Priority-setting for malaria control and elimination in Myanmar:

Geographic targeting based on cost-effectiveness

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A thesis submitted for the degree of

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Abstract

In Myanmar, *Plasmodium falciparum* malaria is important because of both the burden of disease and the emergence of parasites resistant to artemisinin-based therapies. In 2012, concomitant with the lifting of international economic sanctions, funding for malaria control and elimination in Myanmar rose significantly. The University of Oxford was asked to support priority setting by assessing the relative cost-effectiveness of insecticide-treated bed nets and community health workers, particularly with respect to planning in the Myanmar Artemisinin Resistance Containment region along the east of the country. In the context of rising artemisinin resistance and, later, the goal of regional malaria elimination by 2030, reduction in malaria transmission was an important consideration in prioritising between interventions.

A cost-effectiveness analysis was undertaken using both a static decision tree model and a dynamic disease transmission model. Supporting work towards this analysis included a systematic review of dynamic-transmission economic-evaluations and the creation of a data repository to collate governmental and non-governmental malaria case records. In addition, initially unplanned work on economic evaluation methodology was completed; identifying challenges in the application of cost utility analysis to this decision problem and proposing a framework for budget-based geographic resource allocation as an adaptation of standard methods.

The results of this work include a tripling of the number of malaria diagnostic reports available between 2012 and 2014 (71% increase in *Plasmodium falciparum* cases) with this data showing a decrease in *Plasmodium falciparum* cases over time, alongside rising testing rates. Cost utility analysis found that, in general, malaria community health workers are more costly yet more effective than insecticide treated bed nets, though in both cases cost effectiveness is very much context dependent. Geographic allocation analyses using both static and dynamic models illustrate the potential for economic evaluation to provide both more detailed and more practical policy recommendations. Parameter uncertainty was explored in both cases. Some township recommendations were robust to both parameter uncertainty and model variation (structural uncertainty). Viewed through the lens of the Reference Case for Economic Evaluation in Low and Middle Income Countries (published during the course of this DPhil), budget-based geographic resource allocation largely adheres to the healthcare economic evaluation principles and offers improvements to dealing with heterogeneity and resource constraints. This DPhil recommends that Myanmar malaria policy is tailored to reflect geographic variation in intervention cost-effectiveness, rather than focusing on universal coverage, and illustrates a framework for economic evaluation to support budget-based geographic allocation.

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The author was the primary contributor to all material presented in this thesis with support from DPhil supervisors. Additional contributions by others are outlined below.

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Chapter 3: Primary author with review from DPhil supervisors and support in cross-checking a subset of literature review papers against a checklist of reporting standards

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Drake T, Kyaw S, Kyaw MP, White L, Smithuis F, Day N, Cost effectiveness and resource allocation of malaria control in Myanmar: A modelling analysis of bed nets and community health workers. Malaria Journal (2015) 14:376

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List of Abbreviations

3MDG	Three Millennium Development Goals Fund
APLMA	Asia Pacific Leaders Malaria Alliance
BMGF	Bill and Melinda Gates Foundation
CCA	Cost Consequence Analysis
CEA	Cost Effectiveness Analysis
CET	Cost Effectiveness Threshold
CHEERS	Consolidated Healthcare Economic Evaluation Reporting Standards
CHW	Community Health Worker
CUA	Cost Utility Analysis
DALY	Disability Adjusted Life Year
DMR	Department of Medical Research
DT-EE	Dynamic Transmission Economic Evaluation
GCEA	Generalised Cost Effectiveness Analysis
GDP	Gross Domestic Product
GMS	Greater Mekong Subregion
HIC	High Income Countries
HITAP	Heath Intervention Technology Assessment Programme (Thailand)
ICER	Incremental Cost Effectiveness Ratio
IP	Implementing Partner
ITN	Insecticide Treated Bednet
LMIC	Low and Middle Income Countries
MARC	Myanmar Artemisinin Resistance Containment Region

MOCRU	Myanmar Ocford Clinical Research Unit
MORU	Mahidol Oxford Tropical Medicine Research Unit
NMCP	National Malaria Control Programme
QALY	Quality Adjusted Life Year
PSA	Probabilistic Sensitivity Analysis
WHO	World Health Organisation
CHOICE	Choosing Interventions that are Cost Effective
YLL	Years of Life Lost

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INTRODUCTION SECTION

Chapter 1 Healthcare priority setting

1.1 Chapter summary

Healthcare economic evaluation is a tool used to inform healthcare decisions by comparing the costs and consequences of alternative courses of action. The field is relatively new, today's most common methods originated in the 1970's and initiatives seeking to both develop and standardise methodology are ongoing. Cost-effectiveness analysis (CEA), a standard healthcare economic evaluation framework, compares courses of action by dividing the difference in costs by the difference in effects; the so-called incremental cost-effectiveness ratio (ICER). A critical weak point in contemporary CEA is the difficulty in defining an appropriate cost effectiveness threshold; a metric that defines the ratio of costs to health gains that should be expected for spending to be considered cost-effective. This is especially true for most low and middle income countries. Notable initiatives to support healthcare economic evaluation in global health are the World Health Organisation's Choosing Interventions that are Cost-Effective programme (WHO CHOICE) and, more recently, a methodological Reference Case developed by the International Decision Support Initiative and backed by the Bill and Melinda Gates Foundation.

1.2 Healthcare priority setting and economic evaluation

At the most general level, healthcare spending improves population health through the purchase of healthcare services. In addition to the financial or economic[1] cost of these goods or services there is an opportunity cost. That is, a decision to use resources in support of one healthcare programme means these resources are not available to use elsewhere. This opportunity cost is the driving motivation behind healthcare priority setting. Prima facie, spending money on healthcare is good and recommendations not to fund particular policies can be unpopular. Yet since demand for healthcare will always exceed the supply of resources, poor healthcare spending decisions effectively prevent the existence of more beneficial alternatives. The principle of opportunity cost and the healthcare foregone by poor healthcare spending decisions underpins the importance of well-informed priority setting.

In market-based provision of healthcare, priority setting is democratised through the separate choices made by individuals when consuming healthcare. However, as famously argued by Kenneth Arrow, there are several aspects of healthcare that constitute significant barriers to optimal distribution of resources by markets (1,2). Limitations of market-based provision of healthcare include the asymmetry of information between the patient and healthcare worker and their roles or agency in decision making. That is, the complexity of modern medical knowledge and available interventions is such that patients, unlike regular consumers in a market, do not possess the relevant information to decide whether to take a

[1] Economic cost: The value of goods or services expressed in monetary terms, rather than the money required or used to purchase them. For example, donated good have an economic cost but no financial cost.

particular course of action. As such, an issue of agency arises where the healthcare worker must guide the patient through the decision-making process, often advising on what they believe to be the best approach (with corresponding uncertainty that the agent must also decide on whether and how best to convey to the patient). A further limitation to market-based provision of healthcare is the role of externalities. A competitive market model assumes only the individuals involved in a transaction are affected by it taking place. In healthcare, and in particular for infectious diseases, the actions of individuals can affect the health of others. For example, prevention or treatment for one person affects onward transmission of disease and therefore affects the risk of disease faced by the wider population. Markets do not factor in these externality effects when allocating resources and may therefore produce sub-optimal results. Most societies today draw on some mix of public and private healthcare services. Healthcare economic evaluation, defined as "the comparative analysis of alternative courses of action in terms of both their costs and consequences" (3), is an increasingly common approach used to support healthcare priority setting in the provision of public healthcare services, including those provided by non-governmental organisations.

Early work in the 1970's by Weinstein et al. on optimisation using ratios of costs and consequences in time developed into contemporary cost-effectiveness analysis (4,5). A decade later in 1987, Drummond and others published "Methods for the Economic Evaluation of Healthcare Programmes", a seminal textbook now in its fourth edition (3), that brought a degree of standardisation to healthcare economic evaluation methods. Further standardisation, was brought through the introduction of a methodological "reference case", that emerged from a consensus panel in the US in 1996 (6), with a second iteration of

the initiative in 2016 (7). Similarly in the UK, a set of economic evaluation guidelines published in 1996 (8) and statement on best practices in 2013 (9), have supported the standardization of methods and reporting, improving the comparability of results from different studies.

Today, the core principles of healthcare economic evaluation are widely endorsed and in some countries, explicitly integrated into governmental health policy development processes, particularly where public policy plays a central role in healthcare. Notable institutions include the National Institute for Health and Care Excellence (NICE, est. 1999) in England and Wales, the Health Intervention Technology Assessment Programme (HITAP, est. 2007) in Thailand and the World Health Organisation's initiative on CHOsing Interventions that are Cost-Effective (WHO CHOICE, est. 1998). A recent systematic review identified 2844 economic evaluations published between January 2012 and May 2014 worldwide with most undertaken by analysts in Europe or North America (10).

1.3 Healthcare economic evaluation methods

Healthcare economic evaluation is an umbrella term for a range of approaches used to assess the cost and impact of healthcare choices in order to set priorities. Economic evaluation frameworks are differentiated by how health outcomes are valued. Here we focus on the most commonly used frameworks, cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). While CUAs are commonly described as "cost-effectiveness analysis" in a general sense, they specifically refer to evaluations where health outcomes are estimated in terms of health utility, for example Disability Adjusted Life Years (DALYs) or

Quality Adjusted Life Years (QALYs)[2]. Cost-effectiveness analysis, in the narrow technical sense, describes studies using metrics for health outcomes that more directly relate to the condition of interest, for example the number of people tested or treated. In contrast, cost-benefit analysis (CBA) values outcomes in monetary terms. While this has several advantages including easier aggregation and comparison of health and non-health outcomes, there are challenges in placing a monetary value on health. Cost-Consequence Analysis (CCA) summarises quantified and non-quantified impacts alongside expected costs in a single table. Since impacts are not aggregated into a single quantitative metric the reader is instead invited to weigh the balance of costs and consequences in their personal judgement. This can be useful where impacts are not easily combined, for example, programmes with multi-sectoral impacts such as school-based health programmes (11,12). There are also some benefits in terms of communicating both quantitative and qualitative information on the determinants of intervention costs and consequences. For these reasons CCA can be a useful addition to CEA/CUA (11,13,14).

Efforts have been made by some to broaden the evaluative space in terms of outcome measurement and valuation. Standard CUA values QALYs or DALYs equally regardless of the individuals or populations affected. This is captured by the apparently egalitarian refrain "a QALY is a QALY is a QALY", reflecting that health utility metrics are treated in the same way regardless of the demographic, socioeconomic or other characteristic of the populations concerned. While CUA is an extra-welfarist framework as it focuses on health rather than a broader conception of general utility, some have made a case for adaptations to the quasi-

[2] Such evaluations are not utilitarian per se as they capture only health-related aspects of utility.

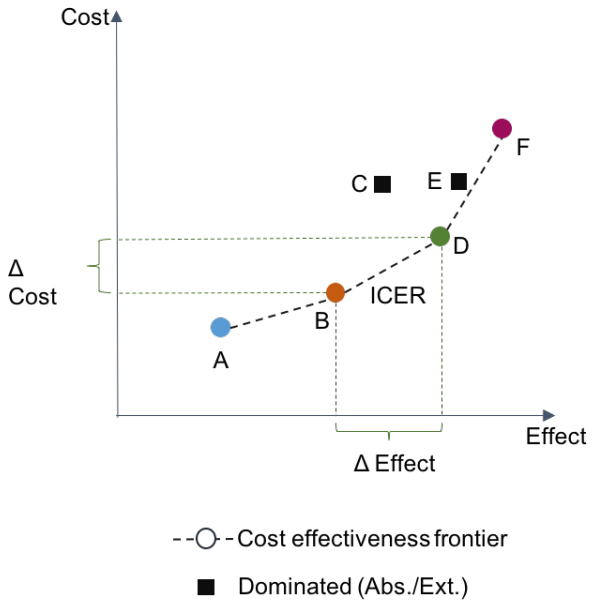
utilitarian CUA framework (15). For example, equity preferences may be incorporated into valuation through weighting coefficients to give greater value to health gains in less advantaged populations (16). Perhaps even more ambitiously, health economists are working towards operational forms of Amartya Sen's capability theory (17,18) as an alternative to health utility in outcome evaluation (19–22).

As mentioned previously, CEA and CUA compare the cost of an intervention with health gains through a ratio; the incremental cost-effectiveness ratio (ICER). That is, a set of mutually exclusive alternative choices is evaluated by comparing the incremental gains with the incremental costs of choosing one option over another (see Box 1). The incremental nature of cost-effectiveness analysis is key to obtaining a result that reflects decision problem. It is relatively easy for a new technology to show value compared with a hypothetical "do nothing" scenario, it is more difficult to demonstrate value compared with the current technology in use. The new technology if commonly more effective but more expensive and to be adopted must demonstrate that the difference in effect is worth the difference in cost.

Box 1: Priority setting using cost-effectiveness or cost utility analysis: A brief summary

Comprehensive descriptions of economic evaluation methods can be found elsewhere (23–25). The most common frameworks, cost-effectiveness or cost-utility analysis, typically include the following steps:

- Define a decision problem in terms of a set of alternative healthcare technologies or services (interventions)
- Measure or model intervention costs and effects
- Express the differences between competing interventions on the cost-effectiveness frontier* as Incremental Cost-Effectiveness Ratios (ICERs)**
- Use a cost-effectiveness threshold (CET) to define the intervention with the highest ICER below the CET as the optimal choice



* All interventions that are not dominated. Interventions A, B, D and F in the example.
** The difference in costs between two alternatives divided by the difference in effects, reflecting the value in replacing one intervention with another.

1.4 Measure or model

There are broadly two approaches to estimating intervention outcomes, measurement and modelling. Randomised controlled trials are a common source of measured outcomes for economic evaluation. The advantages of trial based evaluations are that the trial will generate evidence on health effects and trial data collection systems can often be

harnessed to gather information on resource use. However, trials are also typically designed with clinical or epidemiological rather than health economic end-points in mind and post-hoc or bolt-on economic evaluations can struggle to gather the information required. Trials are usually conducted on a specific population in a specific place and, if the trial is designed to assess efficacy rather than effectiveness, may not be representative of the costs and effects of implementation in the wider population. Additionally, trials may not use comparator group appropriate for a comprehensive decision analysis. Even if well designed for economic evaluation, trials are expensive, requiring resource intensive implementation, monitoring and data collection (24,26).

Economic evaluations are not necessarily linked with active trials and can instead draw on published literature and non-research implementation of interventions of interest. This type of non-trial associated modelling is comparatively inexpensive and while model inputs may, in some cases, be less precise than trial results, they can be more relevant. Additionally, non-trial models can assess a greater range of alternative courses of action than would be feasible, affordable or even ethical in a randomised controlled trial. Non-trial economic evaluation modelling can provide comparatively inexpensive synthesis of available information to support a policy question.

