundas, 1.9 million each in Maluku and Papua. Uniformly, the proportion of people inhabited in stable transmission areas among all main islands in this region. Within stable transmission, between 84.6% and 99.9% of people lived in low endemicity risk in Sulawesi, Maluku and Lesser Sundas. However, in Papua, a high proportion of population at-risk are observed to be at intermediate risk (50%).

4.3.5. Model performance

Table 4.3 shows the outcomes of the model validation exercise. In predicting point-values of *Pf*PR_{2-10} at un-sampled locations, the estimated mean error was 0.08% (in units of *Pf*PR_{2-10}), indicating very small systematic bias. Mean absolute error (i.e average model precision) was estimated at 4.7% *Pf*PR_{2-10}. The correlation coefficient between predicted and observed values was 0.77 indicating strong linear agreement (see also the corresponding scatter plot, Figure 4.6A). Overall, 77% of held-out data were predicted to their correct endemicity class. Only 1.2% of points were assigned to a non-adjacent endemicity class. ROC curves for each endemicity class are plotted in Figure 4.6B. The AUC values were 0.90 for *Pf*PR_{2-10} ≤ 5%; 0.87 for 5% < *Pf*PR_{2-10} <40% and 0.96 for *Pf*PR_{2-10} ≥ 40%, indicating good or excellent class discrimination for all classes. Figure 4.6C shows the coverage plot comparing predicted to actual credible intervals. The plotted line is close to the ideal 1:1 line throughout the range indicating that predicted credible intervals provided an appropriate measure of model uncertainty.

Table 4.3. Summary of the evaluation statistics for predicting point values *Pf*PR_{2-10} and endemicity class.

Evaluation measure	Indonesia
Predicting point values *Pf*PR_{2-10}	
Mean prediction error	0.08%
Mean absolute prediction error	4.7%
Correlation between the predicted and observed data	0.77
Predicting *Pf*PR_{2-10} endemicity class	
AUC ($\leq$ 5%)	0.898
AUC (> 5% to < 40%)	0.866
AUC ($\geq$ 40%)	0.964
Overall % correct	77.2%
$\leq$ 5% classed as $\geq$ 40% (%)	0.3%
$\geq$ 40% classed as $\leq$ 5% (%)	0.9%

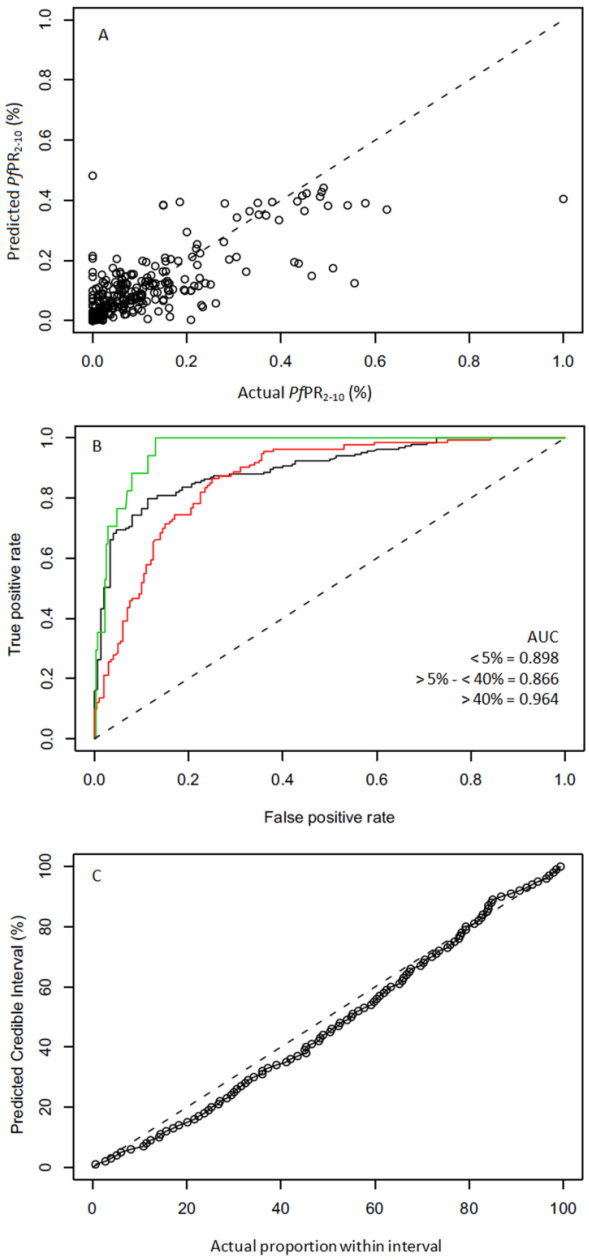


Figure 4.6. Evaluation of model performance. (A) Scatter plot of actual versus predicted point-values of *Pf*PR$_{2\text{-}10}$. (B) Receiver-Operating-Characteristic curves for each *Pf*PR$_{2\text{-}10}$ endemicity class (*Pf*PR$_{2\text{-}10}$ < 5%; 5% < *Pf*PR$_{2\text{-}10}$ < 40%; *Pf*PR$_{2\text{-}10}$ $\geq$ 40%) and associated AUC statistics. (C) Probability-probability plot comparing predicted credible intervals with the actual percentage of true values lying inside those intervals. In the top and bottom plots the 1:1 line is also shown (dashed line) for reference.

4.4. Discussion

A Bayesian model-based geostatistical spatial-temporal platform [15,45] was used to define the spatial limits of *P. falciparum* and its endemicity level in Indonesia. The resulting maps at 1 × 1 km spatial resolution provide a continuous surface of *P. falciparum* malaria risk from an evidence-base of over 2,500 independent estimates of *P. falciparum* malaria prevalence. These resulting estimates of area and population at risk of *P. falciparum* represent a refinement and update for Indonesia of an earlier estimate made for 2007 [15,45]. The substantive difference in methods used to generate the maps means that a comparison between the two is not a valid method for tracking change. The operational importance of such methods in an elimination context is acknowledged, and specific methods are being developed to facilitate the process of tracking change in malaria risk over the time.

4.4.1. *Plasmodium falciparum* maps and the control and elimination objectives of Indonesia

The maps presented here provide detailed insights into spatially varying risk that, in turn, can support a range of strategic planning and wider decision making within the Indonesia Ministry of Health and among its many partners in malaria control and elimination. By means of example we discuss here utility with respect to a comparison of two regions of Indonesia at opposing ends of the transmission intensity spectrum: Java and Papua.

The three provinces of Java (which exclude the national capital area of Jakarta and a special administrative area of the city of Yogyakarta) are densely populated: West Java (42 million), East Java (39.9 million) and Central Java (35.2 million) (Supplementary

Table S7). These three provinces contribute 71.6 million people (54%) of total population at risk of *P. falciparum* in the whole of Indonesia. In contrast, the three provinces constitute only 4.9% (83.163 km^2) of the total area at risk (Supplementary Table S6) with the vast majority living under unstable transmission (68.9 million; 96.3%). The remainder inhabit low endemicity areas (2.6 million; 4.7%). Efforts focused upon Java would result in relatively large gains in reducing the population at risk of *P. falciparum* malaria in all of Indonesia. This is not inconsistent with national plans, both historically and currently, with elimination of malaria from Java planned by 2015. The absolute feasibility of this goal would need to be further assessed with additional work [612].

The situation of malaria in Papua island is entirely different to Java. Papua (the western half of the island of New Guinea) comprises two provinces contributing only 1.4% (1.85 million) of total population at risk of *P. falciparum* in the whole of Indonesia, whilst they occupied over a fifth of total area at risk of *P. falciparum* in this country. About 96% of the population at risk inhabited areas of stable transmission. Among those exposed to stable risk, the proportion of people living in between low and medium risk is essentially similar. Altogether these two endemicity classes contributed 99.7% (1.78 million) of total population at stable risk. The remainder reside in high risk areas (0.3%). Therefore maintaining aggressive control in Papua is critical and will be necessary to continue for the foreseeable future. It is clear that similar evidence-based guides will help untangle the complexity of the malaria epidemiology in Indonesia and that this will need to be augmented by additional work on morbidity and mortality estimation, as well as on *P. vivax* malaria. The prospects for elimination of malaria on Papua by 2030 will hinge upon long-term progress in reducing high risk among relatively low numbers of people scattered across wide and often remote areas. This in turn depends largely upon broader development of healthcare systems delivering prompt diagnosis and

effective treatment, especially at the fringe of reach for such services. Maps like those presented here may bring focus to the placement of resources aimed at this objective.

4.4.2. Spatial variation in map accuracy

The precision of the predicted map (Figures 4.7 and 4.8) is influenced strongly by the density of data points used for analysis as well as the inherent variability of the underlying survey data [613]. About 85% of *Pf*PR data is supplied by three main islands (Sumatra, Papua and Lesser Sundas) which covered 48.7% of 1.68 million km^2 of area at risk of *P. falciparum* in Indonesia. However, only two percent of total *Pf*PR data was assembled from two islands (Kalimantan and Sulawesi) which occupied 40.9% of total area at risk. These maps can help direct future parasitological surveys to areas of maximal uncertainty. At the time of writing, The Global Fund for AIDS, Tuberculosis and Malaria has funded the Indonesian Ministry of Health to conduct a series of malaria surveys covering 51 of 128 districts in Kalimantan and Sulawesi Islands. The assembled data described here guided that commitment of survey resources. Future maps, informed by additional and well-placed data gathering, will similarly do so and yield increasingly reliable distributions of risk.

The reliable distribution of local risk can facilitate travel medicine professionals and travellers in their assessment of the risk of malaria infection in the Indonesian archipelago and Figures 4.7 and 4.8 produced here will help to indicate the spatial accuracy of malaria intensity at detailed tourist destinations. However, the information should not be used directly to estimate risk to individual travellers risk and should never be used as an alternative to formal travel advice. The risk to malaria infection can substantially differ for different travellers taking into account their personal protection and prophylactic measure. The longer they stay in malaria areas, the higher the risk of

contracting malaria. Precautionary measures to prevent mosquito bites should be advised although visiting malaria free zones.

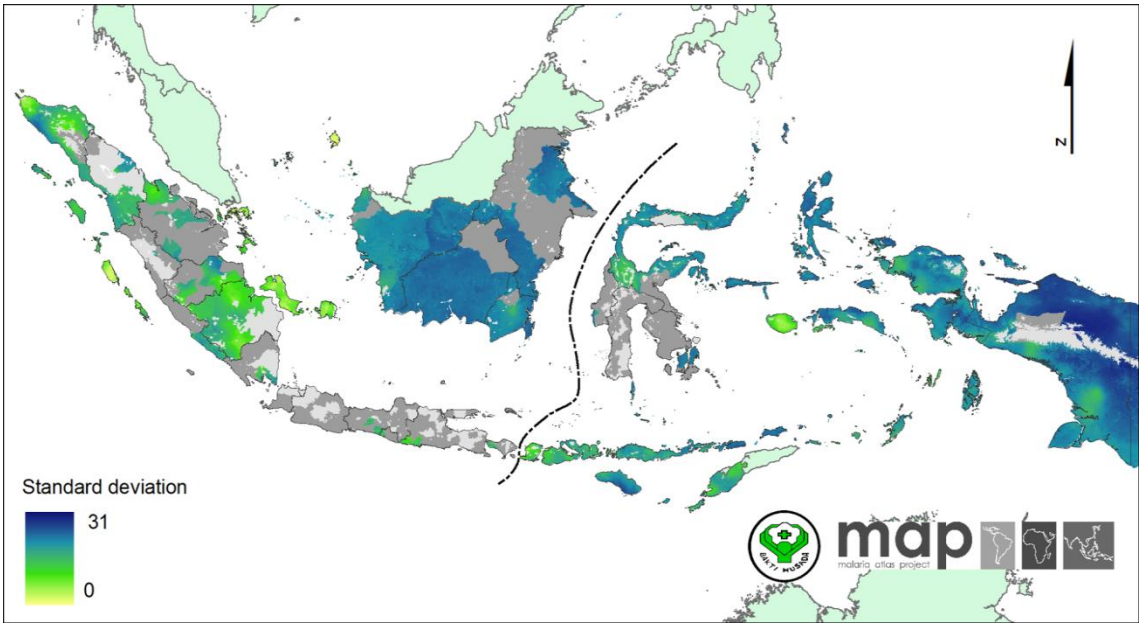


Figure 4.7. The standard deviation map of predicted *Pf*PR$_{2-10}$ within the stable transmission areas. These values indicate an index of relative uncertainty. Dark blue areas represent where predictions were made with large uncertainty. Yellow areas represent where predictions were made with small uncertainty.

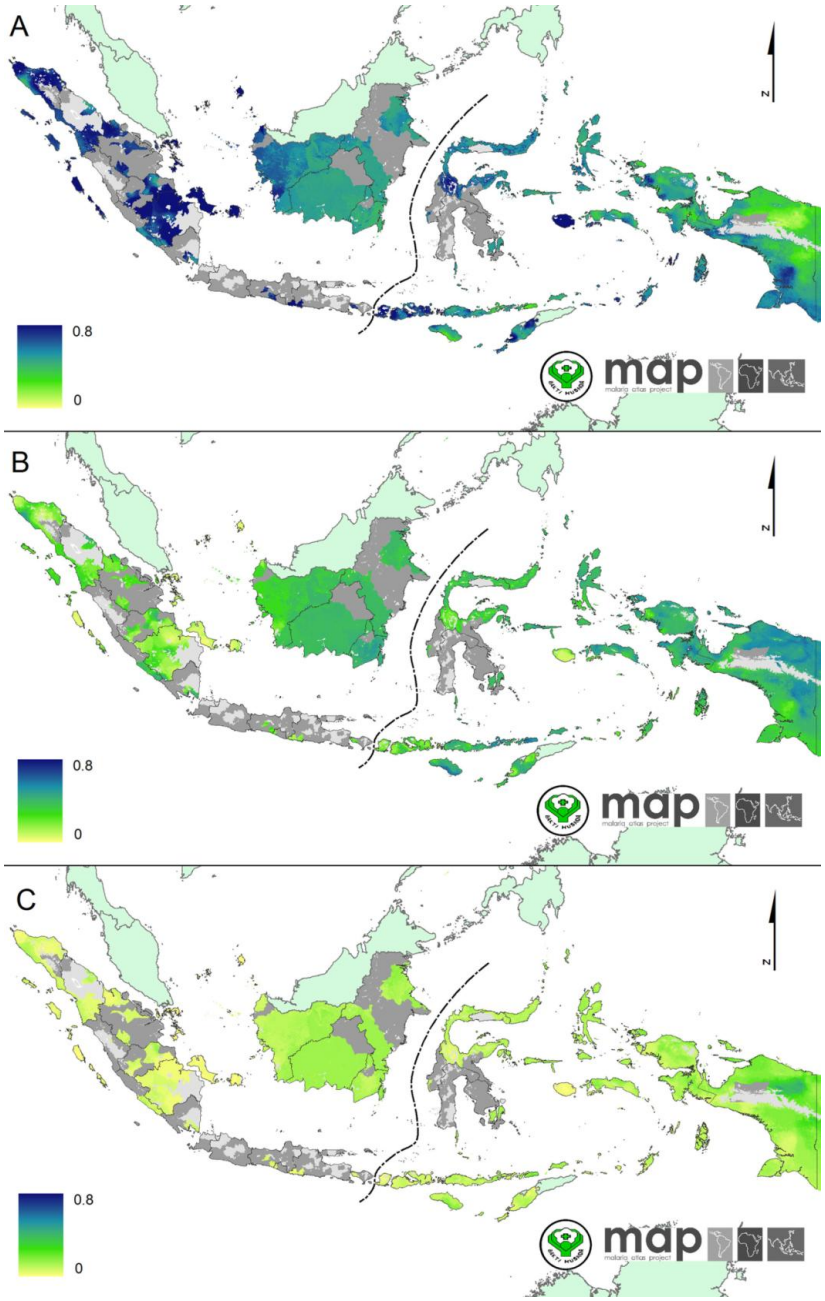


Figure 4.8. The predicted probability of *Pf*PR$_{2\text{-}10}$ falling in each endemicity class within the *Plasmodium falciparum* stable transmission areas. (A) The map of predicted probability of *Pf*PR$_{2\text{-}10}$ falling in the *Pf*PR$_{2\text{-}10}$ $\leq$ 5% endemicity class. (B) The map of predicted probability of *Pf*PR$_{2\text{-}10}$ falling in the 5% < *Pf*PR$_{2\text{-}10}$ < 40% endemicity class. (C) The map of predicted probability of *Pf*PR$_{2\text{-}10}$ falling in the *Pf*PR$_{2\text{-}10}$ $\geq$ 40% endemicity class.

4.4.3. Indonesian challenges to control and elimination

Hay *et al*. [1] suggested a framework of milestones on the path to malaria elimination in the context of MAP outputs. The five stages and their corresponding endemicity levels include: attack (*Pf*PR_{2-10} ≥ 40%), sustain (*Pf*PR_{2-10} > 5% - < 40%), transition (*Pf*PR_{2-10} ≤ 5%), consolidate (*Pf*API < 0.01) and maintain (*Pf*API = 0). In attack and sustain phases, the suggested actions are aggressive, combined and extensive interventions, such as total coverage of artemisinin combination therapies (ACTs), insecticide treated nets (ITNs), indoor residual spraying, and intermittent preventive treatment. When *Pf*PR_{2-10} ≤ 5%, specific and targeted intervention should be implemented, guided by efficient active and passive case detection through surveillance and foci of deliberate control measures. In the consolidation phase, the foci of infection must be eliminated through sustained specific and targeted interventions. After the malaria-free stage is achieved, the ability to detect cases and respond with ACT therapies and other measures, e.g., vector control, will be absolutely necessary.

Adapting such a generic schema to an Indonesia-specific context is required to make progress and this adaptation is on-going. The obstacles and opportunities of malaria control in Indonesia have been recently described in detail [580] and include case detection and surveillance, diagnosis, treatment, and vector control. In addition to substantially increasing access to diagnostic services, the establishment of a robust quality assurance program in support of such services may be essential [226]. Progress in diagnostics is certainly required to overcome the high proportion of clinically diagnosed malaria cases (87%) [580]. The persistent use of chloroquine or sulfadoxine/pyrimethamine, both known to be widely ineffective, to treat clinically diagnosed malaria should be immediately minimized and ultimately abandoned. This requires aggressive strategies for expanding the reach of reliable diagnostic services.

4.4.4. Future work

There are inherent uncertainties in any use of routine malaria case reports to measure risk, driven largely by the completeness and representativeness of data sources [587,614]. While biological masks can help differentiate areas of incomplete reporting from areas of true zero risk, significant efforts will need to be devoted into improving the precision of our estimates in low transmission zones. It is certainly true that people charged with conducting blood surveys in search of malaria parasites are guided by instinct and information to areas where they are most likely to be found. Overcoming this tendency will become especially important as Indonesia progresses towards elimination.