When modelling infectious diseases it may be important to capture not only the direct health benefits of interventions but the effect on disease transmission and the subsequent indirect or externality effects on population health. In healthcare, vaccination is the classic example. The result of mass vaccination is protection not only for those vaccinated but for the population in general through the effect of “herd immunity”. If these externality effects

are not included in the economic evaluation, results may underestimate the true cost-effectiveness of the vaccine. One option available to include these effects in the economic evaluation is to use a model that simulates the transmission of disease over time, so-called dynamic transmission modelling (27,28).

1.5 Cost-effectiveness thresholds

Central to CEA and CUA, and the subject of much debate, is the cost-effectiveness threshold (CET) (4,5,29–38). As outlined in Box 2 the CET is the decision rule used to determine which of a set of mutually exclusive alternative programmes or technologies should be funded. For example, if a CET is set at US$ 1000 per DALY averted then interventions with an ICER less than this value can be considered cost-effective and the option with the highest ICER below the threshold is the optimal choice. CETs can be considered to represent the willingness-to-pay for an additional unit of health or the opportunity cost or healthcare spending at the margin.

Ochalek et al. introduce the concept of supply- and demand-side perspectives on the cost-effectiveness threshold, broadly reflecting resource constraints and societal norms respectively, and suggest that supply-side definitions of CETs are the most appropriate (36). Methods to estimate the supply-side CET have advanced in recent years. In the UK Claxton et al. estimated the supply-side CET through econometric analysis of comparative spending and mortality across programme budget categories in different primary care trusts (39). The resulting estimate of £12,936 per quality adjusted life year (QALY) was lower than previous thresholds used by UK analysts and decision makers. With respect to demand derived CETs, surveys are commonly used to assess individual, population group or societal willingness-to-

pay for health (40,41), and translated by some as an indication of an appropriate CET for that group. Further discussion of CETs and their application in malaria economic evaluations can be found in Chapter 4.

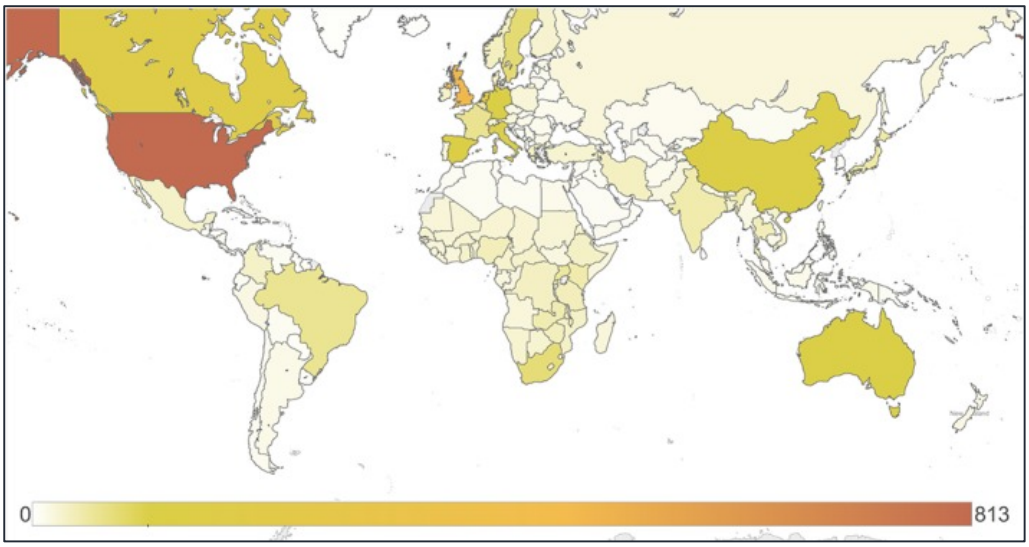
Box 2: Cost-Effectiveness Thresholds

The cost-effectiveness threshold (CET) is considered to represent the willingness-and-ability-to-pay of the Ministry of Health or society in general, and would ideally be set at such a level that it reasonably reflects real budget constraints. In theory the CET is equal to the opportunity cost of alternative public healthcare spending. Defining an accurate CET is a challenge and it is often indexed to the national gross domestic product (GDP) per capita. In low and middle income countries (LMICs), thresholds of 1x and 3x GDP per capita are commonly used (42), though recent studies suggest a lower threshold may be more appropriate (36). An earlier review by Shillcutt et al. summarises the methodological debate in defining CETs in LMICs (43).

1.6 Economic evaluation in low and middle income countries

There is increasing interest in evidence-based priority-setting in low and middle income countries (LMICs). A recent systematic review of the published literature on priority setting frameworks in LMICs found that cost-effectiveness analysis (in the broad sense) was among the most common frameworks with most studies (91%) reporting results in terms of the cost per DALY averted (44). However, relative to high income countries, the number of economic evaluations in LMICs is still low. A recent review of the economic evaluation literature found that 22% of published economic evaluations concern LMICs (4% low income, 18% middle income) (10). A further review of methodological differences between economic evaluations across income groups describes several areas where methods used in LMIC economic evaluation tend to differ from those used in high income settings. In some cases contextual differences will require different methods, however the authors also make some suggestions for improvements including outcome valuation, statistical analysis of cost data, probabilistic sensitivity analysis and the quality of data collection systems (45).

Figure 1: Number of economic evaluations by country 2012-14



Source: Pitt *et al*. (10)

Two initiatives are particularly relevant to economic evaluation methods in LMICs i) the World Health Organisation's Generalised Cost-Effectiveness Analysis (GCEA) framework for priority setting based on an adapted form of cost-effectiveness analysis (46) and ii) the more recent Reference Case, an initiative to support methodological standardisation backed by the Bill and Melinda Gates Foundation (47). Developed at the turn of the millennium, GCEA is a broad framework for health sector priority setting in contexts where health sector optimisation based on incremental analysis was considered impractical. The key innovation is the use of a null comparator when calculating cost-effectiveness ratios.

In GCEA the analyst must *"consider what would happen, starting from today, if all resources in the health sector could be reallocated. The counterfactual against which all interventions should be evaluated is what would happen if none of the current set of interventions were*

implemented. The cost-effectiveness of all possible interventions - individually and in combination - is assessed in relation to this".

This provides a common baseline for league table comparison of any intervention or policy with any other, rather than the set of mutually exclusive alternatives for a single decision problem. While GCEA was developed as a compromise to develop useful generalisable results in absence of superior evidence (48), for some the generalisation approach risks missing crucial local information that could affect policy choices (49). The more recently developed Reference Case for Economic Evaluation aims to improve relevance, reliability and consistency in the economic evaluation evidence base, particularly for LMICs. The Reference Case defines a set of core principles to guide economic evaluation practices as well as specific and prescriptive methodological approaches (47). A recent review by Gray and Wilkinson describes the development of economic evaluation methods including extended discussion of these two initiatives (50).

Chapter 2 Malaria in Myanmar

2.1 Chapter summary

In recent years, the rise in efforts to control and eliminate malaria, particularly *Plasmodium falciparum* malaria, has led to a significant decline in associated mortality and morbidity. Nevertheless, the global burden of disease is still substantial. Myanmar has the highest burden in South East Asia and, in addition to this, has a strategic importance for global malaria control in preventing the spread of *Plasmodium falciparum* strains resistant to artemisinin-based treatments. At the outset of this research, artemisinin resistant strains had been identified in Cambodia and regional malaria control initiatives were directed towards preventing the spread of these strains west through Myanmar, onto South Asia and ultimately Africa. The Myanmar Artemisinin Resistance Containment region (MARC), 52 townships in eastern Myanmar, was defined as a priority area for malaria intervention. Coincident with political changes in Myanmar, international funding for malaria rose sharply from 2012. A central question in malaria policy discussions in Myanmar concerned the relative prioritisation of malaria prevention through (long lasting) insecticide treated bed nets versus improved diagnosis and treatment at the village level, through the training and continued support of community health workers. This thesis describes efforts to assess cost-effectiveness and priority setting of these interventions in the MARC region and methodological work undertaken in this process.

2.2 Malaria

Malaria in humans is caused by five species of the *Plasmodium* parasite; *falciparum, vivax, malariae, ovale* and *knowlesi*. *Plasmodium falciparum (Pf)* is the most widespread and carries a greater likelihood of severe illness. In humans *Plasmodium* parasites invade and proliferate within erythrocytes causing cytolysis or cell rupturing and capillary blockage. Without treatment this can lead to severe pathology including cerebral oedema, severe anaemia and can be fatal (51). Transmission of infection occurs via female anopheline mosquitos which typically feed indoors and at night though behaviour varies between species and crepuscular biting is thought to be more common in South East Asia (52,53). Populations in Africa below the Sahel suffer the majority of the global malaria burden but malaria transmission remains endemic throughout much of the tropics[3] (53).

The twenty first century has seen a surge in efforts in against malaria catalysed by several global initiatives including the Millennium Development Goals (now succeeded by the Sustainable Development Goals), the Global Fund to fight HIV/AIDS, Tuberculosis and Malaria, the President's Malaria Initiative, the Bill and Melinda Gates Foundation and others. With this support total annual spending on malaria has grown to over US$ 2.6 billion globally (56). In most endemic countries in Asia and Latin America, and increasingly in Africa, malaria decision making takes place within the context of a disease elimination goal, though the best path to achieving this goal is far from clear. Key questions facing malaria decision

[3] Though historically malaria has been endemic in temperate parts of North America (54) and Europe including as far north as Finland (55).

makers are whether, where and when to deploy several interventions and programmes, including:

- Scale up vector control (typically through long lasting insecticide treated bed nets)
- Scale up access to malaria diagnosis and treatment
- Forms of mass drug administration (including mass screening and treatment)
- Active case follow-up
- Deployment of an emergent malaria vaccine

The current availability of resources represents an arguably unprecedented opportunity to reduce the global public health burden of malaria and perhaps eradicate the disease altogether. Promising gains have been made, with global malaria associated mortality decreasing by 60% between 2000 and 2015 (down to an estimated 438,000 deaths) (56). It is important to continue to make the most of the currently available resources by spending in a way that maximises impact.

2.3 Myanmar health system

Myanmar is a geographically and demographically diverse country of 51.4 million people comprising a large number of ethnic groups and 137 officially recognised languages (57). During the course of this DPhil Myanmar has undergone historic political changes. Following decades of military rule and internal conflicts a renewed process towards peace and democracy has been underway and has seen the lifting of many economic sanctions previously imposed by the international community. A general election held on 8th November 2015 was won by the National League for Democracy (NLD) led by the Nobel Peace prize winner Aung San Suu Kyi. Daw Suu Kyi is prevented from holding presidential

office as her sons hold British citizenship, though is considered by many to be the *de facto* head of state.

The health system in Myanmar is chronically under resourced. In 2012 government spending on public health was just US$ 1.6 per person per year, with out-of-pocket payments by households accounting for almost 80 percent of total health spending (58). However, there are signs of improvement. A public expenditure review by World Bank reported increasing spending on health and other development priorities. Between 2009 and 2014 there was a nine-fold increase in Ministry of Health spending (59). In December 2016 the NLD government published a brief National Health Plan aiming to "extend access to a Basic Essential Package of Health Services (EPHS) to the entire population by 2020 while increasing financial protection" (60).

The complexity of the Myanmar health sector is a significant challenge. While the Ministry of Health plays a central role, the political administration of the country is fragmented, with public services run by local political groups in some semi-autonomous regions. Moreover, a recent review identified 14 international donor organizations, a further 57 international non-governmental organisations and various national and grass-roots non-governmental organisations playing substantial roles in Myanmar healthcare (61).

2.4 Malaria in Myanmar and the Greater Mekong Sub-Region

The Greater Mekong Sub-region (GMS) is comprised of the countries broadly surrounding the Mekong river in South-East Asia, including Cambodia, China (specifically Yunnan

Province and Guangxi Zhuang Autonomous Region), Laos, Myanmar, Thailand, and Vietnam. There is significant international interest in eliminating *Pf* malaria from the GMS not only because of the health burden but because of the risk posed by emerging *Pf* strains that are resistant to treatment with artemisinin combination therapies (ACTs). Artemisinin based therapies are the first-line malaria treatment for most the world including Myanmar. Unfortunately, as happened several times to previous antimalarials (62), strains of *Pf* that are resistant to artemisinins have emerged. This was identified first in Cambodia (63) and more recently has been documented in Myanmar (64–66) and genetic marker of resistance (K13) has been identified that will aid surveillance of these strains (67). The spread of artemisinin resistant *Pf* to South Asia and Africa would have severe health and economic consequences (68). Myanmar constitutes a potentially critical "corridor'" of resistant strains to South Asia, and efforts to rapidly reduce transmission are, in part, a response to this risk, though most recent genetic evidence suggests that resistance in different locales might be emerging de novo rather than spreading from one place to another (65).

For these reasons elimination of *Pf* malaria is considered an international priority and is well supported by several major donor organisations including the Bill and Melinda Gates Foundation, The Global Fund and several bilateral donors such as USAID and United Kingdom's Department for International Development (DfID). Malaria control and elimination activities are often carried out by international or local non-governmental organisations in collaboration with the governmental National Malaria Control Programmes (NMCPs). The importance of reaching migrant and mobile populations is well recognised and there is interest in improving cross-border collaboration to offer malaria prevention and access to treatment. Nevertheless there are multiple stakeholders in decision making for

national and regional malaria control and elimination and it is in this context that this project seeks to inform the planning process initially in a sub-region of Myanmar.

Myanmar has the highest burden of malaria in the GMS. The World Health Organisation estimates there were between 170,000 and 340,000 cases of malaria in Myanmar in 2015 (53). Approximately 32.1 million people (60% of the country) are thought to live in areas with some degree of malaria transmission. Until circa 2012 it was difficult for many international organisations to operate in Myanmar due to political and economic sanctions. Due in part to the previous political isolation of the country, the published English-language evidence base for malaria in Myanmar prior to 2012 is strikingly thin, comprising only 5% of published English-language malaria research in the GMS between 1933 and 2012 though it has the greatest burden of disease (69). As of 3rd January 2016 47.7% of articles on PubMed with “malaria” and “Myanmar” included in the title or abstract were published since 2013, suggesting an increase in malaria research in recent years.

Malaria in Myanmar is thought to be predominantly transmitted by mosquitos belonging to the *Anopheles dirus* and *Anopheles minimus* complexes, although a wide variety of other species can also be found (53,70). Both *A. dirus* and *A. minius* exhibit outdoor resting and feeding tendencies, which may reduce the effectiveness of key vector control interventions including indoor residual spraying (IRS) and insecticide treated bed nets (ITNs) (70). Malaria transmission exhibits unimodal seasonality characterised by a peak in incidence following high precipitation between April and September. Outbreaks of malaria are precedented but, according to government reports, are in decline (71).

There is also important, if poorly characterised, heterogeneity in Myanmar malaria epidemiology. In common with much of the rest of the Greater Mekong Sub-region, malaria risk is often, though not always, associated with forested areas, and therefore high risk groups include communities living within the forest, forest workers and migrant populations (72). A study in Kachin state found the presence of both *P. falciparum* and *P. vivax* malaria species and that *P. vivax* malaria was comparatively more likely to affect younger people (73).

Acquired or hereditary population characteristics play a key role in the epidemiology of malaria. The prevalence and importance of asymptomatic malaria in Myanmar is not well understood. Textbook theory holds that in lower transmission settings such as Myanmar, asymptomatic malaria is less prevalent, and therefore less important, due to weaker exposure-dependent malaria immunity. However, asymptomatic infections may be critical to the continuation of malaria transmission between seasonal transmission peaks; micro-level heterogeneity of transmission may mean some populations or individuals do acquire partial malaria immunity and consequently constitute an important asymptomatic reservoir of malaria parasites (74).

2.5 Myanmar malaria policy and the MARC region

The initial policy response by the Myanmar Ministry of Health and partners to the emerging risk of artemisinin resistant *P. falciparum* strains was one of containment. In April 2011 much of eastern Myanmar was defined as a priority zone for enhanced malaria intervention and surveillance (75). This zone, termed the Myanmar Artemisinin Resistance Containment

(MARC) region includes a population of 8.71 million and differentiated on two discreet geographic tiers:

Tier 1 - Tanintharyi division, Mon state and Shwegyin township in Bago East.

Tier 2 - Kayin state, Kayah state, four townships in Kachin and the remaining 13 townships of Bago East

Box 3: Myanmar Artemisinin Resistance Containment (MARC) Framework

The framework identifies seven aims for malaria control within the MARC regions.

- To improve access to and use of early diagnosis and quality treatment according to the national treatment guidelines
- To decrease drug pressure for selection of artemisinin resistant malaria parasites by stopping the use of artesunate monotherapies and sub-standard/fake drugs
- To limit the transmission of malaria by vector control and personal protection
- To increase migrant/mobile populations' access to and use of malaria diagnosis, treatment and vector control measures including personal protection
- To support containment of artemisinin resistant parasites through advocacy and behaviour change communication
- To conduct studies and do operational research to support the development of evidence-based containment policies and strategies
- To provide effective management and coordination to enable rapid and high quality implementation of the containment strategy

MARC Tier 1 geographic region within Myanmar

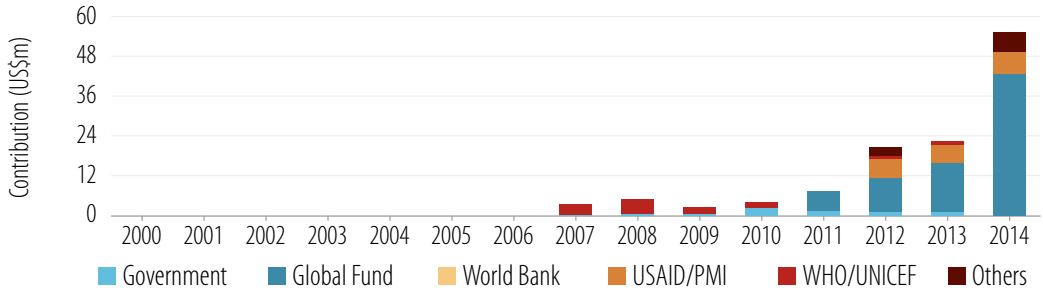
Source: Myanmar Artemisinin Resistance Containment Framework (75); map image produce by author.

Subsequently, the emphasis on containment of resistance was dropped in favour of malaria elimination in Myanmar which aligns with regional goals for elimination in the Greater

Mekong Sub-region (76) and 22 countries in Asia and the Pacific that have committed to malaria elimination by 2030 under the umbrella of the Asia Pacific Leaders Malaria Alliance (77). The 52 MARC townships remained a priority for malaria intervention within the context of countrywide elimination campaign.

Coincident with the political changes in Myanmar and the emergence of artemisinin resistant parasites, there has been a very substantial increase in malaria funding in Myanmar, from less than US$5m prior to 2011 to over US$50m in 2014 (Figure 2). With further increases expected to achieve the goal of elimination by 2030.

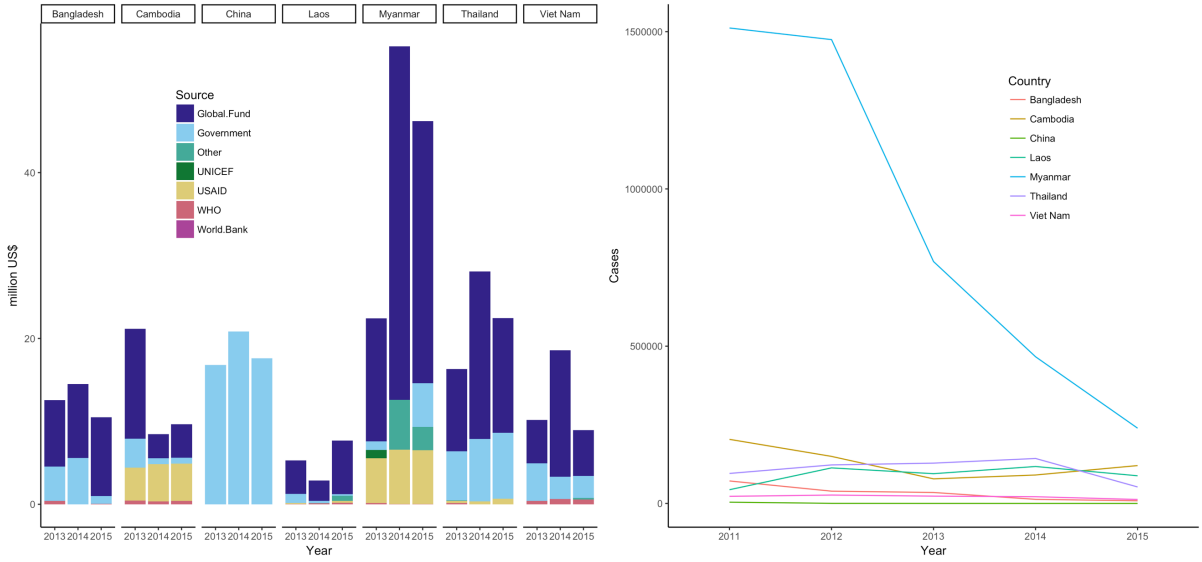
Figure 2: Financing for malaria control and elimination in Myanmar, 2000-2014



Source: World Malaria Report (53)

To place this in context, malaria spending and *Pf* cases as reported to WHO by countries in the Greater Mekong Sub-Region (plus Bangladesh to Myanmar's west) are presented in Figure 3. Reported malaria spending in Myanmar is greater than any other country in the region. Reported *Pf* burden is also greater but declining. Notably, USAID prioritises Myanmar and Cambodia and in China malaria control and elimination is entirely domestically financed.

Figure 3: P*lasmodium falciparum* burden and malaria spending in selected countries



Source: World Malaria Report (53)

While there are various malaria control tools currently available, two interventions receive the majority of malaria control funding in Myanmar:

- Insecticide-treated bed nets (ITN), including long-lasting insecticide-treated nets
- Early diagnosis and treatment through malaria community health workers (CHW)

While financial reports were made available by UNOPS to enable intervention costing, comprehensive historical data on financing by intervention was fragmented across multiple donors and comprised complex contracts often for several activities. A detailed financial review was not carried out as it was considered a lower priority than improving malaria incidence estimates (see Chapter 6).

At the outset of this DPhil in 2013, policy aims for the MARC region centred on universal coverage of ITN with selected allocation of malaria community health workers. However,

some stakeholders maintained that expanding CHW networks should be a higher priority than ITN distribution. In late 2013, the University of Oxford, through the Mahidol-Oxford Tropical Medicine Research Unit (MORU) and the Myanmar Oxford Clinical Research Unit (MOCRU) was asked to contribute to this discourse and address the question: **What is a more cost-effective use of available funds: insecticide treated bed nets or diagnosis and treatment through community health workers?**

The discussion around this question included views from government officials, donors, implementing organisations, research institutions and consultants. Broadly, the case for greater emphasis on ITN distribution centred on the strong evidence base for ITNs as both an effective and highly cost-effective intervention (78,79). ITN distribution is easier to deliver at scale than CHW programmes involving a one-time (or recurrent only over the lifespan of the net) delivery rather than ongoing systems of training, monitoring and support to individuals in communities. Some proponents of ITN investment also considered prevention to be advantageous to treatment in that it stops the problem at source rather than waiting for illness to occur and respond to ameliorate the severity of outcomes through diagnosis and treatment. On the other hand, proponents of greater investment in CHW programmes pointed out that the evidence-base for the effectiveness of ITN is largely based on studies in sub-Saharan Africa and, as noted above, the morning and evening biting habits of mosquito species present in Myanmar would suggest that ITN might be less effective. Moreover, while treatment does directly address health outcomes in clinically ill patients, it also impacts disease transmission. That is, a person with malaria diagnosed and treated quickly will be substantially less likely to transmit the infection onwards, particularly if treated with primaquine (80,81). Lastly, for some stakeholders there was an equity

principle that remote populations should have access to diagnosis and treatment in the eventuality that they become ill, regardless of analysis about where greater gains can be made.

2.6 Research rationale

The malaria economic evaluation evidence base to guide policy makers is substantial and growing. In 2011 a systematic review of the cost and cost-effectiveness of malaria control interventions identified 43 economic evaluations published between 2000 and 2010 (79). A broader review of economic evaluation in low and middle income countries published in 2015 found that malaria comprised 20% (n=41) of the published literature between 2000 and 2013 (82). The most recent and broadest review, identifies a further 29 malaria economic evaluations published between 2012 and May 2014, representing a 13% share of the literature across all disease and income settings (10). Since different time periods are covered by the 2011 and 2016 reviews, there are at least 72 malaria economic evaluations published to date, 40% of which have been published since 2012. While available information on the cost-effectiveness of a range of malaria interventions is increasing, translating this information to inform specific, sub-national malaria policy in Myanmar is challenging.

ITN are most effective against mosquitoes that are nocturnal, endophagic blood feeders whereas most species commonly found in Myanmar tend toward crepuscular and exophagic biting [2–4]. The evidence base for the cost-effectiveness of ITN against malaria spread by the former type of mosquito is strong [5] and previous modelling analysis found that while changes in mosquito biting behaviour could reduce effectiveness, nevertheless ITN could

remain a cost-effective intervention [6]. CHW costs have been estimated in Cambodia [7], Nigeria [8] and across sub-Saharan Africa [9], though none of these studies assessed cost-effectiveness. While the evidence base for malaria interventions is stronger than for many other diseases, it does not provide clear and relevant recommendations in response to the policy question of the moment in Myanmar.

In line with existing best practices a cost-utility analysis was initially planned to assess the cost-effectiveness of malaria insecticide treated bed nets and malaria community health workers in the context of interest; the MARC region. Advocates for each intervention cited the impact on malaria transmission as being an important aspect of the expected health impact. For this reason, it was decided to use a dynamic transmission model to estimate intervention impact, incorporating cost information to allow dynamic transmission economic evaluation (DT-EE) (Chapter 8). However, the lead time to develop and apply a suitable DT-EE model is significant and policy makers were keen to receive results as soon as possible. It was agreed to undertake a rapid analysis using a simpler static decision tree model (Chapter 7), while developing the dynamic model. At the outset of this research (and still today, though to a lesser extent) DT-EE was a niche and emerging approach. A literature review was undertaken to better understand the state-of-the-art, particularly in when applied to LMICs (Chapter 3).

Shortly after beginning work on the project, the importance of malaria incidence data and the limitations of the existing malaria surveillance system became clear. In collaboration with the National Malaria Control Programme (NMCP), the Department for Medical Research (DMR) and the World Health Organization (WHO) country office, the MARC

Malaria Data Repository was established and an office opened in the DMR compound in Yangon. The MARC Malaria Data Repository collected, cleaned and aggregated malaria case data from governmental and civil society organisations with malaria testing and treatment programmes between 2012-14 (Chapter 6). Finally, critical review of economic evaluation methods identified several challenges in addressing sub-national malaria control and elimination planning (Chapter 4). In response, a methodological framework for geographic resource allocation based on cost-effectiveness was developed (Chapter 5).

2.7 Aims and objectives

The original aim of this work was to offer recommendations on prioritising spending between bed nets and malaria community health workers in the MARC region, Myanmar. The objectives are:

- Produce initial analysis of the cost-effectiveness of bed nets and community health workers
- Establish a data repository for malaria cases
- Conduct literature review on dynamic transmission economic evaluations
- Develop geographic budget allocation methodology
- Develop dynamic model and apply within a geographic allocation framework using the updated data from the data repository

REVIEW AND DEVELOPMENT OF METHODS

Chapter 3 Dynamic transmission economic evaluation of infectious disease interventions in low and middle income countries: a systematic literature review

3.1 Chapter summary

Economic evaluation using dynamic transmission models is important for capturing the indirect effects of infectious disease interventions. This review examines use of these methods in low- and middle-income countries (LMIC), where infectious diseases constitute a major burden. The review is comprised of two parts i) a summary of dynamic transmission economic evaluations across all disease areas published between 2011 and mid-2014 and ii) an in-depth review of mosquito-borne disease studies focusing on health economic methods and reporting. Studies were identified through a systematic search of the MEDLINE database and supplemented by reference list screening. 57 studies were eligible for inclusion in the all-disease review. The most common subject disease was HIV/AIDS, followed by malaria. A diverse range of modelling methods, outcome metrics and sensitivity analyses were used, indicating little standardisation. 17 studies were included in the mosquito-borne disease review. With notable exceptions, most studies did not employ economic evaluation methods beyond calculating a cost-effectiveness ratio or net benefit, such as probabilistic analysis, value of information analysis, budget consideration or spatial analysis. Many did not adhere to healthcare economic evaluations reporting guidelines,

particularly with respect to full model reporting and uncertainty analysis. We present a summary of the state-of-the-art and offer recommendations for improved implementation and reporting of health economic methods in this crossover-discipline.

3.2 Background

Economic evaluation of infectious diseases can be complex due to the additional indirect effects of infectious disease interventions. That is, a treated or prevented case is a direct outcome in itself but may also reduce disease transmission including mediation by host immunity and drug resistance. Capturing these additional effects is particularly relevant for interventions and strategies aimed at reducing transmission of infectious diseases and their elimination.

The more commonly used tools of health economic evaluation modellers such as decision trees or 'Markov' models[4] seldom capture these transmission effects. Transmission effects are the focus of the usually separate field of infectious disease mathematical modelling, which aims to simulate transmission in a human population based on human behaviour, biology and epidemiology of disease. By incorporating information on intervention costs and cost of illness, transmission models can be used for economic evaluation, thus capturing both the direct and indirect effects of an infectious disease intervention in the evaluation. This is particularly important for the evaluation of interventions and policies that seek to reduce the transmission of disease, such as mass vaccination, in contrast to interventions

[4] In health economics a Markov model typically uses a pre-defined force of infection. Dynamic transmission models may also hold Markov properties but are not usually referred to as Markov models.

that principally seek to improve direct health outcomes without necessarily impacting disease transmission, such as case management of severe illness. While these joint models can be complex and computationally intensive, they are becoming more widely used as the computing capacity readily available to researchers continues to rise.