The population at risk estimates represent the denominator in deriving morbidity and mortality estimates [615]. Hay *et al*. [93] presented a new cartographic technique to estimate national, regional and global scales of clinical burden of *P. falciparum* malaria. A modelled relationship between prevalence and clinical incidence [616], together with *P. falciparum* malaria endemicity maps were used to estimate incidence in areas of stable transmission. Geostatistical joint simulation was then used to quantify uncertainty in these estimates. However, this work did not provide sub-national level estimates and deriving these would help the Indonesian malaria control agencies forecasting the area-specific requirements for antimalarial drugs, and thereby minimize both health-costly stock-outs and financially costly loss of therapies to expiration [617].
The population at risk estimates will allow malaria control managers to tailor vector control interventions. This can help forecast the number of long-lasting insecticide treated nets (LLINs) that need to be procured and distributed [618]. The cost estimates of scaling up LLIN coverage can also be calculated [619]. This LLIN intervention has important implications in those areas where the interruption of malaria transmission

could be achieved with universal coverage of LLIN in medium transmission intensity (*Pf*PR_{2-10} <40%) [1,620]. However, the distribution of the *Anopheles* vectors and their bionomics need evaluating before the scale up any LLIN intervention. This is also true of the myriad other possible interventions aimed at reducing human-anopheline contact. The selection and investment in specific tools for doing so hinges upon the distribution, density, behaviour and physiology (i.e., resistance to insecticides) of the local anopheline species. The combination of sub-national endemicity maps with maps of the distribution of the dominant *Anopheles* vectors of malaria could empower malaria control managers to formulate evidence-based intervention strategy appropriate to the bionomics of their local vectors [15,41]. This is another significant area of on-going activity.

The assembled survey data described in this report also revealed the almost ubiquitous presence of *P. vivax* malaria in Indonesia. The biological complexity of *P. vivax* relative to *P. falciparum* imposes obstacles to mapping endemicity [45,594] but the 1,732 data points in hand for this parasite represent a wealth of information for working through the technical challenges. That important work is in progress. Malaria elimination aims at all species and the fielding of interventions effective against that biological range will provide conspicuous and likely necessary economies of scale in reaching success.

4.4.5. Conclusions

The comprehensive dataset and the advancement of GIS tools provides the first most update *P. falciparum* endemicity maps and estimates of population at risk in Indonesia that may use for monitoring national scale malaria intervention progress.

4.5. Acknowledgements

Since this thesis was submitted for examination, a modified version of this chapter has been published in *Public Library of Science ONE* (2011; 6: 6). The co-authors are Peter W. Gething [1], Anand P. Patil [1], Hanifah Rogayah [2], Rita Kusriastuti [2], Desak M. Wismarini [2], Siti N. Tarmizi [2], J. Kevin Baird [3,4], Simon I. Hay [1].

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CHAPTER 5

Plasmodium vivax malaria endemicity in Indonesia in 2010

5.1. Introduction

Plasmodium vivax malaria is the most widely distributed species of human malaria, threatening nearly 3 billion people in 95 countries ranging from temperate to tropical in the Americas, Africa, and Asia [45,621]. Unlike the other common cause of malaria, *Plasmodium falciparum*, dormant liver stages of *P. vivax* cause relapses of acute malaria [622]. Despite the reputation of *P. vivax* as a benign infection with very low risk of death, contemporary studies demonstrate substantial morbidity [623-626] and mortality [627-630] burdens in endemic zones.

Drug resistance and neglect of its research in *P. vivax* exacerbates the threat of this infection. The first line therapy against acute attack, chloroquine, has failed in Indonesia [143,580] and parts of Oceania [631], and resistance now threatens the Mekong region [632-635] and the Indian sub-continent [636], where > 90% of *P.vivax* malaria occurs [637]. Although several artemisinin combination therapies (ACT) have shown good efficacy against acute *P. vivax* [638], only primaquine can eliminate the hypnozoite reservoir of infection [639,640]. The safety and efficacy of primaquine, especially when used with an ACT, is virtually unknown in 2012 [641]. The distribution of risk of this infection emerges as a vital consideration in developing strategies that may mitigate this potentially serious threat. This may be especially true in places like

the vast number of islands scattered within the Indonesian archipelago, and those with very limited resources for dealing with such problems.

Other nations have developed such maps. Brooker *et al*. developed a *P. vivax* map for Afghanistan in 2006 at a spatial resolution of 8x8 km using logistic regression models and malaria surveys from 269 endemic villages [27]. Manh *et al*. derived a *P. vivax* distribution map in Vietnam for 2010 using zero-inflated Poisson regression models in a Bayesian framework from 12 months of *P. vivax* malaria reported cases from 670 districts [587]. Reid *et al*. produced a *P. vivax* prevalence map on Tanna Island, Vanuatu in 2008 at 1x1 km resolution using 220 geo-referenced villages and the Bayesian geostatistical logistic regression model [22]. Dogan *et al*. developed *P. vivax* malaria incidence maps at 0.4x0.4 km resolution in Turkey using malaria data from 81 provinces for over 34 years (1975-2008) using a kriging method [642].

This chapter describes the first use of a Bayesian model-based geostatistics (MBG) approach [643] to predict the risk of *P. vivax* malaria in Indonesia in 2010 at a spatial resolution of 1×1 km, using the largest assembled contemporary empirical evidence for any country in Asia. This collaborative effort between the Ministry of Health in the Republic of Indonesia and the Malaria Atlas Project (MAP, http://www.map.ox.ac.uk) aims to equip those responsible for national planning and implementation of malaria control and elimination strategies with an evidence base for the distribution of risk of vivax malaria in Indonesia.

5.2. Methods

5.2.1. Assembling a national database of *Plasmodium vivax* Annual Parasite Incidence data

The Sub-Directorate of Malaria Control at the Directorate of Vector-borne Diseases, Indonesia Ministry of Health in Jakarta routinely collected *P. vivax* Annual Parasite Incidence (*Pv*API) at the district level between 2006 and 2008. The reported cases of confirmed *P. vivax* malaria per 1,000 people were computed for each year by district and averaged over the number of reporting years. Each *Pv*API summary estimate was mapped by matching it to its corresponding first (provincial) and second level (district) administrative unit in a geographic information system (GIS; ArcView GIS 9.3, ESRI, 2008).

5.2.2. Assembling a national database of *Plasmodium vivax* malariometric prevalence

The process of assembling community-based survey parasite prevalence data undertaken since 1985 has been described previously [75]. Data searches for *P. vivax* parasite rate (*Pv*PR) aimed to retrieve data from published and unpublished sources. These searches are an on-going activity of the Malaria Atlas Project (MAP, www.map.ox.ac.uk) and were completed for the current iteration on 25 November 2011. The completed database was checked *via* various levels of exclusion criteria in order to obtain the final input data set for modelling as follows: removing surveys located only to large (> 100 km^2) and small polygons (> 25 km^2), removing those surveys that could not be precisely geo-positioned and removing those that could not

be temporally disaggregated into independent surveys or for which the survey date was unknown. The entire database was then checked to ensure all survey sites were located precisely on grid squares identified as land and within the border of the country. Finally, the database was checked for any spatio-temporal duplicates. The dataset was then stratified into two regions for descriptive purposes, since western and eastern Indonesia are biogeographically distinct regions of the archipelago, typically demarked by the Wallace Line [382].

5.2.3. Assembling Indonesia human population data

Gridded population counts and population density estimates at 1×1 km spatial resolution for the years 1990, 1995 and 2000, both adjusted and unadjusted to the United Nations' national population estimates were provided by The Global Rural Urban Mapping Project (GRUMP) *beta* version [589,590]. The adjusted population counts for the year 2000 were projected to 2010 by applying the relevant national urban and rural growth rates by country [591] using methods described previously [592]. The urban growth rates were applied to populations residing within the GRUMP-defined urban extents [589], and the rural rates were applied elsewhere. National 2010 totals were then adjusted to match those estimated by the United Nations [593]. These population counts were then stratified nationally by age group using United Nations-defined [593] population age structures for the year 2010 to obtain population count surfaces for the 0-5 years, 5-14 years and ≥ 15 years age groups. This population surface was extracted for Indonesia and aligned to all other spatial data grids used in the analysis.

5.2.4. Defining the limits of *Plasmodium vivax* transmission

Annual Parasite Incidence data at district level in 33 endemic provinces were sourced to define the spatial limits of *P. vivax* transmission in 2010. Following previously defined protocols [45], classification of risk based on *Pv*API data assigned areas at no risk (zero annual incidence over three years), unstable (mean annual incidence less than 0.1 per 1,000 people per annum) or stable risk (mean annual incidence higher than 0.1 per 1,000 people per annum). These polygon-based data were then rasterised to 1×1 km spatial grids. A temperature mask was then applied on *Pv*API data-defined limits of transmission [643]. This biological mask delineated areas where low temperatures were likely to inhibit parasite development in anopheline vectors [595]. We further modified a decision rule for stable transmission. Within stable transmission limits, pixels predicted with high certainty (probability >90%) of being less than 1% *Pv*PR_{1-99} were downgraded from stable to unstable class. This extremely low prediction was caused by a great abundance of survey data reporting zero prevalence in those areas.

5.2.5. Environmental covariates

A minimal set of covariates were included to inform prediction of the mean function, based on *a priori* expectations of the major environmental factors modulating transmission. These were (i) an indicator variable defining areas as urban or rural based on the GRUMP urban extent product [589,590]; (ii) a long-term average vegetation index product as an indicator of overall moisture availability for vector oviposition and survival [596,597]; and (iii) a *P. vivax* specific index of temperature suitability derived from the same model used to delineate suitable areas on the basis of vector survival and sporogony [595].

5.2.6. Bayesian space-time geostatistical modelling

Bayesian space-time geostatistical modelling for disease prevalence mapping has been fully described [643] and implemented at the national [384] and global scales [643]. The underlying value of *Pv*PR$_{1\text{-}99}$ in 2010, $Pv\mathrm{PR}_{1-99}(x_i)$, at each location x_i was modelled as a transformation $g(\cdot)$ of a spatiotemporally structured field superimposed with unstructured (random) variation $\in (x_i)$. The number of *P. vivax* positive responses ${N_i}^+$ from a total sample of N_i individuals at each survey location was modelled as a conditionally independent binomial variate given the unobserved underlying age-standardized *Pv*PR$_{1\text{-}99}$ value [602]. An age-standardisation procedure [15,603] was implemented to allow surveys conducted in participants of any age range to be converted to the epidemiologically informative 1 to 99 year age range using an algorithm based on catalytic conversion models first adapted for malaria by Pull and Grab [211]. This age-standardisation procedure has been previously adopted for *P. falciparum* [384,643], but the model form has been reparameterised using assembled age-stratified *Pv*PR surveys. Each survey was referenced temporally using the mid-point (in decimal years) between the recorded start and end months. The spatio-temporal component was represented by a stationary Gaussian process $f(x_i, t_i)$ with mean μ and covariance defined by a spatially anisotropic version of the space-time covariance function proposed by Stein [604]. A modification was made to the Stein covariance function to allow the time-marginal model to include a periodic component of wavelength 12 months, providing the capability to model seasonal effects in the observed temporal covariance structure. These effects arise when studies performed in different years but during similar calendar months have a tendency to be more similar to each other than would be expected in the absence of seasonality. The mean component μ was modelled as a linear function of a vector of the selected suite of environmental covariates, $k\colon \mu = \beta_x + \beta k(x)$. The unstructured component $\in (x_i)$ was

represented as Gaussian with zero mean and variance V. Bayesian inference was implemented using Markov Chain Monte Carlo to generate 100,000 samples from the posterior distribution of: the Gaussian field $f(x_i, t_i)$ at each data location, the unobserved parameters β_x, β, and V as stated above and further unobserved parameters defining the structure and anisotropy of the exponential space-time covariance function. Distances between locations were computed in great-circle distance to incorporate the effect of the curvature of the Earth, which becomes important for a nation as large as Indonesia. Samples were generated from the 2010 annual mean of the posterior distribution of $f(x_i, t_i)$ at each prediction location. For each sample of the joint posterior, predictions were made using space-time conditional simulation over the 12 months of 2010 {t = 2010_{Jan}, ..., 2010_{Dec}}. These predictions were made at points on a regular 1×1 km spatial grid. Model output therefore consisted of samples from the predicted posterior distribution of the 2010 annual mean *Pv*$PR_{1\text{-}99}$ at each grid location, which were used to generate point estimates. The uncertainty metric was computed by calculating the ratio of posterior distribution interquartile range to its mean. This standardized metric produced an uncertainty index which less influenced by underlying prevalence levels.

5.2.7. Evaluating model performance

An empirical model assessment was carried out by first selecting a validation set. Ten percent (n = 445) of the full data points were selected using a spatially de-clustered stratified random sampling algorithm, described previously [643]. Those surveys located outside the stable limits of transmission were excluded from selection. Using the remaining 90% (n = 4,012) of data points the model was then re-run to make predictions at the space-time locations of these held-out data. Model performance was then evaluated using two criteria: the ability of the model to (1) predict point-values of

PvPR_{1-99} at validation locations, and (2) to generate credible intervals (CI) that capture appropriately the uncertainty associated with predictions at each location.

The ability of model to predict point-values of *Pv*PR_{1-99} at validation locations was then evaluated by comparing observed values to those predicted (using the posterior mean) by the model at the corresponding locations. Assessment was made using three summary statistics [431,643] including (1) the mean prediction error, (2) the mean prediction absolute error, and the linear correlation coefficient. The mean prediction error measures the bias of prediction and the mean prediction absolute error measures the accuracy of predictions. The correlation coefficient indicates the linear association between predicted and observed values, which was also visualised using a scatter plot [644].

A sample semi-variogram was calculated from standardised model residuals to assess the presence of residual spatial autocorrelation unexplained by the model output. Standardised Pearson residuals were calculated for each validation location [645,646]. This sample semi-variograms was compared to a Monte Carlo envelope computed from 99 random permutations of the same residual set [647]. Where the semi-variogram of standardized model Pearson residuals lies entirely within this envelope, it can be considered as the absence of spatial structure.

The ability of the model to generate appropriate credible intervals was tested via a coverage plot. Working through 100 progressively narrower credible intervals , from the 99% CI to the 1% CI, each was tested by computing the actual proportion of held-out prevalence observations that fell within the predicted CI. Plotting these actual proportions against each predicted CI level allows the overall fidelity of the posterior probability distributions predicted at the held-out data locations to be assessed.

5.2.8. Measuring area and population at risk

The quantification of areas within no risk, unstable and stable category was undertaken by first projecting the predicted class map from geographic to Mollweide equal area projection in ArcGIS 9.3. The areas covered by each category were then calculated in km^2. To derive population at risk within each zone, this categorical map was overlaid with the GRUMP-*beta* 2010 gridded population surface using an exact bespoke algorithm written in Fortran90, and the total population living in each risk category was calculated. These totals were further disaggregated by province level.

5.3. Results

5.3.1. The spatial limits of *Plasmodium vivax* transmission

The 2010 *Plasmodium vivax* malaria risk limits in Indonesia are shown in Figure 4.1. We have estimated that 1.7 million km^2 (89.8%) of a total land area of 1.9 million km^2 were endemic for *P. vivax* malaria (Table 5.1). These endemic areas, a land area of 0.695 million km^2 (40.7%) were unstable transmission zones and 1.014 million km^2 (59.3 %) were stable transmission zones. Stable vivax transmission zones were more common in eastern than western Indonesia (83.5% vs. 33.7%). Further provincial level estimates of areas at risk are provided in the Appendix to Chapter 5 (Supplementary Table S8).

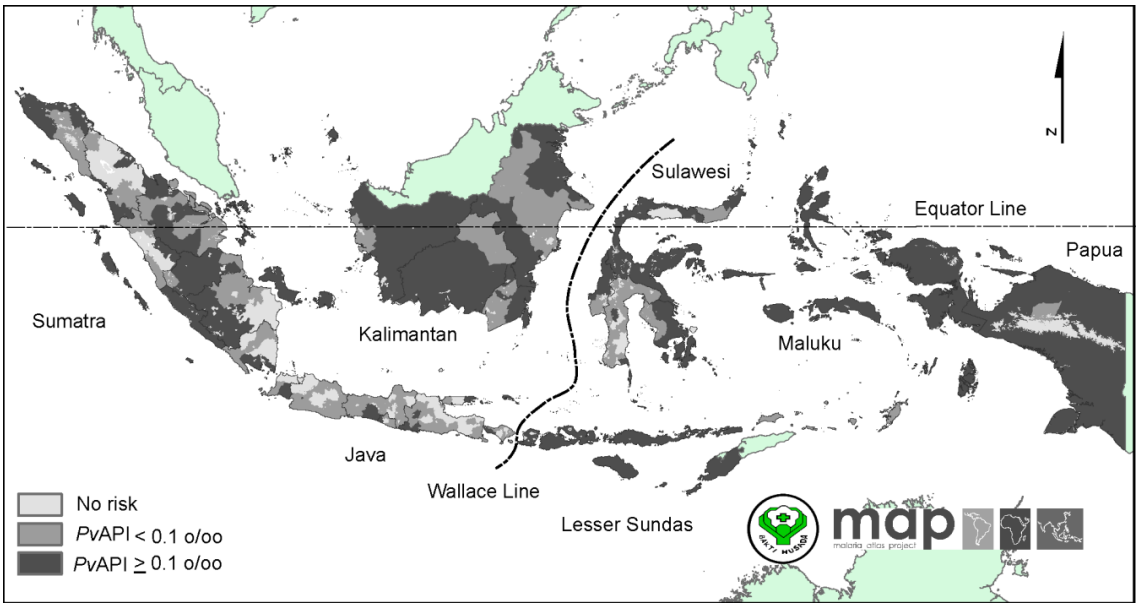


Figure 5.1. The spatial limits of *Plasmodium vivax* defined by Annual Parasite Incidence and the temperature mask. Areas were defined as stable (dark grey areas, where *Pv*API ≥ 0.1 per 1,000 pa), unstable (medium grey areas, where *Pv*API < 0.1 per 1,000 pa), or no risk (light grey, where *Pv*API = 0 per 1,000 pa).

5.3.2. Summaries of *P. vivax* malaria prevalence survey data

A total of 80 different sources from between 1985 and 2010 documented a total of 4,658 independent community surveys of *Pv*PR from 33 *P. vivax* malaria endemic provinces (Figure 5.2). Provinces of Papua/West Papua (n = 1,021), East Nusa Tenggara (n = 734) and Aceh (n = 434) contributed 47% of total data points. After database fidelity checks, a total of 201 survey locations were excluded from modelling because they were polygon data (n = 6), could not be geo-positioned (n = 87), surveys could not be disaggregated temporally (n = 39), were spatio-temporal duplicates (n = 50) or were missing information on the month of survey (n = 19).

Table 5.1. Area and population at risk of *Plasmodium vivax* malaria in 2010 throughout the Indonesian archipelago. No risk, unstable and stable risk areas correspond to *Pv*API = 0 per 1,000 pa, 0 < *Pv*API < 0.1 per 1,000 pa and *Pv*API ≥ 0.1 per 1,000 pa.

Area and population at risk	Region				Total	
	Western		Eastern			
	Value	%	Value	%	Value	%
Area (km^2)	***1,153,945***	***100.0***	***748,886***	***100.0***	***1,902,831***	***100.0***
No risk	143,050	12.4	50,261	6.7	193,311	10.2
At risk	1,010,895	87.6	698,625	93.3	1,709,520	89.8
Unstable	922,284	53.9	73,035	9.8	695,319	36.5
Stable	388,611	33.7	625,590	83.5	1,014,201	53.3
Population	***204,915,987***	***100.0***	***27,628,308***	***100.0***	***232,544,295***	***100.0***
No risk	96,726,120	47.2	6,157,027	22.3	102,926,147	44.3
At risk	108,146,867	52.8	21,471,281	77.7	129,618,148	55.7
Unstable	96,586,342	47.1	6,176,858	22.4	102,763,200	44.2
Stable	11,560,525	5.7	15,294,423	55.3	26,854,948	11.5

Table 5.2 summarizes the remaining 4,457 data points *Pv*PR by region. More *Pv*PR surveys were conducted in the eastern region compared to the western region (58% vs. 42%). Over half of the total data points (57.4%) documented the presence of *P. vivax*. In eastern Indonesia, 73.4% of the surveys reported presence records, compared to 35.6% in western region. Mean *Pv*PR was higher in the eastern than the western region (5.6% vs. 1.5%). The great majority of the *Pv*PR data (91.8%) were obtained from unpublished works. Peer-reviewed sources only contributed about 6% of the total data points. A total of 92% of the full number of *Pv*PR records were obtained

from direct communication with malaria specialists across Indonesia, the Indonesian National Malaria Control Program and National Health Institute of Research and Development. Most of the data incorporated resulted from *Pv*PR surveys conducted between 2005 and 2010 (88.4%). The great majority of surveys included an upper age > 20 years (94.3%). About seven percent of surveys were geo-positioned by Global Positioning Systems (GPS) whilst over 70% of the survey sites were geo-positioned using a combination of paper source, map and geo-referencing techniques. Surveys with small sample sizes (n < 50) represented 8.95% of the total data. The median sample size was 136. The most common sample size in western region was 50-100 people (38.8%) whilst in eastern region was 100-500 people (48.9%). The most commonly recorded malaria diagnostic technique in these *Pv*PR surveys was microscopy method (54%).

The distribution of *P. vivax* malaria surveys was not uniform among the main islands in the archipelago (Figure 5.2). The islands of Sumatra (Western), Papua (eastern) and Lesser Sundas (eastern) were reported as the three richest *Pv*PR data islands with proportions of 32.8%, 22.4% and 19.1%, respectively. Kalimantan was reported as the island with the sparsest *Pv*PR data (3%) followed by Sulawesi (4.6%). In Java, where more districts reported no-risk of vivax malaria, 6.5% of *Pv*PR data were collected between 1985 and 2010.

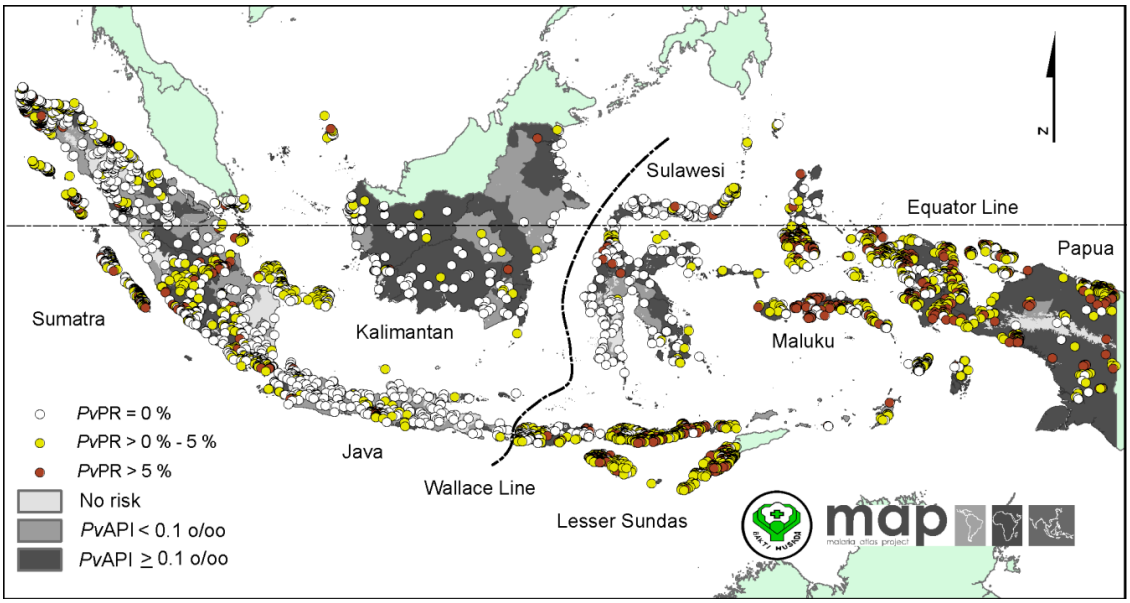


Figure 5.2. The distribution of *Plasmodium vivax* prevalence surveys in Indonesia between 1985 and 2010. The 4,457 community surveys of *P. vivax* prevalence conducted between 01 January 1985 and 25 November 2011 are plotted. The survey data are shown in white (*Pv*PR = 0%), yellow (*Pv*PR > 0% - 5%) and red (*Pv*PR > 5%). Areas were defined as stable (dark grey areas, where *Pv*API ≥ 0.1 per 1,000 pa), unstable (medium grey areas, where *Pv*API < 0.1 per 1,000 pa), or no risk (light grey, where *Pv*API = 0 per 1,000 pa).

Table 5.2. Summary of the important aspects of the *Pv*PR data by main region.

Total records of input data set	Western (n =1,886)	Eastern (n = 2,571)	Total (n = 4,457)	Percentage (100%)
Number selected for model				
Population sample size	426,341	955,469	1,381,810	
Number of *Pv*PR > 0	672	1,886	2,558	57.39
Mean (standard deviation) *Pv*PR (%)	1.49 (3.97)	5.57 (9.27)	3.84 (7.76)	
Median [610] *Pv*PR (%)	0 (0-45.9)	1.87 (0-86.1)	0.62 (0-86.1)	
Primary source of *Pv*PR data				
Peer reviewed sources	104	156	260	5.83
Unpublished work	1,688	2,405	4,093	91.83
Reports (MoH, theses)	94	10	104	2.34
Source of spatial coordinates				
Personal communication	35	39	74	1.66
GPS	129	165	294	6.60
Encarta	235	329	564	12.65
Combination	1,333	1,817	3,150	70.68
Other digital gazettes	112	161	273	6.12
Paper source	4	1	5	0.11
Map	38	59	97	2.18
Time period				
1985-1989	99	11	110	2.47
1990-1994	58	60	118	2.65
1995-1999	35	60	95	2.13
2000-2004	81	115	196	4.39
2005-2010	1,613	2,325	3,938	88.36
Upper age sampled				
≤ 10	17	40	57	1.28
> 10 and ≤ 15	70	10	80	1.79
> 15 and ≤ 20	-	117	117	2.63
> 20	1,799	2,404	4,203	94.30
Diagnostic method				
Microscopy	1,064	1,336	2,400	53.85
RDT	822	1,235	2,057	46.15
Denominator				
1-49	272	127	399	8.95
50-100	732	507	1,290	28.94
101-500	572	1,258	1,779	39.91
>500	310	679	989	22.19
Median (Inter Quartile Range; IQR)	95 (65-321)	197 (100-538)	136 (83-450)	

5.3.3. The spatial distribution of *Plasmodium vivax* malaria endemicity

The continuous predicted surface of *P. vivax* malaria endemicity within the limits of stable transmission is presented in Figure 5.3. The mean of predicted *Pv*PR$_{1\text{-}99}$ was 1.6% with a high degree of heterogeneity ranging from 0.2% to about 11%. In western Indonesia, the predicted *P. vivax* prevalence was uniformly low. Spots of intermediate prevalence *Pv*PR$_{1\text{-}99}$ were observed in eastern Kalimantan. High *Pv*PR$_{1\text{-}99}$ areas were observed in Lesser Sundas, Maluku and Papua. Uncertainty in predicted *Pv*PR$_{1\text{-}99}$ was relatively low in areas with low endemicity and abundance of surveys, such as in parts of Sumatra and Kalimantan (Figure 5.4). However in areas with high variability of prevalence, such as Papua, certainty of predicted *Pv*PR$_{1\text{-}99}$ was relatively lower than other main western islands (Figure 5.4.).

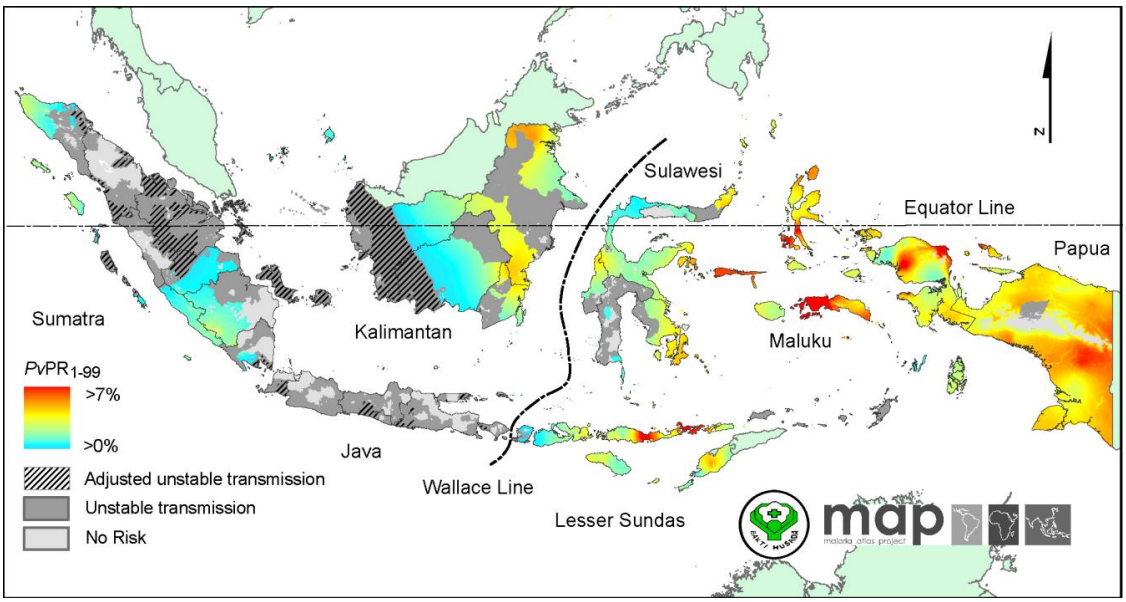


Figure 5.3. The *Plasmodium vivax* malaria *Pv*PR$_{1\text{-}99}$ endemicity map. Model-based geostatistical point estimates of the annual mean *Pv*PR$_{1\text{-}99}$ for 2010 within the stable spatial limits of *P. vivax* malaria transmission, displayed as a continuum of light green to red from 0% to 7% (see map legend). Areas within the stable limits in Figure 1 that were predicted with high certainty (> 0.9) to have *Pv*PR$_{1\text{-}99}$ less than 1% were classified as unstable areas (shaded medium grey areas). The rest of the land area was defined

as unstable risk (medium grey areas, where *Pv*API < 0.1 per 1,000 pa) or no risk (light grey, where *Pv*API = 0 per 1,000 pa).

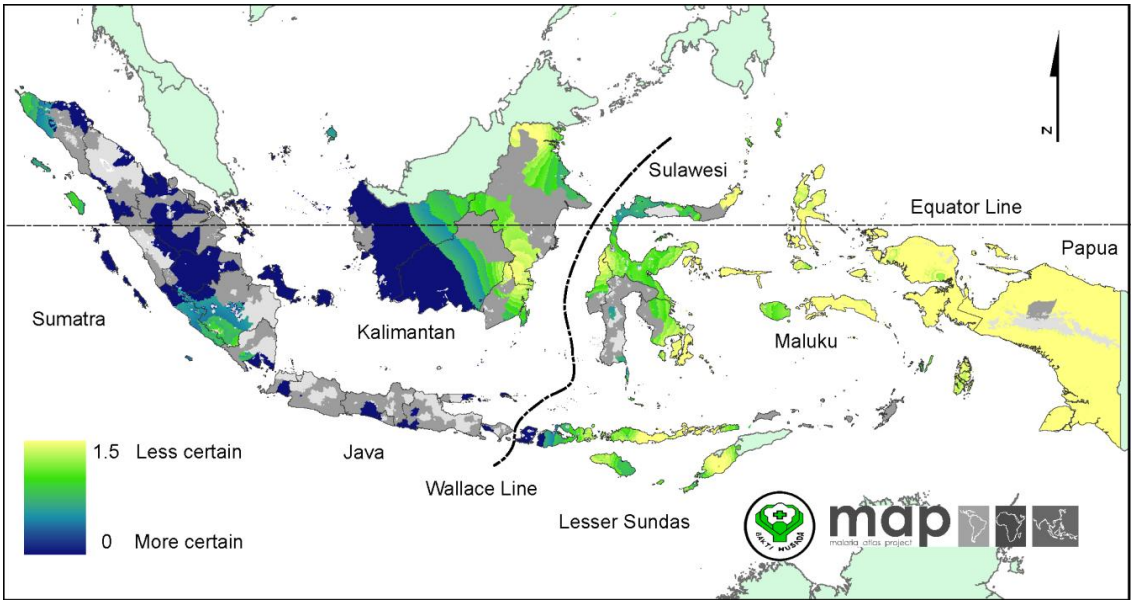


Figure 5.4. The uncertainty map of predicted *Pv*PR$_{1\text{-}99}$ within the stable transmission areas. These values indicate the uncertainty of prediction by using the ratio of posterior inter-quartile range to the posterior mean prediction at each pixel. Large values indicate greater uncertainty. Smaller values indicate higher degree of certainty in the prediction. The rest of the land area was defined as unstable risk (medium grey areas, where *Pv*API < 0.1 per 1,000 pa) or no risk (light grey, where *Pv*API = 0 per 1,000 pa).

5.3.4. The estimation of population at risk of *Plasmodium vivax* malaria

Table 5.1 shows the estimated population at risk of *P. vivax* malaria in Indonesia in 2010. We have estimated that 129.6 million people (55.7%) lived at risk of *P. vivax* transmission. Of these, 102.8 million (79.3%) and 26.8 million (20.7%) inhabited areas of unstable and stable transmission respectively. Further provincial level estimates of population at risk are provided in the appendix to Chapter 5 (Supplementary Table S8).

In the western region, 108.1 million people (52.8%) live at risk of *P. vivax* transmission. On Java and Bali islands, (representing 7% of the land area of Indonesia) nearly 77 million people lived in areas of *P. vivax* tranmission, accounting for 71% of all people at risk in western region. More people in western Indonesia lived in unstable transmission than those of stable transmission (89.3% vs.10.7%). The proportion of the population living in unstable versus stable risk was 99% vs. 1% in Java, 63% vs. 37% in Sumatra and 62% vs. 38% in Kalimantan.

In the eastern region, 21.5 million (77.7%) people live at risk of *P. vivax* transmission. Less people lived in unstable transmission than stable transmission (28.8% vs. 71.2%). All of 10.8 million people lived at risk of *P. vivax* transmission in Sulawesi, followed by 6.7 million in Lesser Sundas, 1.9 million each in both Maluku and Papua. The proportion of the population living in unstable versus stable risk was 49% vs. 51% in Sulawesi, 8% vs. 92% in Maluku, 9% vs. 91% in Lesser Sundas and 3% vs. 97% in Papua.

5.3.5. Model performance

In predicting point-values of *Pv*PR_{1-99} at validation locations, the mean prediction error was -0.43% (in units of *Pv*PR_{1-99}), indicating low bias in predicted *Pv*PR. This value also represented the tendecy to underestimate *P. vivax* prevalence by just under 0.5%. Mean prediction absolute error, which measured the model precision, was estimated at 3.4% *Pv*PR_{1-99}. This value represented the variance between predicted and observed endemicity in each pixel, which is probably due to heterogenity of prevalence in short-range areas or sparsity of data points. The correlation coefficient between predicted and observed values was 0.58, indicating strong linear agreement (see also the corresponding scatter plot, Figure 5.5A). The semi-variograms of the standardized

model Pearson residuals lie entirely within Monte Carlo envelope (Figure 5.5B) which indicated no significant spatial structure. Figure 5.5C shows the coverage plot comparing predicted to actual credible intervals. The plotted line is close to the ideal 1:1 line throughout the range indicating that predicted credible intervals provided an appropriate measure of model uncertainty.

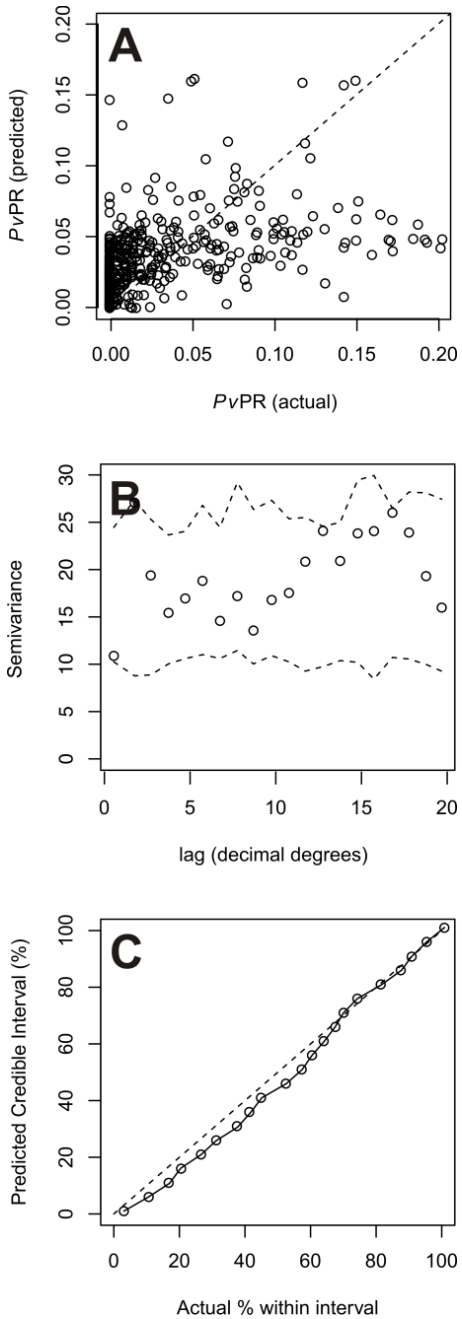


Figure 5.5. Evaluation of model performance. (A) Scatter plot of actual versus predicted point-values of *Pv*PR$_{1\text{-}99}$. (B) Sample semi-variogram of standardized model Pearson residuals estimated at discrete lag and a Monte Carlo envelope (dashed line) representing the range of values expected by chance in the absence of spatial autocorrelation. (C) Probability-probability plot comparing predicted credible intervals with the actual percentage of true values lying inside those intervals. In the top and bottom plots the 1:1 line is also shown (dashed line) for reference.