In 2011, Jit and Brisson published an introduction to methods for modelling infectious diseases for decision analysis (a broader discipline that encompasses economic evaluation) (83) and in 2012 a working group report by Pitman et al. offered some 'best practices' in dynamic transmission modelling for pharmacoeconomics (27). In this review, the term dynamic transmission economic evaluation (DT-EE), is defined as a study using a model where the force of infection is dependent on the model state in a previous time-step and that makes a comparison of the costs and effects of one or more interventions or events. DT-EE methodology has thus far been developed primarily by researchers in HIC settings. Yet, infectious diseases are overwhelmingly a problem of low- and middle-income countries (LMICs), where evidence-based decision making stands to make a far greater impact on health. Mosquito borne diseases such as malaria and dengue are a major burden in LMICs yet almost absent from HICs. In recent years resources available for the control and elimination of mosquito borne diseases, particularly malaria, have increased dramatically. Political commitment to the elimination of malaria is strong but the practical approach to achieve this remains unclear.

There are no previous systematic reviews on the state-of-the-art of DT-EE, whether in HICs or LMICs, that I have found. This review aims to understand the extent to which DT-EE

studies are being conducted in global health and the quality of this literature base in terms of health economics methodological and reporting standards.

3.3 Methods

The review is comprised of two parts: first, a broad summary of DT-EE studies in all infectious disease areas published in the peer-reviewed literature since 2011; and second, a more in-depth review of DT-EE studies of mosquito-borne disease interventions. The two-part review provides both an understanding of the application of these methods across varied disease specific research 'silos' while also facilitating a more detailed review of a specific disease area. In this case, models of mosquito borne diseases share core structural similarities in the diseases' transmission dynamics, in contrast to different structures for sexually transmitted or airborne diseases for example.

Studies are included in the general review if: i) the paper compares costs and effects of an infectious disease intervention; ii) the model includes a dynamic force of infection (i.e. incidence, a rate at which the susceptible population acquire the infection) which depends on the prevalence of infection at a previous time point; iii) the paper was published between 1st January 2011 and 31st May 2014 and iv) the study focuses partially or entirely on a population in a low- or middle-income country according to World Bank definitions (84). The time period for inclusion in the all-disease review is restricted to recent years due to the time required to screen articles against the inclusion criteria and to focus on the contemporary state-of-the-art in DT-EE. Studies are included in the review of mosquito borne diseases if they meet criteria i-iii above and evaluate one or more interventions against a mosquito borne disease. The publication year restriction is relaxed to include

additional studies identified through further searches and reference screening published at any time.

3.3.1 Search strategy

The literature search is outlined in Figure 4. The MEDLINE database was searched for and was applied to the MEDLINE database. There are four main components to this initial search:

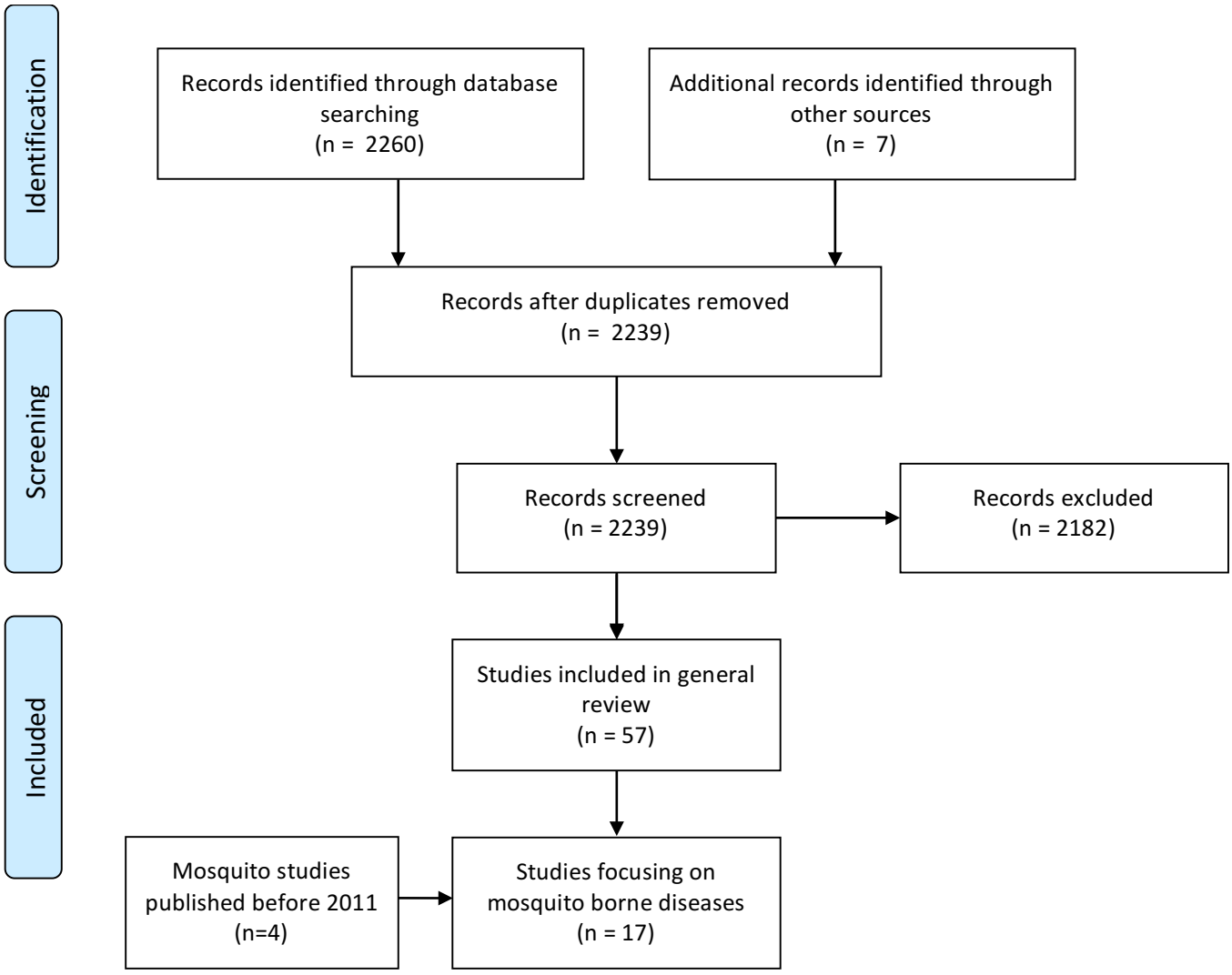
- Cost OR economic* (wildcard is used to include word extensions), AND;
- Infectious OR communicable, AND;
- Dynamic OR transmission, AND;
- Date: Jan 2011 – May 2014

The terms “cost” and “economic*” were restricted to title or abstract, while other terms were applied to any field. This search strategy aims to be as sensitive as possible while returning a feasible number of abstracts to be screened. Secondly, the initial search results were supplemented by a series of additional disease-specific searches:

- (transmission OR dynamic) AND ((compartmental model OR stochastic*) OR individual based model) AND
- cost[Title/Abstract] AND effect*
- Date: Jan 2011 – May 2014
- Specific disease e.g. HIV OR AIDS OR HIV/AIDS
- Disease-specific search terms included: HIV/AIDS, malaria, tuberculosis, influenza, schistosomiasis, polio, respiratory syncytial virus, hepatitis, human papillomavirus,

measles, rabies, cholera, pneumococcal disease, meningococcal disease, dengue, rabies, yellow fever and ebola.

Figure 4: Database search and screening of identified records



Further studies were identified through snowballing, whereby additional relevant papers are found through the reference lists of eligible studies or in other relevant reviews (85–87). Because of the nature of the inclusion criteria, abstracts were often insufficient to judge eligibility and full-text screening was frequently necessary to determine eligibility for inclusion. A cross check of the search was performed on a comprehensive database of health economic evaluations complied by Pitt et al. (10). No additional articles meeting the inclusion criteria were identified.

The review of mosquito-borne disease DT-EEs includes all those in the all-disease review as well additional studies published prior to 2011. Additional studies were identified through disease-specific searches outlined in Figure 4 and screening of references lists of identified studies and a recent review of mosquito borne disease transmission models (86).

3.3.2 Data extraction

Both the general and mosquito borne disease reviews include data extraction on six fields: disease, intervention, model, outcome measure, sensitivity analysis and journal (Table 1). Some studies included more than one disease, outcome measure or sensitivity analysis and so totals may exceed 100%. Data extraction for both the general and mosquito-borne disease reviews was undertaken by two independent reviewers. Differing results were resolved by discussion until consensus was reached.

Table 1: Data extracted for all-disease review

Field	Definition
1. Disease	The infectious disease(s) subject to analysis
2. Intervention	The healthcare technology or programme subject to analysis
3. Model	The type of model used. Options include: Deterministic compartmental Stochastic compartmental Individual based model Multi-model (two or more of the above)
4. Outcome Measure	The metric used to quantify human health. Options include: Disability-adjusted life-years (DALY) Quality-adjusted life-years (QALY) Life-years (LY) Infections averted Number of deaths or mortality rate Net health or monetary benefit (NHB or NMB) Fixed endpoint (e.g. elimination)
5. Sensitivity or uncertainty analysis	The approach taken to quantify potential variation in model results. Options include: Univariate deterministic Multivariate or scenario Probabilistic Structural
6. Journal	The name of the publication featuring the study

Reporting standards have been developed within the field of healthcare economic evaluation so that readers might appraise the methodological integrity of a study. The most recent and widely accepted reporting standard is the Consolidated Healthcare Economic Evaluation Reporting Standards (CHEERS) guidelines (9). In the mosquito borne diseases review all studies, including supplementary materials, were reviewed against the CHEERS

guidelines. Data extraction focused on reporting of the basic economic evaluation framing indicators such as perspective; costs details; model description and; sensitivity or uncertainty analyses (points 6, 8, 9, 13b, 15, 16, 17 and 20b). In addition, the use of advanced techniques were recorded: including probabilistic decision analysis (such as cost-effectiveness acceptability curves), value of information analysis, resource allocation modelling or programme budgeting and marginal analysis and spatial analysis.

The synthesis of the review examines whether relevant health economic methods are commonly employed and well reported and makes recommendations for future studies.

3.4 Results

3.4.1 Search results

The database searches identified 2260 published studies for screening (Figure 4). A total of 57 DT-EEs were identified for the all-disease review (88–144). From this set, 13 studies of mosquito borne diseases, plus a further 4 studies of mosquito borne diseases published prior to 2011, were included in a more detailed review (94–96,100,102,119,120,126–129,132,136,145–149).

Summary of recent DT-EEs in LMICs

By far the most common disease studied in DT-EEs was HIV/AIDS (n=30, 53%), followed by malaria (n=11, 19%). A range of interventions were studied including vaccination (n=14, 25%) and pharmaceutical therapy as either treatment (n=7, 12%), prophylaxis (n=5, 9%) or mass administration (including mass screening and treatment) (n=4, 8%). Eighteen studies

used a model to consider multiple interventions simultaneously (32%). As with economic evaluation in other disease areas, pharmaceuticals and other health technologies are better represented than non-technological interventions (150). This review finds only one study that focuses on a non-technological intervention (behaviour change of concurrency in sexual partnerships) (105).

The majority of studies (n=33, 58%) used a deterministic compartmental model, while eighteen studies (32%) used an individual-based model. Three studies (5%) used a stochastic implementation of a compartmental model and a further three studies (5%) deployed multiple model structures. A range of outcome metrics were reported, the most common of which were infections averted (n=40, 69%) and disability-adjusted life-years (DALYs) (n=22, 38%). The majority of studies (n=41, 72%) reported two or more outcome measures. Elimination was used as an outcome metric by two studies (4%). While not all studies performed explicit sensitivity analysis, all went some way towards exploring variation in results. The majority of studies conducted univariate sensitivity analysis (n=32, 78%), multivariate or scenario analysis (n=27, 66%) and/or probabilistic analysis (n=19, 46%). Probabilistic analysis was in some cases incorporated into the transmission model from the outset rather than conducted as a post hoc sensitivity or uncertainty analysis. Results for the all-disease review are summarised in Table 2. Studies were published in a wide range of journals. The most common journal was PLoS One (n=8, 14%). PLoS Medicine, Vaccine, AIDS, and Malaria Journal had all published four studies each (7%).

Table 2: Review of DT-EEs in low and middle income contexts (all diseases, 2011 to May 2014)

Field	Frequency	%
Disease		
Cholera	1	2%
Dengue	2	4%
HIV	26	46%
Human Papilloma Virus	2	4%
Malaria	11	19%
Measles	3	5%
Pandemic influenza	1	2%
Rabies	1	2%
Seasonal influenza	1	2%
Tuberculosis	2	4%
Hepatitis A	1	2%
Hepatitis B	1	2%
Herpes Simplex Virus	1	2%
HIV and tuberculosis	2	4%
HIV and schistosomiasis	2	4%
	57	100%
Intervention Type		
Contact reduction	1	2%
Diagnostic	3	5%
Mass Treatment	2	4%
Mass Screening and Treatment	2	4%
Multiple	18	32%
Prophylaxis	5	9%
Screening	1	2%
Treatment	7	12%
Vaccine	14	25%
Vector Control	4	7%
	57	100%
Primary Outcome		
Disability adjusted life year	22	38%
Elimination	2	3%
Infections averted	40	69%
Life Year	12	21%
Mortality	16	28%
Net Health Benefit	4	7%
Net Monetary Benefit	4	7%
Quality adjusted life year	14	24%
	114	197%
Model Type		
Deterministic Compartmental	33	58%
Stochastic Compartmental	3	5%
Individual	18	32%

Multi-model	3	5%
	57	100%
Sensitivity Analysis		
Univariate	32	78%
Multivariate or Scenario	27	66%
Probabilistic	19	46%
Structural	5	12%
	83	202%

3.4.2 Review of Mosquito Borne Disease Studies

Of the eighteen studies of mosquito borne diseases sixteen consider malaria interventions and two dengue interventions. Full results for these studies can be found in Table 3. A range of interventions were evaluated including vaccination (n=4, 22%), treatment (n=3, 17%), vector control (n=4, 22%), mass screening (n=1, 6%) and intermittent preventive treatment (IPT) (n=1, 6%). Some studies evaluated multiple integrated approaches (n=4, 22%). The evaluation perspective and time horizon were generally identifiable but often not explicitly stated. The same number of studies purported to take a societal perspective (n=7, 39%) as a provider perspective (n=8, 45%) but it was not always clear that all relevant societal costs, such as patient financial costs and the opportunity costs of patient and caregivers' time, are included in studies reporting a societal perspective. Time horizons varied considerably and most studies did not include time horizon in the sensitivity analysis. There is a loose trend towards shorter time horizons in more recent studies. The most common outcome metrics reported were DALYs (n=9, 50%) and infections averted (n=10, 56%). No studies explicitly cited elimination as an outcome metric; four studies (24%) use the relatively uncommon Net Health Benefit metric. Clear and detailed costing information is only reported in full in a minority of studies. Cost information is in some cases fragmented in different sections of

the paper or supporting documents and is usually not tabulated with the other model parameters.