5.4. Discussion

This report describes the spatial limits and level of endemicity of *Plasmodium vivax* in Indonesia. The continous surface *P. vivax* malaria endemicity maps at 1×1 km spatial resolution were generated from an evidence base of nearly 4,500 independent estimates of *P. vivax* malaria prevalence across this archipelago and the use of a Bayesian model-based geostatistical spatial-temporal platform, similar to that applied for *P. falciparum* [384,643]. These estimates of area and population at risk of *P. vivax* represent improved and updated estimates from those made for 2009 [45]. The detection of *P. vivax* using the Rapid Diagnostic Tests (RDTs) accounted for 46% of assembled malaria prevalence surveys. RDTs are known to be less sensitive than expert microscopy and molecular detection, especially at low parasite densities, which tends to result in higher false-negative rates and, thus, lower observed *Pv*PR [219,648-650]. However, precise quantitative adjustments for these factors are not readily available and we have not assessed the impact of this low sensitivity of RDTs on our endemicity estimates.

5.4.1. Indonesian challenges to control and elimination

Options for malaria preventive measures [651] to reduce the risk of *P. vivax* malaria in Indonesia are limited. No contemporary work has demonstrated the impact of district or

nationwide implementation of larvicides, larvivorous fish, or source reduction by environmental management upon malaria transmission. Low coverage rates of insecticide-treated nets (ITN) and their usage, low proportions of houses with screening in endemic zones, variable practices in personal protection represent obstacles to efforts to eliminate malaria transmission in Indonesia. The challenge is further complicated by the unusually diverse mix of 20 *Anopheles* vectors with varying bionomics [652] and interspersed distributions, as recently shown by comprehensive distribution maps of dominant malaria vectors [43]. Another important problem is the availability of reliable diagnostics, which may currently identify fewer than 20% of malaria attacks [580]. A clinical diagnosis in Indonesia prompts therapy with chloroquine or sulfadoxine-pyramethamine, despite widespread resistance to these drugs by both *P. falciparum* and *P. vivax* malaria [580]. Indonesian authorities acknowledge diagnostics as their primary challenge in malaria control.

In the context of controlling or, especially eliminating endemic *P. vivax*, chemotherapeutic attack on the hypnozoite reservoir of infection may be a key consideration. However, the only drug available for this purpose, primaquine, threatens to potentially seriously harm patients with G6PDd [653]. Laboratory screening of those at risk of this harm is not currently practical as part of routine care in Indonesia. The G6PDd prevalences were documented between 1-8% in this archipelago [654-658]. Although most authoritative agencies recommend a daily dose of primaquine of 0.5 mg/kg for 14 days [659], especially in Southeast Asia [660,661], this regimen is relatively threatening without G6PDd screening, and the Indonesian authorities thus recommend 0.25 mg/kg for 14 days [103]. Even this lower dose, however, is potentially dangerous and many providers in Indonesia may be reluctant to prescribe it, much less encourage patients to be fully adherent. It may thus be appreciated that G6PDd

constitutes a very significant challenge to the Indonesian authorities striving to achieve their declared elimination goals [662].

This risk map of *P. vivax* malaria in Indonesia provides an evidence base which the Indonesian authorities may refer to when developing strategies for the systematic elimination of malaria transmission. The steep challenges imposed by diagnosis, resistance to chloroquine, and the potential harm caused by primaquine may be rationally considered beyond nation-wide solutions. Instead, the resources required to overcome these challenges may be focused upon specific sites where control measures are most needed or where elimination may be realistically within reach. Further, maps of G6PDd prevalence, and some understanding of the distribution of the most vulnerable variants, may also guide balance of risk and benefit with primaquine strategy, policy and practice brought to bear by the authorities [663].

5.4.2. Further work

The Malaria Atlas Project developed cartographic techniques to estimate clinical burden of *P. falciparum* malaria by using a continuous relationship model between paired *P. falciparum* prevalence and clinical incidence [93,616]. A non-parametric Bayesian inference was chosen to define this relationship [616]. Space-time joint simulation was then used to measure uncertainty of these clinical burden estimates [93]. In order to achieve similar estimates for *P. vivax*, further work is needed to resolve the association between prevalence of *P. vivax* and clinical incidence. This is especially challenging with the added dimension of relapse and further clinical attacks from a single infectious event. Nonetheless, such estimates constitute vital evidence in rational allocation of limited resources in a nation facing multiple infectious disease threats to the public health.

A glance at the geography of Indonesia reveals yet another challenge faced by the authorities in realizing and maintaining the elimination of malaria from any given island. People from the heavily populated islands of Java and Bali represent a significant proportion of those engaged in the economic development of the many sparsely populated outer islands of the archipelago and it is unknown how many travel back and forth between these islands. These movements incur substantial risk of importing and re-establishing malaria transmission on Java and Bali. MAP and its Indonesian partners will explore techniques to estimate specific patterns and numbers of human movements among the islands in order to identify specific and high priority threats to elimination. The feasibility of such exploration has been facilitated by the advance of geographical information systems, spatial statistics, and anonimized mobile phone records [612,664,665] allowing for the tracking of movement of mobile phones among the communications masts that serve them.

5.5. Conclusions

The maps presented in this report constitute part of a suite of GIS tools aimed at providing the authorities in Indonesia responsible for malaria control with evidence-based means of focusing their resources to where they are most needed and may be most effectively applied. Maps of endemicity of both important species of parasite, coupled with estimates of population at risk and clinical burden, along with the geographic distribution of G6PDd prevalence and patterns of internal migration compose that envisioned suite.

5.6. Acknowledgements

Since this thesis was submitted for examination, a modified version of this chapter has been published in *Public Library of Science ONE* (2012; 7: 5). The co-authors are Peter W. Gething [1], Anand P. Patil [1], Hanifah Rogayah [2], Elvieda Sariwati [2], Niken W Palupi [2], Siti N. Tarmizi [2], Rita Kusriastuti [2], J. Kevin Baird [3,4], Simon I. Hay [1].

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CHAPTER 6

The clinical burden estimates of *Plasmodium falciparum* and *Plasmodium vivax* in Indonesia in 2010

6.1. Introduction

Malaria infections due to all five species of human malaria parasites cause a devastating burden of disease, including fatalities, severe and life-threathening conditions, loss of income and productivity [666,667]. Several attempts have been made to quantitatively evaluate the magnitude of the malaria burden globally and nationally, i.e. mortality [4,668] and clinical cases [93,669]. In this chapter, clinical attack rates for both *P. falciparum* and *P. vivax* infections will be quantified for national malaria burden estimates. Clinical attack rate is defined as the cumulative proportion of the population that experiences a symptomatic episode of malaria over a defined time period [670].

Determining burden estimates is an important public health consideration in countries pursuing malaria control or elimination objectives [93,671,672]. Reliable estimates of malaria burden are required for setting national malaria priorities in order to rationalize and maximize impact of limited resources and to advocate for financial support [673,674]. Information on the malaria burden is essential to compare targets with existing levels of health services, to identify under-served areas and to target

interventions to high-priority areas and to quantify the demand for diagnosis and treatment services [675-686].

Quantifying malaria burden can be achieved using routine surveillance data from an accurate, complete and timely malaria reporting system [687,688]. Three dimensions should be established prior to using malaria information through routine channels: temporal coverage, spatial coverage and complete detection coverage [671]. Temporal coverage means that health facilities report every month, and spatial coverage means every health facility nationwide - including non-government health facilities - reports through this system. Complete detection coverage means all malaria events are captured by either active or passive case detection. However, on the national level, full coverage in temporal, spatial and detection is highly exceptional [614,676,689,690]. Low rates of care-seeking behaviour at health facilities, unreliable diagnoses, poor record keeping and inefficient data transfer and collation systems, contribute to what is very often extremely low quality malaria surveillance data [688].

In the absence of complete and accurate health information, extensive efforts have been made by the World Health Organization (WHO) [377] and the Malaria Atlas Project (MAP) [93] to describe the estimates of burden of malaria in endemic areas. The WHO approach uses routine surveillance reports of malaria cases compiled by health ministries, adjusted to take into account incomplete case detection, the potential for over-diagnosis of malaria among patients with fevers, and the way patients use public and private health services [669]. The MAP approach uses a cartographic method that utilizes population-based surveys of parasite prevalence and case incidence from selected locations to generate maps of case incidence per 1,000 population across malaria endemic regions globally [616]. For Indonesia, these approaches resulted in estimates of 9.3 million clinical cases in 2006 by the WHO for

combined *Plasmodium* malaria [48] and of 12.3 million clinical (95% credible interval 6.2-20.9 million) cases in 2007 by the MAP for *P. falciparum* malaria alone [93]. However, these burden estimates provided insufficient detail of spatial resolution.

Previous extensive works have generated continuous prevalence surfaces of *P. falciparum* or *P. vivax* in Indonesia for year 2010 with a spatial resolution 1x1 km [384,691]. In this thesis work, we will make the first attempt to quantify the number of clinical cases for both *P. falciparum* and *P. vivax* in Indonesia in 2010 using the MAP cartographic method. These estimates were then compared with estimates reported by the Indonesian Ministry of Health. This collaborative effort between the Ministry of Health in the Republic of Indonesia and the Malaria Atlas Project aims to more reliably estimate burdens, and in so doing, help identify under-reporting and inform malaria control and elimination strategy and tactics. .

6.2. Methods

The Indonesian spatial limits of *P. falciparum* and *P. vivax* transmission were defined using the 2010 assembled national case reported data expressed as *P. falciparum* annual parasite incidence (*Pf*API) and *P. vivax* annual parasite incidence (*Pv*API). These Annual Parasite Incidence data were sourced from 495 districts in 33 endemic provinces. Classification of risk based on *Pf*API or *Pv*API data assigned land areas at no risk (zero annual incidence), unstable (annual incidence less than 0.1 per 1,000 people per annum) or stable risk (annual incidence higher than 0.1 per 1,000 people per annum) [384,691]. These polygon-based data were then rasterised to 1x1 km spatial grids. A temperature mask was then applied on *Pf*API or *Pv*API data-defined limits of transmission [643,692].

The extensive efforts to investigate the association between malaria prevalence and clinical incidence has been previously described for *P. falciparum* malaria [616] and will be described elsewhere for *P. vivax* malaria [693]. Firstly, from formal literature searches, the Malaria Atlas Project identified *P. falciparum* and *P. vivax* longitudinal community-based malaria incidence surveys involving prospective active case detection (ACD) of fever cases. Additional inclusion criteria were (i) all fever cases were examined for the presence of either *P. falciparum* or *P. vivax* parasites in the peripheral blood; (ii) surveys covered all age groups in the sampled population from birth to adulthood; and (iii) surveys were undertaken over at least one complete 12 month period to account for seasonal variation or were within a defined (by vector surveillance) period of transmission. The presence of self-reported or measured fever in a subject who had either coincidental *P. falciparum* or *P. vivax* infection of any parasite density defined as a minimum definition of "clinical malaria".

Where reports included an estimate of *Pf*PR or *Pv*PR, these prevalance data were then correspondingly matched. To date, 114 (Asia: 74) and 83 (Asia: 66) geo-referenced incidence survey records have been integrated in a global database of *P. falciparum* and *P. vivax* prevalence-incidence association, respectively. The observed prevalence data were then adjusted to age-standardized prevalence of age 2-10 years for *P. falciparum* (*Pf*PR_{2-10}) and of age 1-99 for *P. vivax* (*Pv*PR_{1-99}) using an algorithm based on catalytic conversion models first adapted for malaria by Pull and Grab [211]. In this work, we exclude records from outside the Asian continent to explore the relationship between age-standardized *P. falciparum* or *P. vivax* prevalence and observed clinical incidence.

The number of cases in each active case detection study was modelled as the outcome of a negative binomial process parameterised by the average parasite rate

over the survey period in the age-standardized year old age group ($\bar{p}$) and the effective length of the survey (T) [616]. :

$$h(\bar{p},T) \sim \text{NegativeBinomial}\left(r(\bar{p}), \frac{r(\bar{p})T}{r(\bar{p})+q(\bar{p})}\right),$$
$$\bar{p} = \frac{1}{T}\int_{t}^{t+T}(g(p(x,\tau),a_*))d\tau$$

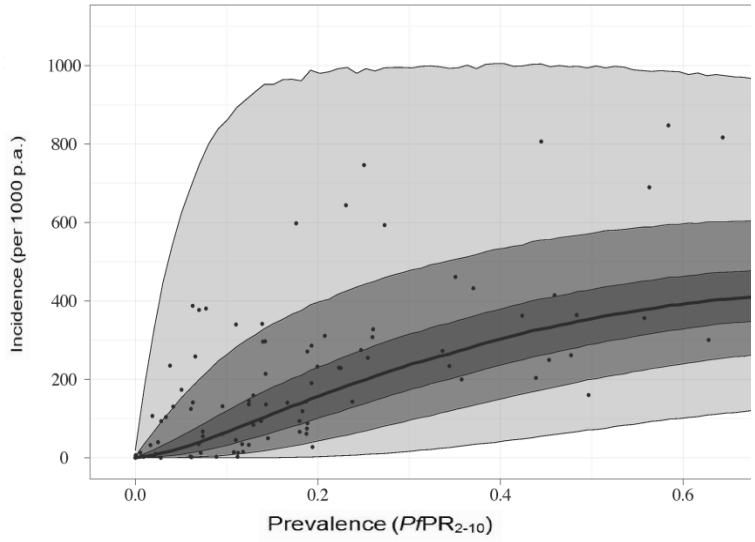
The function r was an increasing parabolic function of average parasite rate and the mean incidence q was assigned a Gaussian process prior. The posterior distribution of the random function which gave the overall relationship between average parasite rate and incidence, was used directly in the current work. The relationship between prevalence and incidence for *P. falciparum* and *P. vivax* is presented in Figure 6.1.A and B.

The generation of clinical incidence estimates were separately defined for unstable transmission and stable transmission zones [93]. In areas with unstable transmission, an assumption of uniform incidence density of 1 case per 10,000 people per year was introduced [93]. This rate was multiplied by the Indonesian population surfaces for 2010 and aggregated to obtain provincial, regional and national estimates for these unstable areas. In areas with stable transmission, a mathematical relationship between incidence and prevalence that was previously explained was applied [93].

The continuous surfaces of age-standardized 2-10 years for *P. falciparum* malaria prevalences (*Pf*$PR_{2\text{-}10}$) and 1-99 years for *P. vivax* malaria prevalences (*Pv*$PR_{1\text{-}99}$) have been previously produced within stable transmission at spatial resolution 1x1 km in 2010 in Indonesia [384,691]. A Bayesian model-based geostatistical platform was used to predict these estimates derived from 2,516 community surveys for endemicity intensity estimates of *P. falciparum* and 4,568 surveys for *P. vivax* undertaken between 1985 and 2011 across 33 provinces in the Indonesian archipelago [384,691].

Having defined a mathematical model defining incidence as a function of prevalence for every pixel, the mean continuous prevalence surfaces in stable transmission limit were converted into a number of clinical incidence per 1,000 population per year. For each parasite, these incidence densities were then multiplied with the 2010 population surface to obtain a realisation of the number of clinical cases in 2010 for each pixel. These numbers were then summarized for provincial, regional and national levels. Combining these estimates for all areas of transmission risk resulted in separate estimates of clinical cases of *P. falciparum* malaria and *P. vivax* malaria in Indonesia for 2010. These burden estimates were then compared with the figures available from the national routine reporting system. The dataset was then stratified into two regions for descriptive purposes, since western and eastern Indonesia are biogeographically distinct regions of the archipelago, typically demarcated by the Wallace Line [382].

A) *Plasmodium falciparum*



B) *Plasmodium vivax*

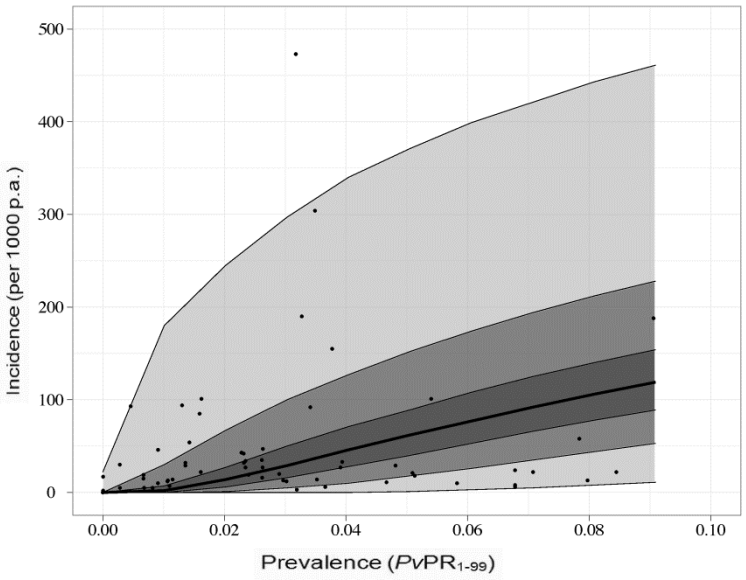


Figure 6.1. The relationship between age-standardized 2-10 year old of *P. falciparum* malaria prevalence and *P. falciparum* clinical incidence (A) and the relationship between age-standardized 1-99 years of *P. vivax* malaria prevalence and *P. vivax* clinical incidence (B). The light grey, medium grey and dark grey regions define the 95%, 50%, and 25% credible intervals, respectively. The solid black line is the median, and the data are shown as black dots.

6.3. Results

6.3.1. *Plasmodium falciparum* clinical attacks estimates in Indonesia

A continuous map of *P. falciparum* incidence predictions in units of cases per 1,000 population per annum and clinical attack estimates in units of cases per year per pixel within risk limits is provided in Figure 6.2 and 6.3, respectively. Higher clinical incidence densities were observed in eastern Indonesia than in western Indonesia. The national clinical attacks of *P. falciparum* were estimated as 7.7 million cases in 2010 with 5 million cases (64%) occurring in western areas and 2.7 million cases (36%) in eastern areas (Table 6.1). The cartographic estimates were higher than the routine reporting based estimates at national (30-fold), western (104-fold) and eastern areas (13-fold).

Regional, main islands and provincial summaries of estimated and reported cases for *P. falciparum* malaria are summarized in the Appendix to Chapter 6 (Supplementary Table S9). According to our estimes, Sumatra suffered the largest proportion of *P. falciparum* clinical attacks estimated nationally (30.9%) and followed by Kalimantan (21.3%), while the current reporting system captured the majority of cases in Papua (42.4%) and Lesser Sundas (29.9%). The three main provinces that contributed substantially to the national estimates were North Sumatra (9.3%), West Kalimantan (8.6%) and Eastern Lesser Sundas (7.5%). Twenty nine of 33 provinces were estimated to have higher estimates (> 5 times). The four remaining estimated provinces of Yogyakarta, Papua, West Papua and Banten had lower estimates (< 5 times), .

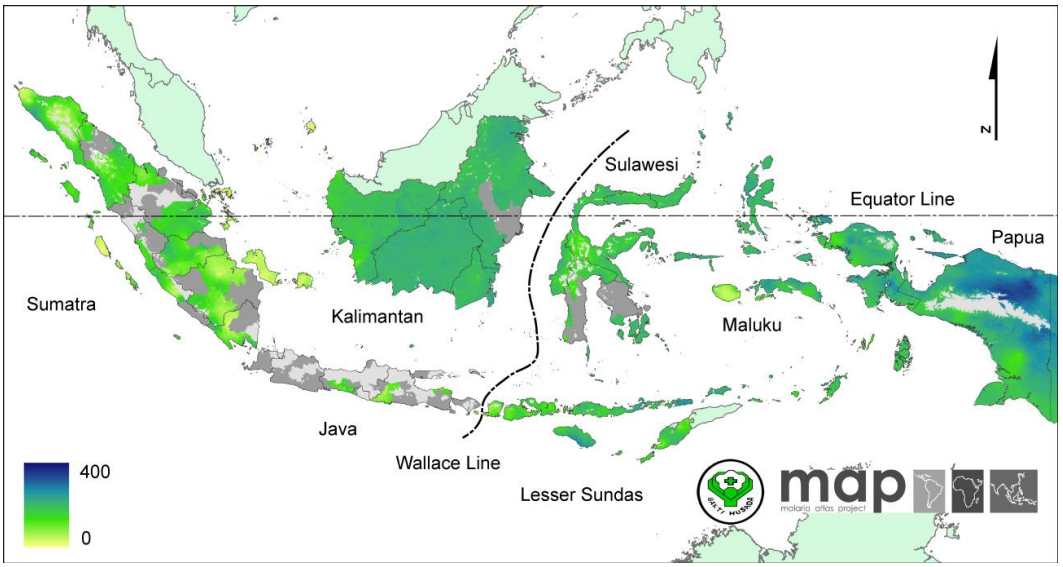


Figure 6.2. National clinical incidence estimates of *P. falciparum* in 2010. Clinical incidence estimates of *P. falciparum* per 1 x 1 km pixel displayed on a colour scale between 0 and 400 cases per 1,000 population per year within the stable limits of *P. falciparum* transmission. Light grey and medium gray areas indicates no malaria risk (*Pf*API = 0 per 1,000 population pa) and unstable risk (0 < *Pf*API < 0.1 per 1,000 population pa).

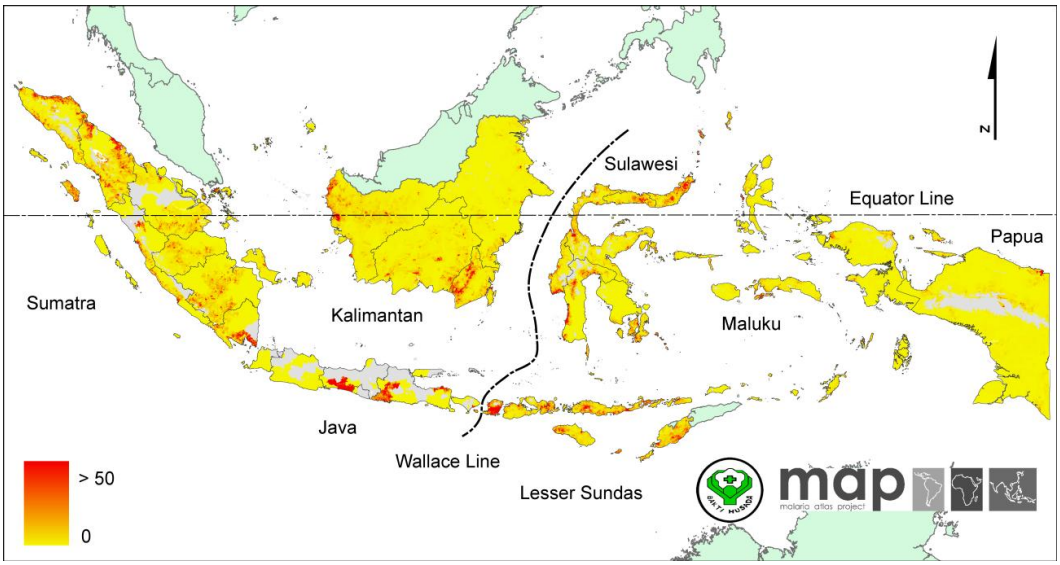


Figure 6.3. National clinical estimates of *P. falciparum* attacks in 2010. Clinical estimates of *P. falciparum* attacks per 1 x 1 km pixel displayed on a colour scale between 0 and 50 cases within the stable limits of *P. falciparum* transmission. Light grey and medium gray areas indicates no malaria risk (*Pf*API = 0 per 1,000 population pa) and unstable risk (0 < *Pf*API < 0.1 per 1,000 population pa).

6.3.2. *Plasmodium vivax* clinical attacks estimates in Indonesia

Figures 6.4. and 6.5. provide a continuous map of *P. vivax* incidence predictions in units of cases per 1,000 population per year and clinical estimates of *P. vivax* attacks in units of cases per year per pixel within risk limits in Indonesia, respectively. Higher clinical incidence densities were observed in eastern Indonesia than in western Indonesia. There were an estimated 1.5 million national cases in 2010 with 0.6 million cases (39.4%) occurring in western areas and 0.9 million cases (60.6%) in eastern areas (Table 6.1). The cartographic method produced estimates higher by as much as 5.8 times for all risk areas, 9.1 times in western areas and 4.6 times in eastern areas.

Supplementary Table S10 summarizes regional, main islands and provincial estimates and reported cases for *P. vivax* malaria (see the Appendix to Chapter 6). The largest proportion of *P. vivax* clinical attacks estimated nationally were contributed by Sumatra (24.1%) and Sulawesi (23%). In contrast, the current reporting system captured the majority of *vivax* cases in Papua (34.6%) and Lesser Sundas (27.8%). Three main provinces contributed substantially to the national estimates: Eastern Lesser Sundas (14.6%), Maluku (6.9%) and Papua (6.6%). The majority of the provinces (24/33) were estimated to have higher clinical attacks than estimated by the routine surveillance report (> 5 times). Four estimated provinces had estimates less than two times that of the routine surveillance report, including West Kalimantan, West Papua, Riau Islands and Papua.

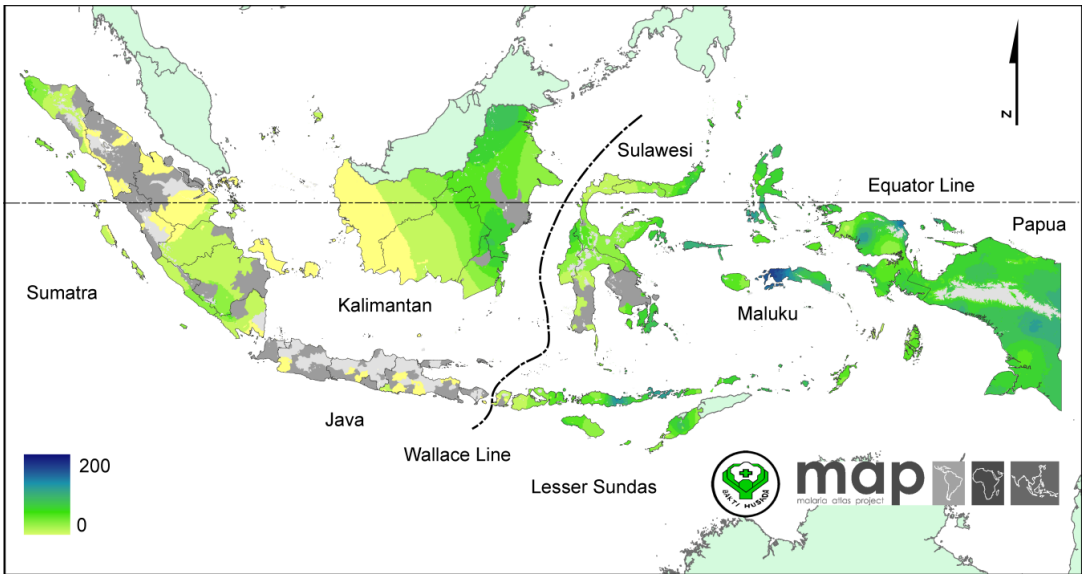


Figure 6.4. National clinical incidence estimates of *P. vivax* in 2010. Clinical incidence estimates of *P. vivax* per 1 x 1 km pixel displayed on a colour scale between 0 and 200 cases per 1,000 population per year within the stable limits of *P. vivax* transmission. Light grey and medium gray areas indicate no malaria risk (*Pv*API = 0 per 1,000 population pa) and unstable risk (0 < *Pv*API < 0.1 per 1,000 population pa).

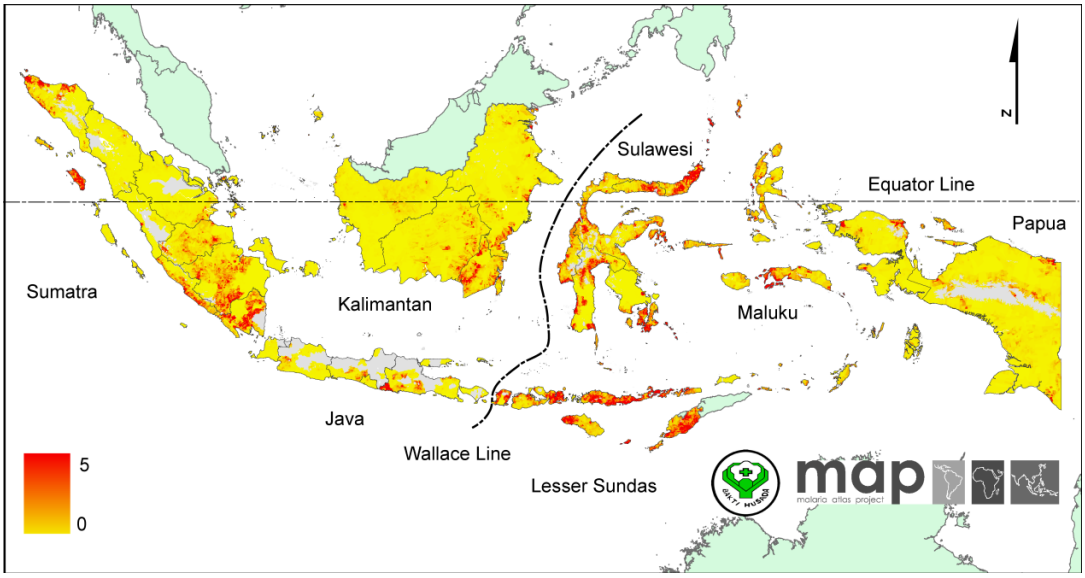


Figure 6.5. National clinical estimates of *P. vivax* attacks in 2010. Clinical estimates of *P. vivax* attacks per 1 x 1 km pixel displayed on a colour scale between 0 and 50 cases within the stable limits of *P. vivax* transmission. Light grey and medium gray areas indicates no malaria risk (*Pv*API = 0 per 1,000 population pa) and unstable risk (0 < *Pv*API < 0.1 per 1,000 population pa).

Table 6.1. Estimated and reported numbers of *P. falciparum* and *P. vivax* clinical attacks in 2010 throughout the Indonesian archipelago. Unstable and stable risk areas for *P. falciparum* malaria correspond to 0 < *Pf*API < 0.1 per 1,000 pa and *Pf*API ≥ 0.1 per 1,000 pa. Unstable and stable risk areas for *P. vivax* malaria correspond to 0 < *Pv*API < 0.1 per 1,000 pa and *Pv*API ≥ 0.1 per 1,000 pa.

Parasite species and area at risk	Western		Eastern		Total		
	Estimated	Reported	Estimated	Reported	Estimated	Reported	Estimated/ Reported
P. falciparum							
Unstable risk	6,068	*1,372*	771	*283*	6,839	*1,655*	*4.1*
Stable risk	5,009,082	*46,927*	2,777,651	*208,338*	7,786,733	*255,265*	*30.5*
All Risk	*5,015,150*	*48,299*	*2,778,422*	*208,621*	*7,793,572*	*256,920*	*30.3*
P. vivax							
Unstable risk	6,183	*1,328*	763	*259*	6,946	*1,587*	*4.4*
Stable risk	606,761	*65,878*	939,991	*203,237*	1,546,752	*269,115*	*5.7*
All Risk	*612,944*	*67,206*	*940,754*	*203,496*	*1,553,698*	*270,072*	*5.8*

6.4. Discussion

This report describes the first estimates of clinical attacks of *P. falciparum* and *P. vivax* in Indonesia in 2010 at high spatial resolution. We have estimated 7.7 million clinical attacks of *P. falciparum* and 1.5 million clinical attacks of *P. vivax* in 2010. Our estimates differ substantially from that presented by the Indonesian national malaria reporting system that reported 0.26 million cases for *P. falciparum* and 0.27 million cases for *P. vivax* for 2010. Our work was driven by the assumed uniform incidence density for the estimations in unstable risk areas and derived incidence densities using a relationship of incidence-prevalence for the estimations in stable risk areas. Credible confidence intervals of estimates were not calculated as a geostatistical space-time joint simulation approach to generate burden realisations at each pixel is computationally expensive for this exercise.

6.4.1. Challenges to estimate malaria burdens

The cartographic methodology applied here has unique strengths compared to routine surveillance systems. Even though routine surveillance allows more real-time assessment of changes [694], there are potential confounders of using routine surveillance to estimate clinical attacks [669], such as the extent to treatment seeking behaviour, patient use public sector health facilities, accurate diagnoses and reporting completeness. Additionally, this cartographic method is able to facilitate malaria incidence estimates in areas with poor quality of routine surveillance report. Measuring malaria incidence is costly to conduct and could be complicated for local malaria control program. In absence of local longitudinal survey in many endemic areas, the cartographic method should be used synergistically to cover large geographical areas given that continuous surfaces of standardized parasite prevalence is available.

Nevertheless, the cartographic method has at least two main challenges. Firstly, defining incidence cases in *P. vivax* infections is more difficult. Unlike *P. falciparum* infections, *vivax* infections are both sporozoite-borne and hypnozoite-borne [695]. A new parasitemia does not necessarily demonstrate a recent sporozoite attack. In endemic areas, it is not possible to distinguish new infections from old relapses as they are clinically equivalent [696], and molecular technologies to discriminate them is not yet possible. Secondly, assembled incidence rates were gathered from various levels of malaria endemicity. If incidence studies have been done in areas of relatively high incidence, then extrapolating these incidence rates from these sites to populations at lower risk would lead to overestimates of case incidence.

6.4.2. Estimation implication to control and elimination effort

Analysis of clinical incidence estimates of malaria may indicate a higher number of malaria infections outside the eastern part of Indonesia. Even though higher endemicity areas were observed in the eastern region, more people lived in *P. falciparum* risk areas of in the western part of Indonesia than in the eastern region (112.1 million vs 20.7 million) [384]. Taking into account the population density, there are more clinical attacks in the western region than in the eastern region (5.5 million vs 2.7 million). Nationally, Sumatra contributed the majority of *P. falciparum* clinical attacks (30.9%), while Papua contributed less than 5% of the national burden. In terms of *P. vivax* clinical attacks, this model revealed substantial infections occurred in western region, with Sumatra and Kalimantan that contributing to nearly 40% of the national burden. These estimated differences in the national burden landscape should assist malaria control authorities and research partners to re-evaluate priorities and strategic direction to address potential sources of infections in the western part of the archipelago.

The reliability of the malaria national reporting system in Java should be critically evaluated and strengthened using these new estimates. Our burden estimates generated as much as 526-fold and 23-fold higher levels of *falciparum* and *vivax* malaria infections occurring on this island, respectively. Two provinces (Central and Eastern Java) contributed substantially to the island burden estimates (>84%). Meanwhile, the current annual blood examination rate (ABER) for these provinces were very low (<1%), resulting in the low adequacy of case detection coverage. Any compromise in case detection jeopordize the fight to eliminate malaria from the Indonesian archipelago [697].

A range of factors constrain the reliability of routinely reported malaria data through the national health management information system in Indonesia, including rates of care-seeking, diagnostic practices, record keeping and reporting rates. High proportion of clinical cases without either microscopically or rapid diagnostic examination were observed. For example, the Health Offices of Maluku and North Maluku Provinces reported over 24,000 clinical cases undiagnosed in 2010 [220,698]. Microscopically-based case detections should be mandatory to detect malaria carriers in high endemicity areas [699-702]. At the same time, local malaria authorities in low endemicity areas should use more sensitive diagnostic tools to detect low-parasite-density infections [3,703,704].

6.4.3. Opportunities to improve the Indonesian malaria surveillance system

The national malaria surveillance system should be improved by incorporating the morbidity experienced by communities generated at private clinics, physicians and hospitals. The Indonesia Basic Health Research found that five percents of over

250,000 interviewed respondents across the archipelago utilized these facilities to seek treatment [705]. Over 1,300 hospitals keep the details of malaria data and do not share reports to the National Malaria Control Program [72]. Connecting and collating all these data from a hospital-based reporting system to obtain a better picture of malaria morbidity is essentially enormous task. The advancement of information technology and advanced geostatistical space-time framework should assist in the incorporation of data from all health facilities to the national malaria surveillance data [706-710].

The implementation of a reliable and regular reporting system among districts, province and the Ministry of Health should be permanently established. Lack of coordinated data gathering and reporting among these administrative levels is fully acknowledged by the Indonesian Malaria Control Program [711]. The monthly transfer of data among district, provincial and national offices is currently done by hand delivery, fax or email. This procedure creates long delays in reporting and the massive burden of integrating data from over 8,200 primary health centers in nearly 500 districts across Indonesia. The realisation of nearly USD 6 million funded by the Global Fund for AIDS, Tuberculosis and Malaria to strengthen monitoring and evaluation capacity in Indonesia [711,712] should assist in producing a new comprehensive web-based malaria reporting system to replace the previous reporting system.