Half the malaria studies (n=9, 50%) originated from one institution and used versions of the same “Open Malaria” individual-based model. One other malaria study (6%) used a different individual-based model, while the remaining five malaria studies and two dengue studies (11%) used deterministic compartmental models. Most studies (n=11, 61%) referred to previously published work for a full description of the transmission model. In some cases, but not all, a brief description of the model was provided. Conversely, the three studies (17%) by Okosun and colleagues focused primarily on reporting the description and behaviour of the model, such as the identification of equilibria, model boundaries and optimal control points (127–129). In these studies, less attention was paid to the description of and justification of economic or operational factors. A majority of studies conducted a multivariate or scenario sensitivity analysis (n=10, 56%) and just under half conducted probabilistic analysis (n=8, 44%). A common theme in the quantification of parameter sensitivity or uncertainty is that studies frequently focus principally on epidemiological parameters. In the majority of studies (n=10, 56%) cost parameters were not included in the sensitivity or uncertainty analysis or were treated separately. The most common funder was the Bill and Melinda Gates Foundation (n=7, 39%). One study (6%) was funded by a commercial bed net manufacturer.

Table 3: DT-EEs in low and middle income contexts (mosquito borne diseases, any publication year)

First Author	Year	Country or Region	CHEERS review: Perspective (6.)	Intervention (7.)	Time horizon (8.)	Health Outcome Measure (10.)	Describes costs including sources and approximations using opportunity cost (13b.)
Okell	2014	Africa	Provider	Treatment	5 years	Infections averted	Clear description of costs and sources.
Stuckey	2014	Kenya	Societal	Multiple	5 years	DALY & infections averted & mortality	Clear description of costs and sources.
Briët (a)	2013	not specified	Provider ("health system")	Vector control	Lifetime of the intervention	DALY & NHB	Refers to previous paper.
Briët (b)	2013	not specified	Provider ("health system")	Vector control	Lifetime of the intervention	DALY & Infections averted & NHB	Some information but not comprehensive.
Briët (c)	2013	not specified	Provider ("health system")	Vector control	60 years	DALY & NHB	Some information but not comprehensive.
Crowell	2013	sub-Saharan Africa	Provider	MSAT	1 year	Infections averted	Clear description of costs and sources.
Okosun (a)	2013	not specified	Not found	Multiple	140 days	Infections averted	Little information.
Durham*	2013	Brazil	Societal (but only cost of vaccine and cost of illness)	Vaccine	73 years	DALY & NHB	Some information. Cites a study on the cost of dengue treatment in the Americas, little information on processing or generalisability.
Okosun (b)	2012	not specified	Not found	Multiple	1 year	Infections averted	Little information.
Maire	2011	sub-Saharan Africa	Societal	Vaccine	10 years	DALY	Clear description of costs and sources.
Ross	2011	sub-Saharan Africa	Provider (implied)	Intermittent presumptive treatment	10 years	DALY	Some information. Describes intervention costs but does not report case management unit costs in the methods.
Okosun (c)	2011	not specified	Not found	Multiple	100 days	infections averted	Little information.
Luz*	2011	Brazil	Societal	Vector control	5 years	DALY	Clear description of costs and sources (in web appendix).
Tediosi (a)	2009	Tanzania	Societal	Vaccine	10 years	DALY & infections averted	Clear description of costs and sources, although referencing is relied on.
Worrall	2008	Zimbabwe	Provider	IRS	6 years	Cases averted	Clear description of costs and sources.
Tediosi (b)	2006	Tanzania	Societal	Vaccine	20 years	DALY & Life Years & infections averted & mortality	Clear description of costs and sources, although referencing is relied on (reference paper is part of the same journal supplement).
Laxminarayan (a)	2006	sub-Saharan Africa	Societal (implied)	Treatment	10 years	Mortality	Clear description of costs and sources, although cost parameters are not tabulated.
Laxminarayan (b)	2004	sub-Saharan Africa	Provider (implied)	Treatment	5, 10 and 20 years	Infections treated	Clear description of costs and sources, although cost parameters are not tabulated.

*Dengue studies, all others are on malaria.

CHEERS review (continued)	Describe and justify model (15.)			Parameter uncertainty for all parameters and structural uncertainty (20b.)		Advanced Analyses			
First Author	Model type	Model platform	Pre-published model (Y/N)	Sensitivity analysis methods used	Includes cost parameters?	Probabilistic Decision Analysis (Y/N)	Value of information Analysis (Y/N)	Resource Allocation or Programme Budgeting (Y/N)	Spatial Modelling (Y/N)
Okell	Individual	not specified	Y	Univariate & Probabilistic	N	N	N	N	Y
Stuckey	Individual	Open Malaria	Y	Univariate & Probabilistic & Structural	Only univariate	N	N	N	N
Briët (a)	Individual	Open Malaria	Y	Probabilistic	N	N	N	N	N
Briët (b)	Individual	Open Malaria	Y	Probabilistic	N	N	N	N	N
Briët (c)	Individual	Open Malaria	Y	Scenario & Probabilistic & Structural	N	N	N	N	N
Crowell	Individual	not specified	Y	Multivariate	N	N	N	N	N
Okosun (a)	Deterministic	Mathematica	N	Scenario	N	N	N	N	N
Durham*	Deterministic	not specified	N	Scenario & Probabilistic	Y	Y	N	N	N
Okosun (b)	Deterministic	not specified	N	Scenario	N	N	N	N	N
Maire	Individual	not specified	Y	Probabilistic	Y	Y	Y	N	N
Ross	Individual	not specified	Y	Multivariate	Y	N	N	N	N
Okosun (c)	Deterministic	not specified	N	Scenario	N	N	N	N	N
Luz*	Deterministic	not specified	Y	Probabilistic	Y	Y	N	N	N
Tediosi (a)	Individual	not specified	Y	Multivariate	Mentioned but not quantified in main paper	N	N	N	N
Worrall	Deterministic	Excel	Y	None (in model description paper)	-	N	N	N	N
Tediosi (b)	Individual	not specified	Y	Scenario	Y	N	N	N	N
Laxminarayan (a)	Deterministic	not specified	Y	Scenario	Y	N	N	N	N
Laxminarayan (b)	Deterministic	not specified	N	Univariate	Y	N	N	N	N

The majority of studies (n=14, 78%) did not use advanced health economic methods (Table 3). The study by Maire et al. is a notable exception as it used a complex dynamic transmission model to undertake probabilistic decision analysis and also performed a value of information analysis (120). The two dengue studies also employed probabilistic decision analysis and presented results in terms of a cost-effectiveness acceptability curve (102,119). Okell et al. undertook spatially explicit analysis, applying their model to country specific data in sub-Saharan Africa (126). No studies included resource allocation or programme budgeting in their analysis.

3.5 Discussion

This review outlines the literature base for dynamic transmission economic evaluation in LMICs and appraises reporting practices and health economic methods for a smaller number of studies addressing mosquito-borne disease.

The first section of the review outlines the scope of the literature across all disease areas. The majority of studies consider either HIV or malaria. Both diseases are the focus of major global efforts to reduce disease transmission and both are relatively well financed. The potential impact of efficient resource allocation is therefore greater and research funds are more readily available. There were notably fewer studies on other major infectious disease burdens in LMICs, including tuberculosis, pneumonia and diarrhoeal disease. This is likely to be due to challenges in modelling disease transmission particularly for pneumonia and diarrhoeal disease where multiple aetiologies exist. Tuberculosis, like HIV and malaria, has a dedicated modelling consortium to support a range of modelling studies including DT-EEs (151).

The role of DT-EE is particularly important in the evaluation of vaccinations and in the comparison of multiple interventions. For single intervention evaluations, vaccination was the most common intervention. This is not surprising given the level of investment in the development and implementation of vaccination programmes and that key benefits of vaccination programmes include herd immunity[5] and a reduction in disease transmission which is best captured using dynamic transmission modelling. The largest share of studies evaluated multiple interventions and intervention combinations rather than single interventions. This is probably related to the relative ease with which transmission models can incorporate additional interventions and intervention interactions. Alternative health economic models such as decision trees are usually developed for a specific intervention and although they can be used for comparing multiple interventions, modifying them to include additional interventions and interactions between interventions can be difficult and cumbersome.

The second stage of the review appraises health economic methods and reporting for set of mosquito-borne disease studies using existing guidelines for reporting economic evaluations (9), explores the handling of parameter uncertainty as well as the use of advanced economic methods and makes recommendations for future DT-EE.

Comprehensive reporting is key to good quality economic evaluation. In some cases, very few of the CHEERS checklist points were reported well. While this is understandable in that these studies often originate in the discipline of mathematical modelling, which does not share these reporting norms, transmission modelling studies that make comparisons of cost and health impact are de

[5] Population health impact arising from mass vaccination is greater than the sum of individual vaccine protection. Unvaccinated individuals also benefit from immunity of the 'herd'.

facto economic evaluations. This review finds three areas where reporting can be improved: evaluation perspective, costing and model description.

The perspective of the study should be clearly stated and applied equally to costs and effects. Costing methods and data sources should be clearly described including the approach to discounting, currency exchanges and a justification of what resources were costed. Several studies reference previously published work to describe the transmission model. Full reporting of all model and analytical information in the main body of a paper may not be feasible if the journal does not support technical appendices. However, without clear communication of methods to the reader, complex models must be taken on trust. Where possible model description should be reported in full. Overall, adherence to best practices for undertaking and reporting economic evaluation would improve quality and communication in DT-EEs. Publication of these studies is across a wide range of journals with diverse specialisations. If the rate of publication continues to rise, a dedicated journal may help to improve methodology and reporting practices.

The two studies by Laxminaryan et al. are worth noting in that they tackle the critical question of antimicrobial resistance (145,146). Dynamic transmission models are an important tool in modelling the spread of antimicrobial resistance, and the incorporation of costs into these models has the potential to quantify the economic impact in addition to the health impact. This is a critical component in the evaluation of diagnostics and other interventions that can mitigate the emergence and spread of resistance. The capacity to incorporate the impact of interventions on the dynamics of drug resistance is a further example of the flexibility of dynamic transmission modelling.

Analysis and communication of uncertainty is particularly important in LMIC DT-EEs. A potential risk in layering complex analyses on complex models is that detail and complexity can create a perception of validity. Moreover, in LMICs data collection systems face considerable challenges and the resulting data sets may be far from robust. Thorough sensitivity or uncertainty analysis is therefore essential. While all studies in this review conducted sensitivity analysis to some degree, in many cases the approach was partial or treated economic and epidemiological parameters separately. This is likely because the model is developed as a transmission model which is then adapted to perform economic evaluation but can lead to misinterpretation if confidence or credible intervals are reported for a cost-effectiveness ratio, but only epidemiological parameters have been included. Pitman et al. point out that a comprehensive probabilistic analysis may also be problematic if parameter values cannot be assumed to be independent i.e. if there are unidentified joint parameters (27). However, if researchers can address this then probabilistic analysis is likely to be the best approach to quantifying parameter uncertainty. Indeed, parameter fitting processes more common in transmission modelling methods offer some opportunities for fitting correlated parameters (152). Otherwise, a univariate analysis that includes both economic and epidemiological parameters can highlight key determinants of model uncertainty, allowing direct comparison of uncertainty or sensitivity for all model parameters. A comprehensive appraisal of parameter uncertainty can be supplemented, but not replaced, by further scenario or multivariate sensitivity analysis. This can, for example, elucidate operational decisions such as seasonal timing of vaccination or required vaccine uptake at different assumptions of efficacy.

Box 4: Key recommendations for dynamic transmission economic evaluations

- All epidemiological and economic parameters are fully described and tabulated
- All studies report a basic description of the model structure and key assumptions. For journals that support web appendices the transmission model should be described in full including model equations, software platform and all analytical processes involved in parameterisation.
- Economic parameters are included along with epidemiological and other parameters in sensitivity and uncertainty analyses.
- Where appropriate, studies go beyond simple cost effectiveness ratio or net benefit calculation and employ advanced economic evaluation methods
- If publications in this area continue to rise, a dedicated journal could improve methodology and reporting standards

Source: Author's recommendations

Most studies did not employ advanced health economic methods and went no further with economic analysis than calculating disaggregated costs and effects, a cost-effectiveness ratio or net benefit. Those that did (119,120) illustrate some of the advantages of probabilistic decision analysis, including cost-effectiveness acceptability curves (CEACs), and value of information analysis. For example, the inclusion of CEACs goes some way toward dealing with the uncertainty related to the fact that cost-effectiveness thresholds for LMICs are usually not well defined.

Value of information analysis can indicate the potential value of further research into a decision problem. The key piece of information provided by value of information analyses is typically an estimate of the monetary value of completely reducing uncertainty in the decision problem, known as the Expected Value of Perfect Information (EVPI). If the cost of further research to reduce this uncertainty is greater than this value then the research is not warranted and conversely if the value of information is much greater than the cost of research then further research could be of benefit, depending on the extent to which the uncertainty could be resolved (24). Maire et al. estimate the

EVPI of a pre-erythrocytic malaria vaccine to be $ 1.9 billion, suggesting that further research to better inform the decisions could be worth investment. This type of analysis can be extended to estimate the Expected Value of Partial Perfect Information (EVPPI), the value of reducing uncertainty in a specific parameter or group of parameters, providing more detailed information on the value of uncertainty relating to specific parameter. For example, the potential value of reduced uncertainty in vaccine effectiveness. In general, the application of advanced economic evaluation methods in more DT-EEs could yield useful results.

None of the studies reviewed were found to quantitatively consider resource allocation or programme budgets. This is not usual in cost-effectiveness analysis since the CET should in principle reflect affordability, as discussed in Chapter 1. However, in practice the absence of well-defined CETs in LMICs has led to policy recommendations that are described as cost-effective but are unlikely to be affordable within local resource constraints, discussed further in Chapter 4. Thus, in some cases it may be useful for cost-effectiveness analysis, and therefore DT-EEs, to explicitly consider the budget implications of policy recommendations. A review of priority setting studies including but not limited to cost-effectiveness analyses found that approximately one third considered affordability (44)[6].

This review has several limitations. The set of studies identified was reviewed with the aim of describing the scope, methods and reporting practices of DT-EEs from the perspective of a health economist. An evaluation of transmission modelling methods was beyond the scope of this review. Correctly identifying DT-EEs is a challenge as there is no specific or succinct label for this type of

[6] The author contributed to this review during the course of the DPhil but did not lead and so none of the content has been included in this thesis.

study. Studies can originate from mathematical modelling or economic evaluation disciplines and each has its own standards and reporting norms. Studies that are a combination of both transmission modelling and economic evaluation methods often do not signpost this clearly in the abstract and it was frequently necessary to refer to the full text. Even then eligibility for inclusion in the review was not always clear as economic evaluations that do not dynamically model disease transmission also use terms such as 'dynamic' and 'transmission' (not incorrectly) to describe aspects of their models. The full all-disease review is therefore limited in its time period due to the challenges of the search and screening processes. Despite the challenges in the search, this study identifies two literature sets representing a powerful yet relatively uncommon combination of methods. To our knowledge this is the first review of this literature base.