Evidence has demonstrated that web-based surveillance data could improve the timeliness and completeness of data collection and reporting [336,344,713-720]. Collecting and entering health data into an electronic surveillance system using mobile phone technologies text messaging applications has been demonstrated as one possible method [336,721-723]. This technology could feasibly be implemented to support nation-wide network-based malaria reporting system and could transform how the country collects, analyzes and reacts to malaria information [724-726]. With nearly

77,000 masts across the archipelago, the ability to maximize the value of communication technology should be a critical milestone in the field of malaria elimination in Indonesia.

6.5. Conclusions

This finding shows Indonesia is likely to have high under-reporting rates of malaria burden across the archipelago. The estimated burdens presented highlight the need to increase the detection and diagnosis coverage. Introducing web-based malaria reporting is imperative to monitoring the quality of surveillance and evaluating intervention progress. In Java and Bali where the goal is to eliminate malaria in 2015, more concerted efforts are required to investigate human movement patterns, control imported malaria cases, interrupt local transmission and maintain a high quality malaria surveillance system.

6.6. Acknowledgements

I sincerely thank to the colleagues from the Indonesian National Malaria Control Program and 33 provincial malaria managers who generously contributed to the national assembly of routine surveillance malaria data.

CHAPTER 7

General Discussion and Conclusions

7.1. Discussion

This thesis has described the challenges and opportunities involved in controlling/eliminating malaria in Indonesia and the prospects for eliminating malaria nationally, and has explored the role of cartographic tools in providing evidence-based assessments of burden. Extensive malaria studies published in Indonesia from early 1900s were thoroughly reviewed to present the evolving dynamic of endemic malaria.

Infections among the anopheline mosquito vectors of malaria were also examined: approximately 1,300 records reporting *Plasmodium* spp. infections (sporozoites or oocyst stages) for 29 *Anopheles* species were available from Indonesia between 1919 and 2010. The presence of 20 *Anopheles* species or species complexes of malaria vectors was confirmed across the country. A series of comprehensive evidence-based maps of *Anopheles* malaria vector mosquito species distributions were produced from nearly 260 sources that documented the presence of those species in over 750 independent sites.

Nearly 4,500 data points indicating malaria prevalence were extracted to generate the first contemporary high spatial resolution endemicity maps of *P. falciparum* and *P. vivax* in Indonesia. Bayesian model-based geostatistical procedures were used to predict a continuous surface of its endemicity, with uncertainty estimates. The

corresponding human populations at risk were also estimated regionally and provincially. Approximately 133 million people in Indonesia lived at risk of *P. falciparum* transmission in 2010. More people inhabited areas of unstable transmission than stable transmission (70%:30%). Among those exposed to stable risk, the vast majority lived at low risk areas (93%). There were an estimated 7.7 million *P. falciparum* clinical infections in 2010. Nearly 130 million people in Indonesia lived at risk of *P. vivax* transmission in 2010 (most of whom were also at risk from *P. falciparum*). Among these, 79% inhabited unstable transmission areas and 21% resided in stable transmission areas. Most Indonesians living with endemic *P. vivax* experienced relatively low risk of infection. *P. vivax* infections resulted an estimated 1.5 million clinical cases in 2010.

The summarised literature reviews and results from the spatial modelling indicate that useful and practical strategic plans should be aimed at better equipping malaria control and elimination in Indonesia.

7.2. Project Strengths

Developing evidence-based strategic plans for malaria control and elimination in an archipelago of nearly 17,000 islands stretched across more than 5000km is a seriously challenging endeavour. Indonesia has a long and renowned history in the early research and discoveries of malaria, and subsequently in the successful use of environmental control methods to combat the vector and disease transmission. Research presented in Chapter 2 demonstrated that (1) malaria represents an important public-health challenge for Indonesia and (2) there are gaps in the evidence base supporting the development of better tools aimed at equipping malaria control and elimination in this country. The summarized available evidence has identified lessons

learnt and the gaps remaining despite 100 years of historic development of important methods of control in Indonesia. Designing an achievable research agenda that aims to fill in such gaps and inform control and elimination strategy is vitally important to overcome the daunting diversity of transmission dynamics and locally-specific character of malaria in Indonesia.

Evidence-based vector control strategies require accurate and current knowledge of the identity, distribution and bionomics of the key malaria vectors in different localities in Indonesia. The research work in Chapter 3 accomplishes the aim of producing an updated overview of the known distribution and bionomics of the 20 confirmed malaria vector species or species complexes within Indonesia. A review of the status of insecticide susceptibility of eight malaria vector species is also provided in order to illustrate the general paucity of information on this important topic. Gaps in existing knowledge of the transmission epidemiology of malaria have been identified. A series of evidence-based distribution maps of confirmed malaria vector mosquitoes are produced as tools for the Indonesian health authorities and other organizations so that their resources may be focused on the times and places that will ensure vector control interventions can have greatest impact. The combination of sub-national endemicity maps with maps of the distribution of the dominant *Anopheles* vectors of malaria could empower malaria control managers to formulate evidence-based intervention strategies appropriate to the bionomics of their local vectors.

This research work generated the tools that may improve national planning for the implementation of malaria control and elimination strategies. The prediction risk maps of *P. falciparum* and *P. vivax* malaria in Indonesian in 2010 at high spatial resolution are produced as baseline maps (Chapters 4 and 5). The use of a national database of Annual Parasite Incidences for both parasite species, as well as environmental

covariates and malariometric prevalence data analysed within a Bayesian model-based geostatistical framework has generated the spatial limits of malaria transmission, the spatial distributions of malaria endemicity and their corresponding uncertainty estimates. The population at risk of malaria has been estimated nationally, regionally and provincially. These detailed maps of malaria risk are designed as tools to guide the strategic distribution of limited fiscal resources, expertise and, importantly, social and political capital in meeting declared elimination objectives. Creating these baseline maps will also prove to have been essential as control progresses because the maps allow identification of the main foci of active transmission and bring into focus efforts to interrupt sources of residual transmission, allowing importation risk in areas that have been cleared of malaria to be limited.

This research work was designed to comprehensively inform the Indonesian national evidence-based malaria control strategies to reach pre-elimination targets by 2020 and and to be free of malaria in 2030. The direct and extensive evidence of malaria that informed the cartographic model yielding estimates of clinical cases for *P. falciparum* and *P. vivax* in Indonesia in 2010 is the principal strength of this work (Chapter 6). Comparisons between burden estimates generated by this model and the standard estimates based on reported surveillance data were done for *P. falciparum* and *P. vivax*. The differences in these estimates suggest very wide gaps in established reporting systems. Reliable information on the malaria burden is essential in comparing targets with capacity for delivery of health services, in identifying areas of under-reporting, and in quantifying the demand for delivery of diagnosis and treatment services.

7.3. Project Limitations

Elimination feasibility requires the simultaneous consideration of technical and operational constraints [727]. Assessment of technical feasibility needs estimates of the intensity of endemic transmission and malaria importation rates, whilst operational feasibility is affected by local political and financial environments, health-system capacity and the size of populations at infection risk [620]. *Plasmodium falciparum* and *Plasmodium vivax* endemicity maps and their corresponding estimates of population at risk have been produced [384,691]. However, this research project assumed static populations and did not explore malaria importation risk from mobile populations and the impact this may have on operational feasibility assessments of malaria elimination in Indonesia. Understanding how parasites are imported between regions is therefore an important goal and would enable control programs to target the principal sources of malaria [728]. This remaining task will be further explored in the near future.

Another limitation of this project is that estimating true clinical incidence of *P. vivax* malaria infection is challenged by at least by two main factors: the biology behind relapse [729] and the development of immunity [730]. Recurrent vivax parasitemia following primary attack may originate from failed therapy against asexual blood stages (recrudescence), exposure to further infectious anopheline mosquitoes (reinfection), or hypnozoites (relapse). Discriminating these events using molecular technologies is not yet possible [695]. Anti-disease immunity to malaria is acquired from exposure to malaria infection and develops more quickly with frequent exposure and can lead to a reduction in the acute clinical symptoms of disease. Immunity to *P. vivax* is acquired more rapidly than to *P. falciparum* [731]. The presence of anti-disease immunity in individuals may result from a high proportion of asymptomatic *P. vivax* infections in

communities. This type of infection imposes difficulties in estimating clinical vivax malaria incidence.

7.4. Recommendations

Lessons from the eradication/eliminating initiatives of smallpox, poliomyelitis, and measles are that research should accompany elimination efforts from the outset [732]. The need for a comprehensive research agenda for malaria eradication has been also recognized, including diagnoses [733], antimalarial drugs [640], vector control [734], monitoring-evaluation [735] and health systems [736].

In this project, I have reviewed the century-long efforts to research and control malaria in Indonesia, and evaluated the prospect of reaching pre-eliminating malaria. Cartographic tools were developed to support control planning. It is clear that better research and collaboration between control managers and researchers is essential to develop the evidence-based tools to detect, diagnose and treat malaria more effectively. Accordingly, four strategic directions are recommended to address the most urgent problems for malaria control in Indonesia (Table 7.1).

Table 7.1. Proposed evidence-based strategic plans for controlling and eliminating malaria in Indonesia.

Strategic plans	Proposed activities
Improving detection and diagnosis coverage	• Increasing malaria detection coverage in provinces with medium-high malaria under-reporting rates. • Increasing the capacity of malaria microscopists to provide reliable diagnosis.
Providing better access to antimalarial drugs	• Evaluating the extent of the persisting practice of engaging chloroquine and

	sulfadoxine/pyrimethamine against both *P. falciparum* and *P. vivax* malaria in both the public and private sectors. • 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. • Measuring the relative contribution of the hypnozoite reservoir to the burden of parasitemia in given communities with endemic *P. vivax* malaria. • Assessing the efficacy of primaquine as a gametocytocide and hypnozoitocide, including the characterization of G6PD deficiency variant diversity, distribution and relative sensitivity to primaquine using randomized controlled trials.
Improving vector control	• Utilizing molecular entomology tools to update keys to the anopheline fauna of Indonesia, determining the presence of cryptic species and sibling species composition and detecting their roles in the transmission of malaria. • Assessing the efficacy of ITN or IRS intervention against malaria in hypo- and mesoendemic settings using randomized controlled trials. • Conducting local entomological surveys to gather data on the feeding behaviour, host preference and peak feeding periods. • Comprehensive monitoring of insecticide susceptibility using standardised tests against the local main vectors species.
Improving surveillance	• Identifying demographic groups at highest risk of severe and complicated malaria using prospective hospital-based studies in various endemic settings.

- Developing malaria surveillance systems linked to geospatial mapping systems aimed at focusing control resources and effort where most needed or most likely to succeed.
- Developing a web-based malaria surveillance system.
- Developing an assessment of human population movement and the risk of malaria importation.

7.5. Future Priorities

Immediate priorities for research are improvements to surveillance data which guide policy makers in moving from control to elimination [737]. Malaria-free and low-endemicity zones occur on the islands of Java and Bali, where about 60% of Indonesians live. Malaria authorities aim to eliminate malaria by 2015 from both islands. However, the current estimates revealed extremely high under-reporting rates (>95%). Maintaining adequate malaria surveillance measures for the years required to eliminate relapsing malaria such as *P. vivax,* will be very difficult [696]. Improved detection coverage should be implemented as a means of interrupting transmission, but perhaps more importantly for sustaining that achievement and preventing the re-introduction of malaria by mobile populations. Quantifying those movements, along with understanding the geographic and demographic dimensions of such movements will be key to combatting threats to sustaining elimination.

Further research should explore other threats to elimination. Human mobility plays an important role, but other factors, such as measures of receptivity to reintroduced malaria by the abundance and behaviour of mosquito vectors, are also important [728].

Developing a quantitative framework of human mobility and a feasibility assessment for malaria elimination in the Indonesian archipelago are key future challenges. Three research priorities address these: 1) quantifying human movement patterns using mobile phone data to quantify/confirm movement of individuals from high to low transmission areas, and movement of susceptible individuals from low to high and back to low transmission areas, 2) quantification of important malaria and outbreak risks, 3) mapping strategic operational feasibility of malaria elimination that includes receptivity to reintroduced malaria. This is a necessary audit that is important operationally to define within-country differences that might affect the feasibility of elimination and the range of challenges faced by districts.

7.6. Conclusions

Indonesia is an archipelago nation that faces the serious challenge of eliminating malaria. A major reservoir of undiagnosed malaria cases creates a significant obstacle to robust evaluations of progress made towards elimination. High mobility of populations among islands is another of the country's difficult impediments to sustaining elimination gains. Knowledge and information of local malaria epidemiology should be presented to add more value in planning, monitoring and evaluation. Evidence-based local interventions and strategies to continue strengthening diagnosis, access to effective antimalarial drugs, effective vector control, and a far more robust surveillance system are essential. The training of the next generation of malarialogists should be made to build up and strengthen research infrastructure and capacity in this country.

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Appendix

This Appendix includes the following supplementary information:

1. Appendix to Chapter 2
2. Appendix to Chapter 3
3. Appendix to Chapter 4
4. Appendix to Chapter 5
5. Appendix to Chapter 6

Appendix to Chapter 2 – *Malaria distribution, prevalence, drug resistance and control in Indonesia*

This appendix includes:

Supplementary References

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Supplementary Tables

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- Supplementary Table S2. *Plasmodium falciparum* resistance to sulphadoxine-pyrimethamine throughout the Indonesian archipelago 372
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Supplementary References to Table 2.2. Sources from which the database of distribution of human *Plasmodium* was regained.

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 were listed these following references:

Island	References
Sumatra	[132,144,149,184,311,315,509,657,738-760]
Java/Bali	[76,116,217,534,549,753,761-772]
Kalimantan	[773-776]
Sulawesi	[455,658,777-789]
Maluku	[299,546,790]
Lesser Sundas	[77,138,224,347,791-808]
Papua	[150,213,215,230,231,435,477,484,512,513,801,809-826]

Supplementary Table S1. *Plasmodium falciparum* resistance to chloroquine in Indonesia 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	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	1,306	862	66	15	486	358	74
Total	1973-2005	116	2,967	1,539	52	73	1,743	1,022	59

The database of *P. falciparum* resistance to CQ was retrieved from these following references: Sumatra [130,132,137,294,827-834]; Java/Bali [130,136,745,765,768,827,835-840]; Kalimantan [131,134,135,774-776,841-847]; Sulawesi [131,786,834,848,849]; Maluku [131]; Lesser Sundas [77,131,138,792,797,850,851]; Papua [120,131,135,142,512,790,813,824,826,852-862].

Supplementary Table S2. *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. falcifarum* resistance to SP was retrieved from these following references: Sumatra [130,294,743,748,827,828,831, 863,864]; Java/Bali [745,765,827,829,836,838,839,863,864]; Kalimantan [774,842,843,865]; Sulawesi [130,827,864,866]; Maluku (none); Lesser Sundas [851,864]; Papua [139-142,512,790,857,860,867].

Supplementary Table S3. *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 [294]; Java/Bali [746,765,868]; Kalimantan [842,843,865]; Sulawesi [130]; Maluku (none); Lesser Sundas [868]; Papua [142,512,853].

Supplementary Table S4. *Plasmodium vivax* resistance to chloroquine throughout the Indonesian archipelago.

Islands	Year of sample	*In-vivo* test			
		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 [132,748,832,869,870]; Java/Bali [835,836]; Kalimantan [775]; Sulawesi [786]; Maluku (none); Lesser Sundas [77,797,871-874]; Papua [117,120,143,145,790,813,858,875-877].

Appendix to Chapter 3 – *The distribution and bionomics of* Anopheles *malaria vector mosquitoes in Indonesia*

This appendix includes:

Supplementary References

- Supplementary References to Table 3.1. Sources from which susceptibility of *Anopheles* mosquitoes to *Plasmodium* spp. infections was acquired 376
- Supplementary References to Table 3.2. Sources from which natural sporozoite infections of *Anopheles* mosquitoes to *Plasmodium* spp. infections was acquired 378
- Supplementary References to Figures 3.2 – 3.21. Sources from which the database of distribution of *Anopheles* malaria vector mosquitoes in Indonesia was acquired 380
- Supplementary References to Table 3.3. Sources from which the database of blood feeding preference/human blood index of *Anopheles* malaria vector mosquitoes was acquired 383

Supplementary Table

- Supplementary Table S5. The typical larval habitats of *Anopheles* malaria vectors in Indonesia 384

Supplementary References to Table 3.1. Sources from which susceptibility of *Anopheles mosquitoes* to *Plasmodium* spp. infections was acquired.

The database of susceptibility of *Anopheles* mosquitoes to *Plasmodium* spp. infections in Indonesia was acquired from the following references:

Species or species complex	References
An. aconitus	[36,38,39,381,386,387,402,405,408,423,444,504,509, 529,534,558,878-883]
An. aitkenii	[34]
An. albotaeniatus	[36,38,881-883]
An. annularis	[34,36,386,402,405,418,463,503,504,521,529,534,878, 879]
An. balabacensis	[402,408,416-418,422,423,486,566,884]
An. bancroftii	[171,435,436,465]
An. barbirostris	[34,36,38,381,386,402,405,408,418,423,443-446,455, 463,465,470,496,521,527,529,544,558,566,878,879, 881-883,885,886]
An. barbumbrosus	[465,470,471]
An. crawfordi	[465,496,566,748]
An. farauti s.l.	[36,171,387,435,436,477,565]
An. flavirostris	[39,405,408,418,423,470,486,492,521,887]
An. hyrcanus	[36]
An. indefinitus	[381,405,418,566,879,883]
An. karwari	[34,171,436]
An. kochi	[34,36,39,381,386,387,402,405,408,423,471,496,503, 504,509,521,529,546,558,566,748,878,879,881-883]
An. koliensis	[40,171,436,477,512,514]
An. leucosphyrus	[34,36,416,443,470,509,517,882]
An. longirostris	[171,436]
An. maculatus s.l.	[34,36,39,386,402,405,408,418,423,444,486,521,529, 563,879,881,882]

Species or species complex	References
An. nigerrimus	[36,39,387,463,470,496,521,524,558,563,566]
An. parangensis	[443,445,465,527]
An. peditaeniatus	[405,496,529,566,878]
An. punctulatus	[34,40,171,381,436,477,512,514,881-883]
An. sinensis	[34,38,39,381,496,509,529,534,536,566,748,878,881, 883]
An. subpictus s.l.	[34,36,38,39,381,402,418,443-446,465,470,471,493, 503,504,527,540,541,543,544,546,558,878,886]
An. sundaicus s.l.	[32,34,36,38,39,156,381,405,418,444,470,496,509,529, 536,540,543,544,558,560,563,566,748,881,887,888]
An. tessellatus	[36,39,387,402,405,418,443,465,496,521,534,546,566, 748,878,879]
An. umbrosus	[32,36,38,509,563,881,882,887]
An. vagus	[36,386,402,405,408,418,423,444,463,465,486,503, 504,521,529,546,566,878,879,881,882,889]

Supplementary References to Table 3.2. Sources from which natural sporozoite infections of *Anopheles mosquitoes* to *Plasmodium* spp. infections was acquired.