Dynamic transmission economic evaluation is an emerging field at the intersection of two disciplines and is particularly relevant to LMICs, where infectious diseases constitute an enormous burden on human health. This review outlines the current landscape in this field and identifies priority areas to improve the implementation of methodology and reporting.

Chapter 4 Malaria and economic evaluation methods: Challenges and opportunities

4.1 Chapter summary

There is a growing evidence base on the cost-effectiveness of malaria interventions. However, certain characteristics of malaria decision problems present a challenge to the application of healthcare economic evaluation methods. This chapter identifies five such challenges. The complexities of i) declining incidence and cost-effectiveness in the context of an elimination campaign; ii) international aid and its effect on resource constraints; iii) supranational priority setting, all affect how health economists might use a cost-effectiveness threshold. Consensus and guidance on how to determine and interpret cost-effectiveness thresholds in the context of internationally financed elimination campaigns is greatly needed; iv) Malaria interventions are often complimentary and evaluations may need to construct intervention bundles to represent relevant policy positions as sets of mutually exclusive alternatives; v) Geographic targeting is a key aspect of malaria policy making that is only beginning to be addressed in economic evaluations. An approach to budget-based geographic resource allocation is described in (Chapter 5) and addresses some of these methodological challenges.

4.2 Introduction

There is a growing body of evidence on the cost-effectiveness of malaria interventions. As described in Chapter 2, there are at least 72 malaria economic evaluations published to date, 40% of which have been published since 2012. While dedicated reviews of the cost-effectiveness of malaria interventions are periodically undertaken, the translation of this evidence-base to specific

and detailed malaria control or elimination strategy presents some challenges. During the course of the DPhil working closely with policy makers in Myanmar, several challenges to the translation of economic evaluation evidence to policy were identified. This Chapter describes these challenges and offers some partial solutions for certain decision contexts.

4.3 Elimination: Intervention cost-effectiveness decreases with incidence (or appears to)

In the context of disease elimination it is possible to draw a distinction between two types of economic evaluation i) evaluation of the policy of elimination (or eradication (153)) and ii) evaluation of the component interventions required to achieve elimination.

Economic evaluation of malaria or other elimination campaigns are relatively uncommon; a systematic review in 2015 identified 43 economic analyses though many are not economic evaluations[7] (154). Such evaluations are methodologically challenging due to the complexity of elimination campaigns and expected impacts. In malaria the expected benefits of elimination are not only to population health but various other sectors including, though evidence is mixed: education (155,156), tourism (157), and economic productivity (158,159). Cost benefit or cost consequence analysis (11) can be used to appraise the multi-sectoral impacts of elimination. As a framework cost-benefit analysis is more applicable to the evaluation of malaria elimination as a single policy decision than cost effectiveness analysis which is better suited to routine healthcare

[7] Defined by Drummond et al. as "the comparative analysis of alternative courses of action in terms of their costs and consequences"(23)

priority setting. The seminal cost-benefit work by Sabot *et al*. found that “financial savings should not be a primary rationale for elimination, but that elimination might still be a worthy investment if total benefits are sufficient to outweigh marginal costs” . Reviews of cost-benefit evidence by Mills *et al*. (160) and, more recently, by Shretta *et al*. (161) find that, in general, the benefits of malaria elimination outweigh the costs. However, the quality of evidence and methodologies applied is variable. To capture the full costs and benefits of an elimination campaign, the evaluation time horizon must extend some years beyond the expected date of elimination and consider non-health, macroeconomic impacts. Such analysis inherently entails a great degree of uncertainty, in particular due to influence of secular trends that can play a decisive role in driving transmission. It is very difficult to anticipate the impact of economic development, deforestation or climate change on malaria and such factors could play important roles over the course of 10 or 20 years. There is also a risk of failure, either through never reaching elimination (162) or from a post-elimination resurgence of transmission (163) and these eventualities should be considered explicitly in decision making on malaria elimination.

Routine economic evaluations of malaria interventions typically take shorter time horizons, evaluating the differences in direct health impact or reductions in transmission over the short term or up to the point of elimination (164). Evaluations comparing specific interventions rarely, if ever, include post-elimination benefits. The consequences of this are important when evaluating malaria interventions in the context of elimination since without the quantitative consideration of post-elimination effects, for example the likelihood of malaria resurgence, the cost-effectiveness of interventions may be under-estimated. More precisely, without consideration of post-elimination effects the cost-effectiveness of interventions will appear to decline exponentially as malaria

transmission falls on the path to elimination since the absolute health impact will fall faster than costs.

Malaria intervention costs are wholly or partially fixed with respect to malaria incidence. The costs of prevention activities such as bed net distribution are unaffected by malaria incidence, as is the cost of mass drug administration or improved diagnosis. Even for case management focused interventions, the commodity costs that would be variable with incidence comprise a minor proportion of total programme costs (165). In other words, a non-negligible portion of intervention costs is fixed with respect to malaria incidence. Any decrease in cost due to lower incidence will be proportionally less than the change in health impact and the cost-effectiveness ratio will rise. This is illustrated in Figure 5 with two arbitrary interventions, one with fixed costs with respect to incidence and one with partially fixed costs.

Figure 5: General relationship between intervention cost-effectiveness and declining disease risk

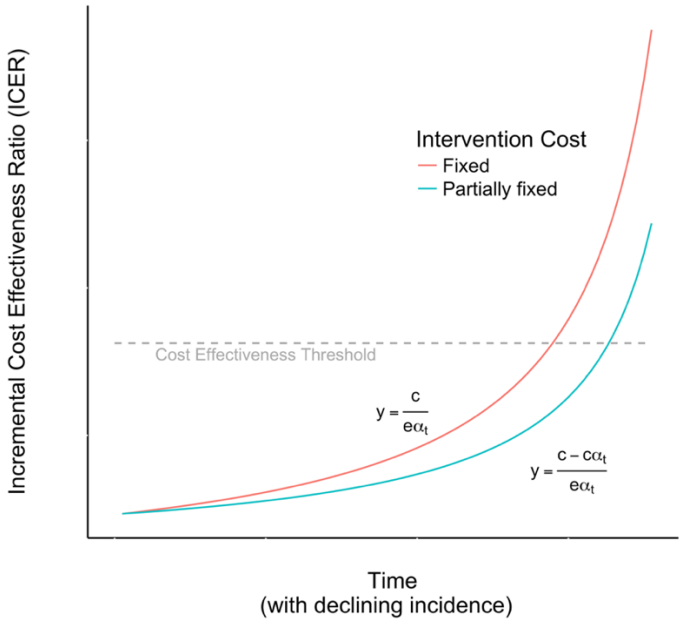


Figure Caption: i) Intervention with fixed costs with respect to incidence, including prevention activities such as vector control or vaccination; ii) Intervention costs are partially variable with incidence, including diagnosis and treatment based interventions. Notation: $\alpha = incidence$; $c = cost$; $e = effectiveness$; $t = time$. A time horizon that excludes post-elimination benefits is assumed.

If the campaign is successful and incidence declines, so too (almost paradoxically) does the apparent cost-effectiveness of the interventions. At some point on the decline in transmission, the relevant incremental cost-effectiveness ratios (ICERs) will no longer fall under the appropriate cost-effectiveness threshold (CET) (see Box 1 and Box 2, Section 1). Prima facie, it is not possible to achieve malaria elimination without investing in cost ineffective interventions because the benefits of investing in the late phases of malaria elimination lie in the difficult-to-define post-elimination period.

An opportunity to move past this challenge perhaps lies in the elimination decision itself. Whether based on quantitative analysis of the costs and benefits of elimination or not, a political decision to

aim for elimination implies that spending on this goal is perceived to be worthwhile. If the elimination goal is a genuine commitment it perhaps implies a shift in the objective of *routine* malaria economic evaluation from allocative efficiency across the health sector in general, to what could be considered technical efficiency within the elimination campaign.

In many cases, malaria elimination will not be achievable within local resource constraints. For various reasons, international donor organisations may support financing of a campaign to achieve malaria elimination. This reality decouples malaria spending from health sector benchmarks of efficiency such as an appropriate CET (if it could be defined). In this case, for decisions on the allocation of malaria funds to specific interventions, the CET may be discarded as the representative of resource constraints in favour of a budget, which for malaria is often known and ring-fenced, at least in the short run (166). Here, the appropriate budget size for the malaria elimination campaign remains an unanswered question; one with diverse stakeholders and further complications to the application of a CET that reflects health sector constraints (section 4.0).

An elimination policy does not mean that routine economic evaluation has reached the end of the road and that all spending to reach this goal can be considered value for money. Economic evaluation remains a valuable source of information that can support planning to achieve maximum impact on health, but consensus and clearer guidance is needed for analysts and users in the application and interpretation of economic evaluations in the context of disease elimination.

4.4 International aid: Available resources exceed local funding constraints

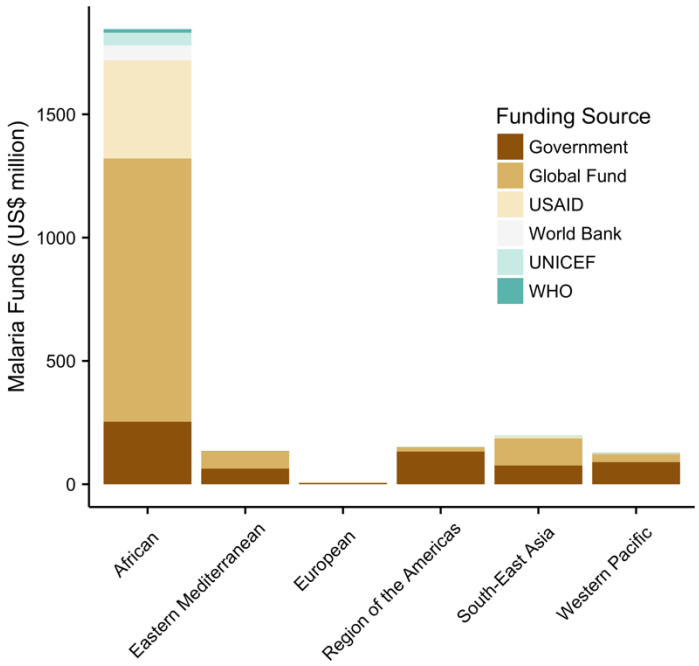
In the past decade, international aid has transformed malaria control and elimination efforts. In 2014, recipient countries reported receiving almost US$ 2 billion in financial aid for malaria control and elimination, comprising 76% of all malaria spending (Figure 6) (56). Putting to one side the

complications of using CETs in the context of disease elimination, how does international aid affect economic evaluation decision rules?

The purpose of international aid is to overcome the severe resource constraints faced by LMICs. While there is a longstanding debate surrounding so-called vertical aid (167,168), earmarked disease specific funding continues to facilitate the implementation of malaria programmes that otherwise would not have been affordable. As outlined in Box 2 Section 1, a cost-effectiveness threshold is used to represent the resource constraints of the society or healthcare provider. Regardless of the cost-effectiveness threshold chosen, on introducing a non-negligible sum of aid the CET would, in theory, need to be raised to reflect the increase in healthcare services now affordable to this society. It may be that across the health sector total aid inflows are not significant however in many countries there is substantial additional financing directed specifically towards malaria control and elimination. In these contexts a CET that accurately reflects governmental or societal constraints may be inaccurate in reflecting resource constraints in malaria planning.

The appropriate CET is typically not well known, particularly in LMICs, and as such base case results should be interpreted using a range of CETs. This can be extended to reflect parameter uncertainty using probabilistic sensitivity analysis with a cost-effectiveness acceptability curve, presenting changes in the likelihood of alternative choices being optimal across a range of CETs. Nevertheless, again, consensus is needed on whether and how to adjust an expected health sector CET where aid affects affordability of malaria control and elimination programmes.

Figure 6: Sources of funding for malaria control and elimination in 2014 (56)



Source: World Malaria Report (53)

4.5 International aid: Supranational priority setting

Economic evaluation typically aims to address allocative efficiency within a nation state. However, before international aid arrives in-country to be allocated to malaria interventions, a series of decisions have already been made regarding which disease areas and which countries to prioritise. The Disease Control Priorities Project, now in its third edition, is the most comprehensive and systematic attempt to facilitate and synthesise evidence on the effectiveness and costs of interventions against major burdens of disease worldwide (169). The section on malaria elimination and eradication synthesises the available evidence but does not attempt explicit priority setting between available interventions or between countries or regions. A further notable initiative is the Copenhagen Consensus which aims to “create a framework in which solutions to the world's big problems are prioritized explicitly” and draws heavily on economic evaluation evidence where

available. The Copenhagen Consensus feature a perspective paper by Raykar and Laxminarayan which includes priority setting of case management and bed net distribution in West Africa and Southern and East Africa (170). Though these recommendations are quite broad compared with the specifics of national or sub-national malaria policy making.

There are several important factors that affect the interpretation of cost-effectiveness evidence for supranational priority setting. As outlined in Box 2, standard decision rules (including GDP indexed CETs) are intended to reflect the resource constraints of a particular country. Therefore, conclusions about whether an intervention is cost-effective (or not) to a large degree reflect the affordability of the intervention in that context as much as the efficiency with which investment may be converted to health gains. For example, a multi country study of pandemic preparedness found that, in general, stockpiling antivirals is not cost-effective for LMICs but may be cost-effective in high income countries (171). As the authors note, the use of GDP based CET's means this conclusion reflects local affordability and does not reflect where investment would yield the most health gains. The reverse would likely be true (172). Decision makers and analysts should therefore not use GDP-based CETs for between country priority setting. Notably, recent work on decision rules for health system strengthening in the context of supranational priority setting focuses on budget allocation rather than threshold analysis (173). To an extent, GDP-based CETs remain relevant to supranational priority setting in terms of allocative efficiency within the health sector that aid is delivered into. However, regional malaria elimination or global eradication is a weakest link global public good. That is, eradication is a public good in that benefits are non-rival and non-excludable and achieving eradication requires effort from all affected countries, with the likelihood of success dependent on the "weakest link" (162). GDP-based CETs are a decision framework for optimal allocation of healthcare resources at the national level yet regional malaria elimination

policy must consider more than simply the efficient allocation of resources from a country perspective.

Supranational priority setting perhaps implies a role for a common or global CET (38), matching the perspective of the funder. That is, health gains are valued equally in all countries and funds directed to where impact is greatest. A global CET might reflect supply-side[8] constraints of international aid budgets or demand-side norms regarding the extent to which poorer countries should be supported to provide healthcare services that would otherwise be unaffordable. GiveWell, an advisory organisation for charity donors, is effectively applying a global CET of US$ 5000 per life saved in their assessments of philanthropic causes and organisations (174). As noted above, cost-benefit analysis often replaces cost-effectiveness analysis for macro-level priority setting. Here the value of health, for example the monetary value placed on a DALY, is analogous to the CET in cost-effectiveness analysis. Raykar and Laxminarayan use common values of $1000 and $5000 per DALY.

Ultimately where real political commitments have been made to achieve malaria elimination then questions on the cost-effectiveness of malaria intervention strategies to achieve this goal are the most relevant question, rather than whether elimination itself is cost-effective. In terms of the overall budget envelope for elimination in different societies and economies (and the potential need for international donors), this will depend on additional factors such as the rate at which local health systems can efficiently absorb additional financing, the period for which this can be sustained, the public-private mix in the health system, equity considerations and the rising ability to draw on in domestic financing.

[8] Ochalek et al. introduce the concept of supply- and demand-side perspectives on the cost-effectiveness threshold broadly reflecting resource constraints and societal norms respectively (36).

4.6 Choosing between compatible interventions

In economic evaluation methodology, a decision problem is typically structured as a set of mutually exclusive alternatives (see Box 1, Section 1). Some malaria decision problems, such as the choice of first line therapy or diagnostic test, fit this framework well (175–177). In other cases, the decision problem entails choosing between interventions that are not mutually exclusive but compatible or even complimentary, such as bed nets and community health workers. In this case, it is not necessary to choose one or the other, it is entirely possible to deliver both. This complicates the rationale for constructing a cost-effectiveness frontier and calculating incremental cost-effectiveness ratios (since these reflect the value of replacing one intervention with another). There are two options available when addressing complimentary interventions.

1. Use a base case comparator scenario for all interventions
2. Construct intervention bundles defined as mutually exclusive alternatives

In the first approach, the costs, effects and cost-effectiveness ratios of intervention options are all expressed in comparison to a common baseline, most likely a null or “no additional intervention” scenario, which is similar in this respect to the generalised cost-effectiveness analysis (GCEA) framework (178). These generalised cost-effectiveness ratios allow the reader to make a judgement about which interventions, in isolation, yield the greatest health gains per unit of investment. The cost-effectiveness rank could be applied to determining the order in which interventions are added to a package of services but may be less applicable when choosing one intervention instead of another (when an incremental cost-effectiveness ratio based on the difference in costs and effects between the two interventions is required). An additional limitation is that intervention interactions are not accounted for. This approach assumes that the costs and, in particular, effects

of intervention A are unchanged by the presence of intervention B, which is rarely a tenable assumption for interventions addressing the same disease.

To incorporate both intervention compatibility and interactions several malaria economic evaluations have constructed priority setting landscapes based on discrete packages of interventions (179–181). Intervention bundles can then be treated as mutually exclusive alternatives and incremental analysis applied to assess the value of switching from one package to another. A limitation of this approach is that the intervention combinations are defined a priori and may restrict the decision space since it may not be possible to include all possible combinations. Input from decision makers into the design of intervention packages will improve the relevance of the evaluation to policy decisions. Evidence users should take care not to interpret the package with the lowest cost-effectiveness ratio as the optimal choice. While the lowest cost-effectiveness ratio represents the greatest health gains in proportion to spending, we may be willing to spend more to obtain further health gains, that is, moving further along the cost-effectiveness frontier.

4.7 Geographic targeting

The epidemiology of malaria varies considerably between different geographical areas. A core aspect of priority setting in malaria control and elimination is to determine which interventions, or combinations of interventions, are provided and where.

There are several options to address geographic heterogeneity in economic evaluation. Stratification of results, sensitivity analysis or scenario analysis can be used to present the cost-effectiveness of healthcare interventions in contexts with certain characteristics. Readers are then free to match their context of interest to the closest example given. In this approach, the reader

still has a degree of work to do in translating from illustrative examples to applied policy, particularly if targeting resources across a large number of geographical units such as districts or townships. Moreover, any distinction between heterogeneity and uncertainty in results may be lost. Calculation of costs, effects and cost-effectiveness in all geographic units of interest would provide a decision maker with a fuller picture of the decision landscape. Decision rules or constraints can then be applied to yield a recommended geographic allocation of interventions according to a CET, or, given the limitations discussed here, direct allocation of a relevant budget. Two recent studies address the geographic allocation of resources in malaria planning (166,179) but such examples are rare and methods are varied.

4.8 Conclusion

This chapter identifies areas where the realities of malaria decision problems affect the application of economic evaluation methods. The complexities of i) declining incidence and cost-effectiveness in the context of elimination ii) international aid and resource constraints and iii) supranational priority setting, all affect how health economists might use a cost-effectiveness threshold. Guidance and consensus regarding best practice on when and how to use a cost-effectiveness threshold for malaria economic evaluation, and the selection or calculation of this threshold, is greatly needed. Alternatively, a policy of malaria elimination may allow economic evaluation to focus on direct budget allocation within the elimination campaign.

Further complexities in the evaluation of malaria control and elimination campaigns are due to the need to choose between and/or deploy multiple often complementary interventions (as compared with choosing between mutually exclusive treatments for a given disease). In order to properly inform priority setting in malaria policy, economic evaluations must be able to assess combinations

of compatible interventions, rather than sets of mutually exclusive alternatives. Assessment of exhaustive sets of intervention combinations is not possible and communication with policy makers will be essential to construct relevant evaluation questions.

Lastly, geographic heterogeneity is not always well recognised, and monolithic deployment of intervention(s) across regions with such heterogeneity can imply misuse of scarce resources. Geographic priority setting is a core element of planning in both the control and elimination of malaria. Economic evaluation based methods may be able to better support local priority setting by incorporating geographic heterogeneity into analyses and making a clear distinction between heterogeneity and uncertainty.

In the case of Myanmar, the *de facto* budget is set each year through separate decision-making processes made by several major donor organisations including the MOH, 3MDG, the Global Fund, USAID, DfID, JICA and others. However, all implementing programmes require endorsement by the Nation Malaria Control Programme, to some degree centralising policy-making despite the various separate budgets which exist and the different processes behind these budget-setting decisions. The following chapter outlines an approach to budget-based geographic resource allocation in malaria planning that is intended to sit in this level of policy-making and addresses several of the challenges outlined here.

Chapter 5 Budget-based geographic resource allocation based on cost-effectiveness: An application to malaria policy

5.1 Chapter summary

Healthcare services are often provided to a country as a whole, though in many cases the available resources can be more effectively targeted to specific geographically defined populations. In the case of malaria, risk is highly geographically heterogeneous and many interventions, such as insecticide treated bed nets and malaria community health workers, can be targeted to populations in a way that maximises impact for the resources available. This chapter describes a framework for geographically targeted budget allocation based on the principles of cost-effectiveness analysis and applied to priority setting in malaria control and elimination. The approach can be used with any underlying model able to estimate intervention costs and effects given relevant local data. Efficient geographic targeting of core malaria interventions could significantly increase impact for the resources available, accelerating progress towards elimination. These methods may also be applicable to priority setting in other disease areas.

5.2 Introduction

Effective spending is critical to malaria control and elimination. While global financing for malaria has risen considerably in recent years (182), it is not possible to provide all malaria interventions to all areas at risk. In addition to ensuring sustained financial and political commitment, policy makers must determine how best to marshal the available resources to maximise impact on malaria burden. Economic evaluation aims to address this question by providing information on the health impact of interventions in proportion to the resources required.

Several reviews have sought to summarise the evidence base on the cost-effectiveness of malaria interventions (79,183,184). This evidence has most clearly informed malaria policy when an intervention was shown to be highly cost-effective in a wide range of settings, supporting generalisable policy recommendations. Examples include the use of artesunate for the treatment of severe malaria (185) and the introduction of point-of-care or rapid diagnostic tests (186–188). However, translating the cost-effectiveness evidence base to inform detailed malaria control and elimination planning can be challenging, as described in Chapter 4.

5.3 The importance of geographic variation in malaria policy

The national malaria control programme manager is faced with, among other things, a toolbox of interventions, a limited budget and a map of malaria risk. With increasingly abundant geo-data on malaria incidence and the use of spatial-statistical models to fill in the gaps, malaria risk maps are increasingly useful and becoming more popular as there is growing recognition of the high degree of heterogeneity in risk within countries, within provinces or districts and even within communities (189). Related to this, most malaria interventions are highly divisible down to the community or patient level and can be targeted to specific, geographically defined populations. These interventions include: bed nets, chemoprevention, indoor residual spraying, larviciding, early detection and treatment through malaria community health workers (CHW), mass treatment and, perhaps soon, vaccination.

In addition to disease risk there are further factors relevant to malaria programming that vary with geography, such as access to treatment and the higher cost of delivering services in remote areas, though the cost of such services may well be considered worthwhile. In many countries efforts are

being made to identify the human and ecological dynamics behind geographic heterogeneity in malaria risk (190,191); trials are underway to identify packages of interventions that could successfully target malaria hotspots (192) and spatial decision support systems are being established (193,194). Locating malaria risk and deciding how to respond to this risk is therefore essential to effective control and elimination.

5.3.1 Geographic heterogeneity and economic evaluation

While geographic heterogeneity is clearly important to malaria policy making, it does not feature prominently in malaria economic evaluations. The impact of variation in malaria risk on cost-effectiveness can be, and often is, assessed by univariate or probabilistic sensitivity analysis. This risks conflating an important distinction between heterogeneity and uncertainty; it may be useful to the decision maker to understand both the differences between geographies and the degree of confidence in this information. Detailed stratification of cost-effectiveness results by disease risk would allow readers to match the characteristics of their context with study findings. However, geographic variation may include multiple variables preventing clear stratification.

Economic evaluation can do more to integrate information on geographic variability in situations where this is central to the policy response. There are several recent examples of studies that model geographic resource allocation for countries or regions in malaria and other disease areas (166,179,195). Though aiming to reconcile costs and consequences, such studies are not always described as economic evaluations, often originating in the disciplines of mathematical modelling or spatial epidemiology. This chapter describes an approach to geographic resource allocation, grounded in economic evaluation methodology.

5.4 Geographic resource allocation

Healthcare economic evaluation models provide estimates of the cost and health impact for interventions of interest. Given relevant local data on demographics, disease risk and other factors for a set of geographically defined populations (hence “geo-units”) such models can provide a menu or league table of interventions or intervention combinations in terms of their expected costs and effects. That is, a modelled estimate of the cost and effect of each intervention option in each geo-unit. The interpretation of such a data set is not trivial and the decision problem addressed in this chapter is to select intervention options for each geo-unit such that health gains are maximised given the resources available.

A wide range of methods are available to model intervention costs and effects including decision trees, compartmental or Markov models and individual based models (23,25,196). Some considerations in model design may include: intervention interactions; the impact on disease transmission as well as health; the marginal effects of one intervention in the presence of another; variations over time and; population behaviour, to name a few. Where multiple interventions are being considered the model may need to be able to simulate their impact in isolation and in varying combinations. It is important to use an outcome measure that adequately captures the impact of all interventions of interest; utility metrics including the disability adjusted life year or quality adjusted life year are appropriate, though some disease specific measures such as reduction in prevalence may be sufficient. Notwithstanding the above, all models are simplifications of reality and the model should be no more complex than is necessary to reasonably estimate intervention costs and effects. There is extensive literature on modelling economic and health impacts elsewhere (24).

Box 5: Geographic resource allocation steps

The starting point of this method is a set of cost and effect estimates for all intervention options in all geographic units of interest. The aim is to select interventions and intervention bundles by geo-unit in such a way that impact is maximised for a given budget.

1. Remove all interventions where there exists an alternative within the same geo-unit that is both more effective and less costly (absolute domination).
2. Calculate incremental cost-effectiveness ratios for all intervention combinations in all geo-units using a common "no additional intervention" comparator.
3. Considering all remaining intervention option in all geo-units, select the option with the lowest ICER to allocate funding. Reduce the budget by the cost of this selection.
4. If the selection displaces another intervention option in its geo-unit then remove the displaced option from the league table and add its cost to the running budget.
5. Recalculate the incremental cost-effectiveness ratio for any remaining interventions in the selection geo-unit, using the newly selected intervention option as the comparator.
6. Remove any intervention options where the ICER is negative (extended domination, the intervention is not absolutely dominated yet does not fall on the cost-effectiveness frontier and thus is not selected at any point
7. Repeat steps 3 to 6 until the running budget is less than the cost of the next selection.

Source: Author

5.4.1 Allocation method

Geographic resource allocation is a variation of the knapsack problem[9] and is analogous to priority setting between healthcare domains in standard healthcare priority setting using cost-effectiveness or cost-utility analysis (4). The allocation problem can be stated as follows:

$$\max \sum_{i \in I} \sum_{g \in G} e_{ig}\, d_{ig}$$

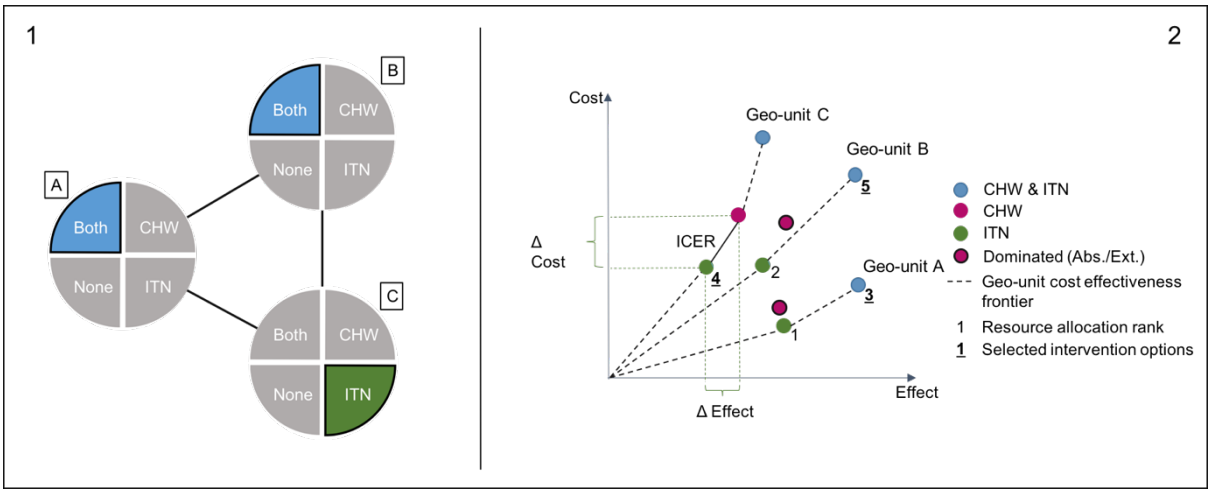
$$s.t. \sum_{i \in I} \sum_{g \in G} c_{ig} d_{ig} \leq b$$

[9] A standard combinatorial optimisation of placing objects of different weights into a knapsack

The sum of intervention effects (e) is maximised subject to a budget constraint (b) on the sum of intervention costs (c), where the set of all interventions (i) in all geo-units (g) are included or excluded using a decision variable (d). The decision variable determines inclusion or exclusion of intervention options and normally $\mathrm{d} \in \{0,1\}$. Obtaining a solution to the optimisation problem is more tractable given an assumption of divisibility (see section 2.3).