The database of natural sporozoite infections of *Anopheles* mosquitoes to *Plasmodium* spp. infections in Indonesia was acquired from the following references:

Species or species complex	References
An. aconitus	[38,39,386,387,402,405,408,423,444,504,529,558,878-881]
An. albotaeniatus	[38]
An. annularis	[386,402,405,418,463,503,504,521,529,878,879]
An. balabacensis	[402,408,416-418,422,423,486,566,884]
An. bancroftii	[171,436,465]
An. barbirostris	[38,386,402,405,408,418,423,443-446,455,463,465,470, 496,521,527,529,544,558,566,878,879,885]
An. barbumbrosus	[465,470,471]
An. crawfordi	[465,496,566,748]
An. farauti s.l.	[171,387,436,477]
An. flavirostris	[39,405,408,418,423,470,486,492,521]
An. indefinitus	[405,418,566,879]
An. karwari	[171,436]
An. kochi	[39,386,387,402,405,408,423,471,496,503,521,529,546, 558,566,748,878,879]
An. koliensis	[40,171,436,477,512,514]
An. leucosphyrus	[416,443,470]
An. longirostris	[171,436]
An. maculatus s.l.	[39,386,402,405,408,418,423,444,486,521,529,563,879]
An. nigerrimus	[39,387,463,470,496,521,524,558,563,566]
An. parangensis	[443,445,465,527]
An. peditaeniatus	[405,496,529,566,878]
An. punctulatus	[40,171,436,477,512,514]
An. sinensis	[38,39,496,529,566,748,878]

Species or species complex	References
An. subpictus s.l.	[38,39,402,418,443-446,465,470,493,503,504,527,540,541, 543,544,546,558,878,886]
An. sundaicus s.l.	[38,39,405,418,444,470,496,529,540,543,544,558,563,566, 748]
An. tessellatus	[39,387,402,405,418,443,465,496,521,546,566,748,878, 879]
An. umbrosus	[38,563]
An. vagus	[386,402,405,408,418,423,444,463,465,486,503,504,521, 529,546,566,878,879,889]

Supplementary References to Figures 3.2 – 3.21 . Sources from which the database of distribution of *Anopheles* vector mosquitoes in Indonesia was acquired.

The database of distribution of *Anopheles* vector mosquitoes in Indonesia was acquired from the following references:

Species or species complex	References
An. aconitus	[34-36,38,39,224,253,270,287,292,315,325-327,339,358, 362,370,371,386,391,392,394,399-408,410,414,415,417, 419,421,425,426,429,432,444,446,451-457,470,487-490, 492,497-499,502-504,522,529,530,534,539,541,545,558, 560,568-571,575,750,767,880,890-939]
An. balabacensis	[403,404,407,408,416-421,424-426,428,429,431,432,488, 489,522,530,569,880,904,932,939-946]
An. bancroftii	[36,433,435,438,910,947]
An. barbirostris	[34-36,38,39,224,230,257,287,292,304,386,391,392,394, 399,400,403-408,410,412,414,415,417-419,421,424-426, 429,431,444-446,451-455,457,459,460,463-465,472,473, 487-490,492,497-499,501,502,506,510,522,525,526,529, 530,534,541,544,545,547,558,560,568,569,750,795,808, 880,885,886,890,891,900,902-905,907,909-911,916-918, 920,926,932-934,936,939,948-959]
An. barbumbrosus	[36,445,451,464,465,470,472,473,530,569,910,911,939]
An. farauti s.l.	[171,303,366,438,477-480,482,511,546,569,910,911,960]
An. flavirostris	[36,304,394,402,403,405,407,408,410,414-416,418,421, 426,428,431,444-446,452,459,470,486-490,492,500, 522,525,529,541,560,569,750,795,880,902,909,910,917, 934,960].
An. karwari	[36,435,750,891,910,932,961]

Species or species complex	References
An. kochi	[34-36,38,386,391,394,399,402-408,410,414-419,421,424-426,428,429,444-446,452,456,457,464,470,472,482,487,489,490,497-504,506,508,510,522,525,526,529,530,534,541,547,558,568,569,748,750,880,891,900,902-905,910,911,916,917,926,932,933,936,948,954,960,962-964]
An. koliensis	[171,303,433,477-479,511-514,574,910]
An. leucosphyrus	[36,416,451,517,560,750,910,933]
An. maculatus s.l.	[34-36,38,304,386,391,392,394,399,402-408,412,414,415,417-421,424-426,429,431,432,444-446,452-454,456,457,470,472,486,488-490,492,497,499,502,506,522,525,529,541,563,568,569,571,575,750,880,891,902,904-906,910,916,917,932,933,937,940-944,946,948,952,954,965-975].
An. nigerrimus	[36,414,451,455,463,464,470,473,498,506,508,525,526,529,530,558,560,563,750,902,910,926,933,934,936,938,954,962,965,976-978]
An. parangensis	[36,410,435,445,455,457,459,464,465,473,910,957]
An. punctulatus	[36,171,302,366,433,435,477-479,511-514,569,910,911,960,979]
An. sinensis	[365,506,510,526,529,530,563,748,750,932,933,952,956]
An. subpictus s.l.	[36,39,304,394,402,405,406,410,412,414,415,418,424,431,444-446,452,454,456,457,459,460,465,470,478,487,490,492,493,501-504,506,522,541,544-548,550,558,560,569,575,795,880,885,886,891,902,904,907-911,932,936,937,953,954,957,962,980-983]
An. sundaicus s.l.	[34-36,39,262,266,291,293,304,340,405,406,410,412,414,415,418,431,444,451,452,454,460,470,487,490,492,506,508,526,529,534,544,545,547,555,557,558,560-563,569,575,746,748,750,795,904,907-911,927,932,937,951,953,954,963-965,969,983-994].

Species or species complex	References
An. tessellatus	[392,394,399,402,405,410,415,417,431,445,446,451-453,455-457,464,465,470,472,473,487,490,498,501,502,506,525,526,530,541,546,547,560,568,569,748,750,880,891,902-905,907,910,916,933,934,936,948,954,956,959]
An. vagus	[36,39,224,292,386,391,392,394,396,399,402-405,407,408,410,414,415,417-419,421,424-426,429,431,444-446,451-457,460,463-465,470,472,473,486-489,492,497,498,500-504,510,522,525,529,530,541,546,547,560,568,569,750,880,889-891,900,902-905,907,909-911,916,917,926,932-934,936,941-943,946,948,952,955,956,958,960,975,995-998]

Supplementary References to Table 3.3. Sources from which the database of blood feeding preference/human blood index of *Anopheles* malaria vector mosquitoes was acquired.

The database of blood feeding preference/ human blood index of *Anopheles* malaria vectors in Indonesia was acquired from the following references:

Species or species complex	References
An. aconitus	[39,325-327,389,390,395-397,407,505,914,919,999,1000]
An. balabacensis	[407]
An. bancroftii	[397]
An. barbirostris	[389,396,397,407,505]
An. farauti s.l.	[479]
An. flavirostris	[407]
An. kochi	[389,396,407,505]
An. koliensis	[479]
An. leucosphyrus	[505]
An. maculatus s.l.	[396,407,505]
An. nigerrimus	[389]
An. punctulatus	[397,479]
An. sinensis	[397,505]
An. subpictus s.l.	[39,389,396,397,505,543,544]
An. sundaicus s.l.	[39,397,505,543,544]
An. tessellatus	[389,396,397,505]
An. vagus	[389,396,407,505]

Supplementary Table S5. The typical larval habitats of *Anopheles* malaria vectors in Indonesia.

Species or species complex	Light intensity		Water Salinity		Water Turbidity		Water Movement		Habitat type	
	Sunlit	Shaded	Brackish	Fresh	Clear	Turbid	Stagnant	Flowing	Natural	Man-made
An. aconitus	●	●		●	●		●	●	marshes, lakes, streams, river beds.	rice fields, fish ponds, irrigation ditches.
An. balabacensis		●		●	●		●		ground depressions, stream-side rock pools, pools under shrubs or low trees, river banks, seepage.	puddles, animal wallows, hoof prints, tyre tracks.
An. bancroftii		●		●	●			●	marshes, pools associated with slow streams, creeks and rivers, ground pools.	heavily shaded irrigation ditches.
An. barbirostris	●	●		●	●		●	●	lagoons, marshes, pools, slow running streams, river banks, springs.	rice fields, fish ponds, drainage ditches, wells.
An. barbumbrosus	●	●		●	●			●	river-banks, clear streams emerging from jungle areas, open grassy ravines.	rice fields.
An. farauti s.l.	●	●	●	●	●		●	●	marshes, lagoons, large and small streams margins and floating wood and other natural debris, river banks.	pools, fish ponds, irrigation ditches, pig-wallows, garden pools, tins, drums, coconut shells, canoes.

Species or species complex	Light intensity		Water salinity		Water turbidity		Water movement		Habitat type	
	Sunlit	Shaded	Brackish	Fresh	Clear	Turbid	Stagnant	Flowing	Natural	Man-made
An. flavirostris		●		●	●		●	●	springs, shaded grassy edges, slow-flowing small streams, pools.	rice fields, irrigation ditches, wells.
An. karwari		●		●	●		●		marshes, small slow moving streams, seepages, ground pools, rock pools, springs.	irrigation canals associated with rice cultivation.
An. kochi	●	●	●	●	●	●	●	●	marshes, pools, small streams.	rice fields, fish ponds, buffalo wallows, wells, ditches, hoof prints.
An. koliensis	●	●		●	●		●		small streams, ground pools, riverside ponds, marshes.	pig ruts and wallows, ditches.
An. leucosphyrus		●		●	●		●	●	marshes, small streams, seepage springs, jungle pools, ground depressions.	fish ponds, wheel ruts, hoof prints

Species or species complex	Light intensity		Water salinity		Water turbidity		Water movement		Habitat type	
	Sunlit	Shaded	Brackish	Fresh	Clear	Turbid	Stagnant	Flowing	Natural	Man-made
An. maculatus s.l.	●			●	●			●	stream-side rock pools, margins of small slow-moving streams, drying river beds, ground seepages, small pools, springs.	rice fields, ponds, ditches.
An. nigerrimus	●			●	●		●		lake margins, marshes, pools, small streams.	rice fields, irrigation channels, large borrow pits.
An. parangensis	●	●	●	●	●	●	●		coastal marshes, pools.	fish ponds, ground depressions.
An. punctulatus	●			●	●	●	●		freshwater coastal marshes, low-lying riverine areas, riverside pools, grasslands, along jungle edges, pools, ground depressions, rock pools in drying stream beds, earthen drains.	foot prints, ditches, pig ruts, pits with grey turbid water, wheel ruts.
An. sinensis	●			●	●		●		lake margins, marshes, small streams, bogs, slow-flowing rivers.	rice fields, borrow pits, fish ponds, irrigation ditches.

Species or species complex	Light intensity		Water salinity		Water turbidity		Water movement		Habitat type	
	Sunlit	Shaded	Brackish	Fresh	Clear	Turbid	Stagnant	Flowing	Natural	Man-made
An. subpictus s.l.	●		●	●	●	●	●	●	tidal lagoons, coastal blocked freshwater rivers and streams, marshes, pools, rocky streams, mangrove forests, springs.	rice fields, fish ponds, furrows in gardens, water tanks, buffalo wallows, brackish ponds, seaweed ponds, irrigation ditches.
An. sundaicus s.l.	●		●	●	●	●	●		lagoons, marshes, pools, seasonally blocked coastal streams.	fish ponds.
An. tessellatus		●	●	●	●	●	●	●	ground pools.	rice fields, fish ponds.
An. vagus	●		●	●	●	●	●		Stagnant margins of streams, river edges, small and swallow pools near beaches, springs.	rice fields, irrigation ditches, wheel ruts, hoof prints, artifical containers (tyres, drums, upturned small boats).

The "●" mark denote the common habitat characteristics of individual *Anopheles* malaria vectors.

s.l. (sensu lato) indicates the existence or possibility of more than one sibling species is representated in Indonesia, therefore collectively expanding the natural and man -made habitats listed.

Appendix to Chapter 4 – Plasmodium falciparum *malaria endemicity in Indonesia in 2010*

This appendix includes:

Supplementary Tables

- Supplementary Table S6. Areas at risk of *Plasmodium falciparum* malaria in Indonesia by provincial, main islands and region level in 2010 389
- Supplementary Table S7. Population at ris*k of Plasmodium falciparum* malaria in Indonesia by provincial, main islands and region level in 2010 392

Suplementary Table S6. Areas at risk *of Plasmodium falciparum* malaria in Indonesia by provincial, main islands and region level in 2010.

Province	Risk area (km^2)						Total area (km^2)
	No risk	Unstable	Stable	*Pf*$PR_{2-10} \leq 5\%$	$5\% < Pf PR_{2-10} < 40\%$	*Pf*$PR_{2-10} \geq 40\%$	
Western	**145,516**	**402,204**	**606,225**	**588,510**	**17,715**	**0**	**1,153,945**
Sumatra	***96,790***	***156,673***	***223,048***	***221,529***	***1,519***	***0***	***476,511***
Aceh	7,930	6,351	42,787	41,642	1,145	0	57,068
Sumatra Utara	36,276	5,217	30,357	30,251	106	0	71,850
Sumatra Barat	13,524	21,976	6,295	6,284	11	0	41,795
Riau	1,618	63,619	24,799	24,799	0	0	90,036
Kepulauan Riau	0	0	9,021	9,021	0	0	9,021
Jambi	2,347	25,101	21,981	21,807	174	0	49,429
Bengkulu	1,156	13,013	9,655	6,932	23	0	21,124
Sumatra Selatan	24,287	89	61,793	61,765	28	0	86,169
Bangka Belitung	358	0	15,952	15,952	0	0	16,310
Lampung	9,294	21,307	3,108	3,076	32	0	33,709
Java/Bali	***41,854***	***90,629***	***6,231***	***6,231***	***0***	***0***	***138,714***
Jakarta	681	0	0	0	0	0	681

Province	Risk area (km^2)						Total area (km^2)
	No risk	Unstable	Stable	*Pf*$PR_{2-10} \leq 5\%$	$5\% < Pf PR_{2-10} < 40\%$	*Pf*$PR_{2-10} \geq 40\%$	
Banten	3,374	6,013	0	0	0	0	9,387
Jawa Barat	14,000	23,162	0	0	0	0	37,162
Jawa Tengah	4,947	27,318	2,086	2,086	0	0	34,351
Yogyakarta	10	2,547	604	604	0	0	3,161
Jawa Timur	17,710	27,921	2,677	2,677	0	0	48,308
Bali	1,132	3,668	864	864	0	0	5,664
Kalimantan	***6,872***	***154,902***	***376,946***	***360,750***	***16,196***	***0***	***538,720***
Kalimantan Barat	1,685	5,926	140,432	140,424	8	0	148,043
Kalimantan Tengah	593	35,445	118,501	118,107	394	0	154,539
Kalimantan Selatan	1,015	4,047	32,521	17,006	15,515	0	37,583
Kalimantan Timur	3,579	109,484	85,492	85,213	279	0	198,555
Eastern	**71,373**	**99,427**	**578,086**	**378,317**	**198,905**	**864**	**748,886**
Sulawesi	***30,349***	***86,853***	***71,028***	***71,013***	***15***	***0***	***188,230***
Sulawesi Utara	96	0	14,687	14,672	15	0	14,783
Gorontalo	6,430	275	5,454	5,454	0	0	12,159
Sulawesi Tenggara	1,515	31,167	4,437	4,437	0	0	37,119

Province	Risk area (km^2)						Total area (km^2)
	No risk	Unstable	Stable	*Pf*$PR_{2-10} \leq 5\%$	$5\% < Pf PR_{2-10} < 40\%$	*Pf*$PR_{2-10} \geq 40\%$	
Sulawesi Barat	2,148	13,222	991	991	0	0	16,361
Sulawesi Tengah	5,011	11,958	44,264	44,264	0	0	61,233
Sulawesi Selatan	15,149	30,231	1,195	1,195	0	0	46,575
Maluku	***504***	***0***	***78,509***	***65,875***	***12,634***	***0***	***79,013***
Maluku	487	0	46,471	37,465	9,006	0	46,958
Maluku Utara	17	0	32,038	28,410	3,628	0	32,055
Lesser Sundas	***1,630***	***0***	***64,803***	***52,236***	***12,567***	***0***	***66,433***
Nusa Tenggara Barat	1,358	0	18,526	18,523	3	0	19,884
Nusa Tenggara Timur	272	0	46,277	33,713	12,564	0	46,549
Papua	***38,890***	***12,574***	***363,746***	***189,193***	***173,689***	***864***	***415,210***
Papua	35,608	12,574	269,681	126,723	142,094	864	317,863
Papua Barat	3,282	0	94,065	62,470	31,595	0	97,347
Indonesia	**216,889**	**501,631**	**1,184,311**	**966,827**	**216,620**	**864**	**1,902,831**

Supplementary Table S7. Population at risk of *Plasmodium falciparum* malaria in Indonesia by provincial, main islands and region level in 2010.

Region/Province	Population (people)						Total population (people)
	No risk	Unstable	Stable	0%< *Pf*PR$_{2-10}$ ≤5%	5%< *Pf*PR$_{2-10}$ <40%	*Pf*PR$_{2-10}$ ≥40%	
Western	**92,753,767**	**87,994,775**	**24,167,445**	**23,517,672**	**649,773**	**0**	**204,915,987**
Sumatra	***22,425,463***	***8,850,714***	***14,451,840***	***14,278,834***	***173,006***	***0***	***45,728,017***
Aceh	854,080	140,671	2,879,917	2,776,794	103,123	0	3,874,668
Sumatra Utara	9,750,071	726,676	2,579,869	2,544,255	35,614	0	13,056,616
Sumatra Barat	2,847,845	1,491,937	100,563	100,448	115	0	4,440,345
Riau	893,711	2,235,767	859,715	859,715	0	0	3,989,193
Kepulauan Riau	0	0	1,219,190	1,219,190	0	0	1,219,190
Jambi	800,579	931,711	791,463	783,587	7,876	0	2,523,753
Bengkulu	276,492	782,066	483,820	483,304	516	0	1,542,378
Sumatra Selatan	3,490,456	85,793	3,749,463	3,746,572	2,892	0	7,325,713
Bangka Belitung	164,738	0	739,955	739,955	0	0	904,693
Lampung	3,347,491	2,456,093	1,047,884	1,025,014	22,870	0	6,851,468

Province	Population (people)						Total population (people)
	No risk	Unstable	Stable	0% < *Pf*PR$_{2-10}$ ≤ 5%	5 % < *Pf*PR$_{2-10}$ < 40%	*Pf*PR$_{2-10}$ ≥ 40%	
Java/Bali	***67,047,647***	***77,173,997***	***3,220,112***	***3,220,112***	***0***	***0***	***147,441,756***
Jakarta	12,523,487	0	0	0	0	0	12,523,487
Banten	8,103,144	1,985,916	0	0	0	0	10,089,060
Jawa Barat	25,129,619	16,926,878	0	0	0	0	42,056,497
Jawa Tengah	5,184,617	28,526,288	1,493,949	1,493,949	0	0	35,204,854
Yogyakarta	3,688	3,372,344	353,670	353,670	0	0	3,729,702
Jawa Timur	15,328,777	23,537,524	1,121,942	1,121,942	0	0	39,988,243
Bali	774,315	2,825,047	250,551	250,551	0	0	3,849,913
Kalimantan	***3,280,657***	***1,970,064***	***6,495,493***	***6,018,726***	***476,767***	***0***	***11,746,214***
Kalimantan Barat	927,565	233,352	2,940,593	2,940,297	296	0	4,101,510
Kalimantan Tengah	57,002	176,962	1,526,361	1,511,421	14,940	0	1,760,325
Kalimantan Selatan	1,367,435	422,531	1,485,498	1,025,365	460,133	0	3,275,464
Kalimantan Timur	928,655	1,137,219	543,041	541,643	1,398	0	2,608,915

Province	Population (people)						Total population (people)
	No risk	Unstable	Stable	0% < *Pf*PR$_{2-10}$ ≤ 5%	5 % < *Pf*PR$_{2-10}$ < 40%	*Pf*PR$_{2-10}$ ≥ 40%	
Eastern	**6,912,056**	**5,538,611**	**15,177,641**	**13,225,290**	**1,946,790**	**5,561**	**27,628,308**
Sulawesi	***5,168,936***	***5,470,351***	***4,800,531***	***4,798,886***	***1,645***	***0***	***15,439,818***
Sulawesi Utara	4,701	0	2,140,889	2,139,244	1,645	0	2,145,590
Gorontalo	174,384	173,575	497,286	497,286	0	0	845,245
Sulawesi Tenggara	311,887	1,229,676	260,800	260,800	0	0	1,802,363
Sulawesi Barat	145,211	625,637	92,963	92,963	0	0	863,811
Sulawesi Tengah	298,205	157,262	1,714,339	1,714,339	0	0	2,169,806
Sulawesi Selatan	4,234,548	3,284,201	94,254	94,254	0	0	7,613,003
Maluku	***5,189***	***0***	***1,949,145***	***1,649,279***	***299,866***	***0***	***1,954,333***
Maluku	3,519	0	1,218,172	1,079,806	138,366	0	1,221,691
Maluku Utara	1,670	0	730,973	569,473	161,500	0	732,643
Lesser Sundas	***1,410,305***	***0***	***6,643,165***	***5,890,218***	***752,947***	***0***	***8,053,470***
Nusa Tenggara Barat	1,367,195	0	2,788,796	2,788,778	18	0	4,155,991
Nusa Tenggara Timur	43,110	0	3,854,369	3,101,440	752,929	0	3,897,479

Province	Population (people)						Total population (people)
	No risk	Unstable	Stable	0% < *Pf*PR$_{2-10}$ ≤ 5%	5 % < *Pf*PR$_{2-10}$ < 40%	*Pf*PR$_{2-10}$ ≥ 40%	
Papua	***327,626***	***68,260***	***1,784,800***	***886,907***	***892,332***	***5,561***	***2,180,685***
Papua	307,133	68,260	1,262,771	520,074	737,136	5,561	1,638,164
Papua Barat	20,493	0	522,029	366,833	155,196	0	542,522
Indonesia	**99,665,823**	**93,533,386**	**39,345,086**	**36,742,962**	**2,596,563**	**5,561**	**232,544,295**

Appendix to Chapter 5 – Plasmodium vivax *malaria endemicity in Indonesia in 2010*

This appendix includes:

Supplementary Table

- Supplementary Table S8. Areas and population at risk of *Plasmodium vivax* malaria in Indonesia by provincial, main islands and region level in 2010 397

Supplementary Table S8. Areas and population at risk of *Plasmodium vivax* malaria in Indonesia by province, main islands and region level in 2010.

Province	Risk area (km^2)			Total area (km^2)	Population (people)			Total population (people)
	No risk	Unstable	Stable		No risk	Unstable	Stable	
Western	**143,050**	**622,284**	**388,611**	**1,153,945**	**96,769,120**	**96,586,342**	**11,560,525**	**204,915,987**
Sumatra	***93,689***	***259,269***	***123,553***	***476,511***	***22,543,764***	***14,707,432***	***8,476,821***	***45,728,017***
Aceh	4,783	27,678	24,607	57,068	786,431	1,224,321	1,863,916	3,874,668
Sumatra Utara	35,594	31,357	4,899	71,850	9,729,105	2,690,212	637,299	13,056,616
Sumatra Barat	12,941	27,729	1,125	41,795	2,833,041	1,593,423	13,881	4,440,345
Riau	1,618	88,418	0	90,036	893,711	3,095,482	0	3,989,193
Kepulauan Riau	0	6,059	2,962	9,021	0	1,135,788	83,402	1,219,190
Jambi	1,243	19,108	29,078	49,429	748,227	800,072	975,454	2,523,753
Bengkulu	494	267	20,363	21,124	251,027	12,786	1,278,565	1,542,378
Sumatra Selatan	23,536	26,237	36,396	86,169	3,461,870	1,151,292	2,712,551	7,325,713
Bangka Belitung	357	15,944	9	16,310	164,738	739,871	84	904,693
Lampung	13,123	16,472	4,114	33,709	3,675,614	2,264,185	911,669	6,851,468

Province	Risk area (km^2)			Total area (km^2)	Population (people)			Total population (people)
	No risk	Unstable	Stable		No risk	Unstable	Stable	
Java/Bali	***44,542***	***93,809***	***363***	***138,714***	***70,511,604***	***76,865,382***	***64,770***	***147,441,756***
Jakarta	681	0	0	681	12,523,487	0	0	12,523,487
Banten	3,334	6,053	0	9,387	8,100,547	1,988,513	0	10,089,060
Jawa Barat	13,446	23,716	0	37,162	24,925,194	17,131,303	0	42,056,497
Jawa Tengah	5,490	28,861	0	34,351	5,846,771	29,358,083	0	35,204,854
Yogyakarta	526	2,635	0	3,161	1,576,124	2,153,578	0	3,729,702
Jawa Timur	19,605	28,340	363	48,308	16,906,146	23,017,327	64,770	39,988,243
Bali	1,460	4,204	0	5,664	633,335	3,216,578	0	3,849,913
Kalimantan	***4,819***	***269,206***	***264,695***	***538,720***	***3,713,752***	***5,013,528***	***3,018,934***	***11,746,214***
Kalimantan Barat	1,534	86,280	60,229	148,043	927,269	2,581,801	592,440	4,101,510
Kalimantan Tengah	370	70,994	83,175	154,539	56,944	532,859	1,170,522	1,760,325
Kalimantan Selatan	999	17,176	19,408	37,583	1,382,456	1,253,595	639,413	3,275,464
Kalimantan Timur	1,916	94,756	101,883	198,555	1,347,083	645,273	616,559	2,608,915

Region/Province	Risk area (km^2)			Total area (km^2)	Population (people)			Total population (people)
	No risk	Unstable	Stable		No risk	Unstable	Stable	
Eastern	**50,261**	**73,035**	**625,590**	**748,886**	**6,157,027**	**6,716,858**	**15,294,423**	**27,628,308**
Sulawesi	***21,621***	***54,524***	***112,085***	***188,230***	***4,577,945***	***5,345,801***	***5,516,072***	***15,439,818***
Sulawesi Utara	2	8,009	6,772	14,783	89	942,211	1,203,290	2,145,590
Gorontalo	6,385	275	5,499	12,159	173,400	173,575	498,270	845,245
Sulawesi Tenggara	1,031	9,101	26,987	37,119	304,388	292,971	1,205,004	1,802,363
Sulawesi Barat	1,232	5,063	10,066	16,361	123,083	457,237	283,491	863,811
Sulawesi Tengah	1,890	483	58,860	61,233	264,188	129,147	1,776,471	2,169,806
Sulawesi Selatan	11,081	31,593	3,901	46,575	3,712,797	3,350,660	549,546	7,613,003
Maluku	***202***	***9,057***	***69,754***	***79,013***	***1,431***	***147,241***	***1,805,662***	***1,954,333***
Maluku	196	9,057	37,705	46,958	1,347	147,241	1,073,103	1,221,691
Maluku Utara	6	0	32,049	32,055	84	0	732,559	732,643
Lesser Sundas	***1,038***	***1,018***	***64,377***	***66,433***	***1,355,225***	***634,739***	***6,063,506***	***8,053,470***
Nusa Tenggara Barat	999	1,018	17,867	19,884	1,344,784	634,739	2,176,468	4,155,991
Nusa Tenggara Timur	39	0	46,510	46,549	10,441	0	3,887,038	3,897,479

Region/Province	Risk area (km^2)			Total area (km^2)	Population (people)			Total population (people)
	No risk	Unstable	Stable		No risk	Unstable	Stable	
Papua	***27,400***	***8,436***	***379,374***	***415,210***	***222,426***	***49,077***	***1,909,183***	***2,180,685***
Papua	26,105	8,436	283,322	317,863	213,471	49,077	1,375,616	1,638,164
Papua Barat	1,295	0	96,052	97,347	8,955	0	533,567	542,522
Indonesia	**193,311**	**695,319**	**1,014,201**	**1,902,831**	**102,926,147**	**102,763,200**	**26,854,948**	**232,544,295**

Appendix to Chapter 6 – *The clinical burden estimates of* Plasmodium falciparum *and* Plasmodium vivax *in Indonesia in 2010*

This appendix includes:

Supplementary Tables

- Supplementary Table S9. Estimated and reported numbers of *Plasmodium falciparum* clinical attacks in Indonesia by provincial, main islands and region level in 2010 402
- Supplementary Table S10. Estimated and reported numbers of *Plasmodium vivax* clinical attacks in Indonesia by provincial, main islands and region level in 2010 406

Supplementary Table S9. Estimated and reported numbers of *Plasmodim falciparum* clinical attacks in Indonesia by provincial, main islands and region level in 2010. Unstable and stable risk areas for *P. falciparum* malaria correspond to 0 < *Pf*API < 0.1 per 1,000 pa and *Pf*API ≥ 0.1 per 1,000 pa.

Region/Province	Unstable risk		Stable risk		All risk		
	Estimated	Reported	Estimated	Reported	Estimated	Reported	Estimated/Reported
Western	**6,068**	**1,372**	**5,009,082**	**46,927**	**5,015,150**	**48,299**	**103.8**
Sumatra	***1,549***	***629***	***2,406,840***	***24,529***	***2,408,389***	***25,158***	***95.7***
Aceh	0	11	409,589	2,494	409,589	2,505	163.5
Sumatra Utara	404	149	720,857	6,543	721,261	6,692	107.8
Sumatra Barat	220	58	99,680	302	99,900	360	277.5
Riau	98	48	244,116	1,165	244,214	1,213	201.3
Kepulauan Riau	0	0	38,136	2,575	38,136	2,575	14.8
Jambi	118	46	157,057	964	157,175	1,010	155.6
Bengkulu	34	12	71,546	784	71,580	796	89.9
Sumatra Selatan	363	134	360,613	3,892	360,976	4,026	89.7
Bangka Belitung	0	0	39,234	4,437	39,234	4,437	8.8
Lampung	312	171	266,012	1,373	266,324	1,544	172.5

Region/Province	Unstable risk		Stable risk		All risk		
	Estimated	Reported	Estimated	Reported	Estimated	Reported	Estimated/Reported
Java/Bali	***4,275***	***608***	***938,832***	***1,186***	***943,107***	***1,794***	***525.7***
Jakarta	0	0	0	14	0	14	0.0
Banten	385	87	0	0	385	87	4.4
Jawa Barat	1,691	195	0	0	1,691	195	8.7
Jawa Tengah	529	180	526,522	829	527,051	1,009	522.3
Yogyakarta	35	17	0	0	35	17	2.1
Jawa Timur	1,476	102	397,428	339	398,904	441	904.5
Bali	159	27	14,882	4	15,041	31	485.2
Kalimantan	***244***	***135***	***1,663,410***	***21,212***	***1,663,654***	***21,347***	***77.9***
Kalimantan Barat	0	0	671,677	12,556	671,677	12,556	53.5
Kalimantan Tengah	0	0	364,392	2,002	364,392	2,002	182.0
Kalimantan Selatan	74	3	462,732	3,131	462,806	3,134	147.7
Kalimantan Timur	170	132	164,609	3,523	164,779	3,655	45.1

Region/Province	Unstable risk		Stable risk		All risk		
	Estimated	Reported	Estimated	Reported	Estimated	Reported	Estimated/Reported
Eastern	**771**	**283**	**2,777,651**	**208,338**	**2,778,422**	**208,621**	**13.3**
Sulawesi	***726***	***257***	***1,205,373***	***8,726***	***1,206,099***	***8,983***	***134.3***
Sulawesi Utara	51	0	263,545	222	263,596	222	1187.4
Gorontalo	17	14	113,178	1,708	113,195	1,722	65.7
Sulawesi Tenggara	97	54	127,298	844	127,395	898	141.9
Sulawesi Barat	0	0	133,591	546	133,591	546	244.7
Sulawesi Tengah	0	0	326,864	4,751	326,864	4,751	68.8
Sulawesi Selatan	561	189	240,897	655	241,458	844	286.1
Maluku	***0***	***0***	***238,172***	***13,883***	***238,172***	***13,883***	***17.2***
Maluku	0	0	133,633	7,254	*133,633*	7,254	18.4
Maluku Utara	0	0	104,539	6,629	*104,539*	6,629	15.8
Lesser Sundas	***45***	***26***	***953,060***	***76,674***	***953,105***	***76,700***	***12.4***
Nusa Tenggara Barat	45	26	372,158	5,921	*372,203*	5,947	62.6
Nusa Tenggara Timur	0	0	580,902	70,753	*580,902*	70,753	8.2

Region/Province	Unstable risk		Stable risk		All risk		
	Estimated	Reported	Estimated	Reported	Estimated	Reported	Estimated/Reported
Papua	***0***	***0***	***381,046***	***109,055***	***381,046***	***109,055***	***3.5***
Papua	0	0	290,792	84,340	*290,792*	84,340	3.4
Papua Barat	0	0	90,254	24,715	*90,254*	24,715	3.7
Indonesia	**6,839**	**1,655**	**7,786,733**	**255,265**	***7,793,572***	**256,920**	**30.3**

Supplementary Table S10. Estimated and reported numbers of *Plasmodium vivax* clinical attacks in Indonesia by provincial, main islands and region level in 2010. Unstable and stable risk areas for *P. vivax* malaria correspond to 0 < *Pv*API < 0.1 per 1,000 pa and *Pv*API ≥ 0.1 per 1,000 pa.

Region/Province	Unstable risk		Stable risk		All risk		
	Estimated	Reported	Estimated	Reported	Estimated	Reported	Estimated/Reported
Western	**6,183**	**1,328**	**606,761**	**65,878**	**612,944**	**67,206**	**9.1**
Sumatra	***1,596***	***543***	***373,364***	***32,560***	***374,960***	***33,103***	***11.3***
Aceh	124	72	75,505	2,162	75,629	2,234	33.9
Sumatra Utara	645	283	27,868	5,448	28,513	5,731	5.0
Sumatra Barat	192	29	3,530	605	3,722	634	5.9
Riau	124	42	9,898	630	10,022	672	14.9
Kepulauan Riau	0	0	4,091	2,658	4,091	2,658	1.5
Jambi	17	19	46,972	3,714	46,989	3,733	12.6
Bengkulu	42	7	30,306	7,840	30,348	7,847	3.9
Sumatra Selatan	366	40	98,878	1,774	99,244	1,814	54.7
Bangka Belitung	0	0	1,984	6,147	1,984	6,147	0.3
Lampung	86	51	74,332	1,582	74,418	1,633	45.6

Region/Province	Unstable risk		Stable risk		All risk		
	Estimated	Reported	Estimated	Reported	Estimated	Reported	Estimated/Reported
Java/Bali	***4,315***	***666***	***34569***	***1,027***	***38,884***	***1,693***	***23.0***
Jakarta	0	0	0	5	0	5	0.0
Banten	385	72	0	0	385	72	5.3
Jawa Barat	1,391	272	4,065	235	5,456	507	10.8
Jawa Tengah	797	199	5,330	331	6,127	530	11.6
Yogyakarta	374	28	0	0	374	28	13.4
Jawa Timur	1,209	67	24,789	451	25,998	518	50.2
Bali	159	28	385	5	544	33	16.5
Kalimantan	***272***	***119***	***198,828***	***32,291***	***199,100***	***32,410***	***6.1***
Kalimantan Barat	0	0	22,413	20092	22,413	20,092	1.1
Kalimantan Tengah	0	8	45,411	7787	45,411	7795	5.8
Kalimantan Selatan	127	60	71,492	2314	71,619	2,374	30.2
Kalimantan Timur	145	51	59,512	2098	59,657	2,149	27.8
Eastern	**763**	**259**	**939991**	**203,237**	**940,754**	**203,496**	**4.6**

Region/Province	Unstable risk		Stable risk		All risk		
	Estimated	Reported	Estimated	Reported	Estimated	Reported	Estimated/Reported
Sulawesi	***641***	***197***	***356,320***	***18,727***	***356,961***	***18,924***	***18.9***
Sulawesi Utara	51	0	100,006	178	100,057	178	562.1
Gorontalo	0	4	23,069	175	23,069	179	128.9
Sulawesi Tenggara	71	58	66,532	1,462	66,603	1,520	43.8
Sulawesi Barat	0	0	26,855	752	26,855	752	35.7
Sulawesi Tengah	34	28	75,600	12,524	75,634	12,552	6.0
Sulawesi Selatan	485	107	64,258	3,636	64,743	3,743	17.3
Maluku	***0***	***0***	***149,333***	***15,698***	***149,333***	***15,698***	***9.5***
Maluku	0	0	107,519	11,500	107,519	11,500	9.3
Maluku Utara	0	0	41,814	4,198	41,814	4,198	10.0
Lesser Sundas	***122***	***62***	***295,401***	***75,235***	***295,523***	***75,297***	***3.9***
Nusa Tenggara Barat	122	62	68,676	4,858	68,798	4,920	14.0
Nusa Tenggara Timur	0	0	226,725	70,377	226,725	70,377	3.2

Region/Province	Unstable risk		Stable risk		All risk		
	Estimated	Reported	Estimated	Reported	Estimated	Reported	Estimated/Reported
Papua	***0***	***0***	***138,937***	***93,577***	***138,937***	***93,577***	***1.5***
Papua	0	0	102,906	64,067	102,906	64,067	1.6
Papua Barat	0	0	36,031	29,510	36,031	29,510	1.2
Indonesia	**6,946**	**1,587**	**1,546,752**	**269,115**	**1,553,698**	**270,072**	**5.8**