The allocation algorithm described here is an adaptation of priority setting using cost-effectiveness analysis rather than an iterative trial-and-improvement optimisation solver, and is illustrated with a simplified example of a decision problem in three geographic units A, B and C. Two interventions, insecticide treated bed nets and malaria community health workers, are available, as well as the combination of both interventions and the option to provide neither. Figure 7 Panel 1 presents this example graphically with information on the costs, effects and allocation results in Table 4. The corresponding cost-effectiveness plane also with the allocation result is presented in Figure 7 Panel 2 and the steps of the allocation algorithm are summarised in Box 5.

Figure 7: Illustrative geographic allocation with cost-effectiveness plane



* Panel 1: A, B and C are illustrative geo-units corresponding to the example described in section 2.1 and Table 4. The highlighted segments denote the intervention options selected to receive funding in the example. Abbreviations: Insecticide treated bed net (ITN), Community health worker (CHW).

Starting with the costs and effect estimates for all intervention options in all geo-units, all dominated interventions (those that are costlier and less effective than an alternative intervention within the same geo-unit) are excluded. Incremental cost-effectiveness ratios (ICERs) are calculated for all interventions using the null or "no additional intervention" scenario as the comparator. Priority setting is then broken down into a series of decisions. The first decision selects the intervention option with the lowest ICER from all non-excluded options in all geo-units. This selection is the choice that produces the maximum expected health gains for the investment (though it may be replaced by a subsequent selection in the same geo-unit). The cost of the intervention is subtracted from the budget and the ICERs for the remaining interventions in the same geo-unit are recalculated using the selected intervention as the comparator (see section 2.2). Any recalculated ICERs that are negative are subject to extended domination and excluded. These recalculated ICERs are those that form the cost-effectiveness frontier for the geo-unit. These steps are repeated, selecting the most cost-effective intervention option, recalculating the ICER and adjusting the budget. If the selection is in a geo-unit where an intervention is already allocated, the

new selection displaces the previous one and the cost of the displaced intervention is returned to the running budget. The process ends when the remaining budget is less than the cost of the next most cost-effective option.

Table 4: Example results table for multiple intervention resource allocation

Geographic Unit	Intervention	Effect (DALYs Averted)	Cost (US$)	Incremental Cost-Effectiveness Ratio (US$ per DALY Averted)		Allocation Result**	Selection Rank
				With Null Comparator	With Frontier Comparator*		
A	ITN	3.73	304	82	82	Displaced	1
	CHW	3.4	380	112	-	Abs. Dominated	
	Both	5.01	498	99	152	Funded	3
B	ITN	3.41	501	146	146	Displaced	2
	CHW	3.62	733	202	-	Ex. Dominated	
	Both	4.29	804	187	344	Funded	5
C	ITN	3.01	533	177	177	Funded	4
	CHW	3.27	767	235	900	Unfunded	
	Both	3.38	933	276	1509	Unfunded	

*A by-product of the allocation process is the CET or willingness-to-pay implied by the relevant budget. The threshold would fall between the least cost-effective intervention that is funded and the most cost-effective interventions that is not. In the example in Table 4 this is between US$ 344 and US$ 900 per DALY averted.

** Given a budget constraint of US$ 2000

Abbreviations: Insecticide treated bed net (ITN), community health worker (CHW), disability adjusted life year (DALY), absolutely (Abs.), extended (Ex.).

Due to the challenges specifying and interpreting cost-effectiveness thresholds (CETs) for malaria control and elimination (197) the approach uses a budget as the resource constraint, which, due to the role of international aid, is often known and ring-fenced. Alternatively, if instead we wish to apply a CET as the resource constraint, each geo-unit can be treated as an isolated decision problem. As before, interventions subject to domination by others within the same geo-unit are

excluded. Then, following standard economic evaluation methods, the cost-effectiveness frontier is identified and ICERs calculated sequentially along this frontier. The intervention option with the highest ICER below the CET is the expected optimal choice in each geo-unit.

A consequence of the budget-based resource allocation approach is to estimate an approximate CET for this context. That is, we know that the threshold would fall somewhere between the ICER of the last intervention option to be funded and the ICER of the next highest unfunded option. In Table 4, this is between US$ 334 per DALY averted (Geo-unit B, both interventions) and US$ 900 per DALY averted (Geo-unit C, CHW).

5.4.2 ICER calculation: Which comparator?

When evaluating intervention options across multiple geo-units, identification of the appropriate comparator is essential to calculation of the correct ICER. Where a new intervention selection replaces a previous one, it is the difference in costs and effects between these alternatives that should be used to decide whether the additional investment justifies the additional benefit. In this respect there is a difference in resource allocation within and between population groups in that within group selection is alternative while between group selection is additive. Figure 8 illustrates this using the second decision step in the example; after selection of ITN in population A the next choice can be to add ITN in population B or C, or to replace ITN in population A with the “Both” option in population A (CHW only is dominated in the example). If one intervention will replace another the appropriate information on which to make this decision is the difference between the costs and health gains between these interventions.

Figure 8: Graphical representation of within and between geo-unit selection

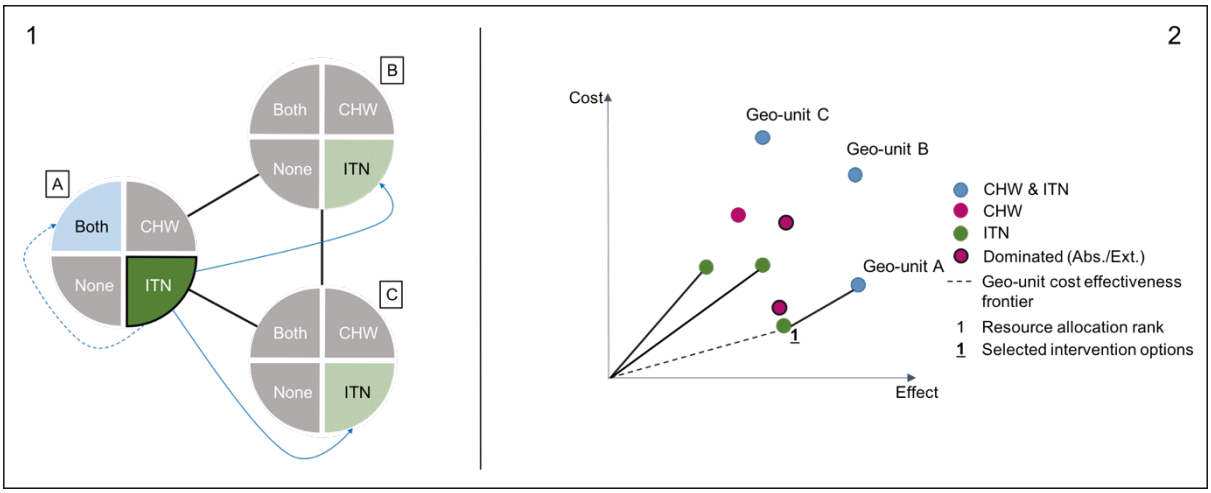


Figure caption: Illustration of within vs between geo-unit selection having initially selected ITN in geo-unit A. Panel 1: A, B and C are illustrative geo-units corresponding to the example within vs between geo-unit selection described in section 2.2. The darker highlighted ITN segment in geo-unit A denotes the intervention selected in the first step and the lighter highlighted segments denote the three options available for selection in the second step. Panel 2 represents the corresponding cost-effectiveness plane. Abbreviations: Insecticide treated bed net (ITN), Community health worker (CHW).

Calculation of the correct ICERs emerges in the process of the algorithm described in section 2.1. At the point of selecting an intervention for inclusion, the ICERs for all remaining interventions within the same geo-unit are recalculated with the selected intervention as comparator, reflecting that within a geo-unit a new selection will replace the previous one.

5.4.3 Geo-units

To address a practical budget allocation problem the geo-units are likely to be pre-established administrative constituencies such as districts, townships or perhaps villages. The choice of administrative level should reflect how the interventions of interest may realistically be implemented. For example, for reasons of pragmatism and economies of scale, mass distribution of goods such as bed nets may be more appropriate to allocate by district or township rather than by village. It is also essential that information such as population and disease risk must be available for

the chosen administrative level. It may also be beneficial to include variable costs for different geo-units and for programme scale (198,199).

Lastly, sequential selection based on ICERs does not necessarily provide a perfectly optimal solution for a discrete allocation problem in that there is a degree of error associated with the residual underspend (200). In cost-effectiveness analysis decision divisibility is assumed, allowing partial implementation of interventions. That is, the decision variable (d) in the knapsack objective function (Section 2.0) may take fractional values. While the assumption of divisibility in cost-effectiveness has been debated (29,30,201) it is reasonable in the context of geographic targeting, where divisibility of intervention decisions by geographic areas is already assumed. Moreover, in the geographic allocation methods described here the divisibility assumption is only necessary at the margin. That is, at end of the allocation algorithm it is assumed the most cost-effective unfunded intervention geo-unit option could be partially implemented using the remaining funds. It may not be necessary to formally include the partial unit allocation as the interpretation of results would not reflect such precision (see section 3.1), as in cost-effectiveness analysis, an underlying assumption of divisibility may be sufficient.

5.4.4 Uncertainty

Assessing and communicating the robustness of results given uncertainty in the model inputs is essential for rigorous economic evaluation. Probabilistic uncertainty can be incorporated into the allocation analysis by assigning sampling distributions to input variables and making repeated simulations of the allocation result (Monte Carlo simulation). A clear distinction can be made between this variation due to uncertainty and variation due to heterogeneity and this is incorporated into the resource allocation analysis described above. The result of a probabilistic

uncertainty analysis would be a probability score for each intervention in each geo-unit that it is the optimal choice given the defined parameter uncertainty. In such a probabilistic (or Bayesian) framework additional decision criteria can be incorporated to reflect decision maker preferences such as aversion to overspend or undersupply (202,203). Univariate or multivariate sensitivity analysis or scenario analysis can be used to assess parameter importance and scenarios of interest. Finally, structural uncertainty can be examined by repeating the allocation analysis with different underlying malaria models.

5.5 Discussion

This chapter describes an approach for the geographic allocation of a given budget using locally specific estimates of the costs and effects of multiple interventions or intervention bundles. This framework is described in the context of malaria policymaking but could be equally relevant in other disease contexts, for example schistosomiasis and soil transmitted helminths (204) or HIV/AIDS (195).

5.5.1 Interpretation

A strength of this approach is that results are clear and directly applicable to the planning process, offering recommendations not only as to which interventions to invest in but where to target them in order to maximise health gains. Moreover, the recommendations are constrained by a relevant budget rather than a cost-effectiveness threshold that, if too high, may recommend unaffordable policies or, if reflecting societal affordability constraints, may underestimate available resources due to international aid. In the context of malaria, budget-based geographic targeting can better reflect a real and timely decision problem than generalised, threshold based economic evaluations.

Nevertheless, a model is a simplification of a complex process and should be interpreted as such. All model inputs, the structure of the underlying model and the resource allocation framework are necessarily limited. While the model results may offer one recommendation, decision makers often have rich knowledge of the local context and should interpret model results as a potentially useful synthesis of relevant information that is nonetheless a simplification.

The budget-based geographic targeting framework, like standard cost-effectiveness (or cost-utility) analysis, focuses on achieving efficiency to maximise health gains. Does this priority-setting framework also support the design of efficient malaria *elimination* strategy? Cost-effectiveness based priority setting based on short-run health impact may be more likely to choose investment in high burden populations, with greater scope for short-run gains, than to select enhanced activities in low-transmission areas to achieve local elimination. Elimination interventions will still be selected for in a budget-based allocation framework but will be selected when i) once disease transmission has become sufficiently low in all populations, ii) investment in high-burden populations is saturated or iii) opportunities for local disinvestment post local elimination are included into the model. Alternatively, it could be decided that separate priority setting frameworks are relevant for control and elimination investment and that while expected health gains can guide malaria *control* planning, alternative processes are needed for elimination strategy design.

5.5.2 Alternative methods

In addition to the methods outlined in this chapter there are alternative approaches to geographic resource allocation. Walker et al. apply a cost minimisation framework and simulate a large number of different allocation options choosing the least costly configuration that achieves a particular end point such as disease elimination (179). The approach differs from budget allocation in that it does

not specify a resource constraint. A possible advantage of this or similar simulation approaches is that optimal solutions can be found for allocation problems without making the assumption of divisibility. A drawback of a simulation approach is the substantial computation time required, notwithstanding techniques to improve efficiency such as simulated annealing. Computation time for the approach described in this chapter is negligible, so dependent only on the underlying cost-effectiveness model. For simple models, probabilistic sensitivity analysis and interactive user interfaces can be possible, both of which are potentially valuable extensions. Lo et al. us a cost-effectiveness threshold to guide geographic targeting of soil-transmitted helminth (see section 5.4.1) (204) and Anderson et al. use what they describe as a "health production function" to determine the rank order of how interventions should be prioritised in different geographic areas. The health production function compares costs and effects of each intervention but the methods are not explicitly grounded in economic evaluation methods (195).

5.5.3 Limitations

There are several limitations to the resource allocation framework described in this chapter. Firstly, all limitations of the underlying model used to estimate intervention costs and effects apply equally to the allocation result. Care needs to be taken when comparing allocation results from different models as characteristics or artefacts of the underlying model could drive important differences in results. Secondly, the method objective is a simple maximisation of health utility. It may be beneficial in some contexts to extend the approach to include non-health benefits such as financial protection (205) or incorporate equity preferences (206). Thirdly, the friction cost of administering targeted, as opposed to universal, healthcare programmes is not included and there may be differences in economies of scale. Incorporation of scale into a variable cost function would be a valuable addition. Fourthly, the budget allocation approach assumes information on what the

budget is likely to be and that this budget is ring-fenced for spending on the allocation problem under consideration. Sensitivity analysis can explore allocation strategies at different budget levels, analogous to sensitivity analysis around the CET. Lastly, the allocation results can only be as good at the input data. Reliable locally specific information on disease risk and other variables such as treatment seeking behaviour or intervention cost, are essential and not always readily available. In particular, the potential bias of under reporting disease burden in areas with poor health surveillance is problematic for any geographic targeting based on such data, whether in a formal allocation framework or otherwise.

5.5.4 Conclusion

Geographic targeting is an increasingly common feature of malaria control and elimination strategy yet does not feature prominently in malaria economic evaluations. This chapter describes a framework for geographic budget allocation grounded in economic evaluation methods. Efficient targeting of core malaria interventions has the potential to increase impact for the resources available, accelerating progress towards disease elimination. These methods will also be applicable to priority setting in other disease areas.

APPLIED ANALYSIS

Chapter 6 The MARC Data Repository: An update on malaria epidemiology in Myanmar

6.1 Chapter summary

Reliable information is essential for malaria policy and planning. The Myanmar Artemisinin Resistance Containment (MARC) region comprises 52 townships in east Myanmar. Malaria prevention and treatment services are provided both by the government and a large number of non-governmental organisations and the private sector. Malaria surveillance is improving but faces challenges due to the complex and continually changing nature of the programmatic environment. The MARC Data Repository was established in collaboration with the National Malaria Control Programme, the Department of Medical Research and the World Health Organisation country office, to maximise the quality of available information on the distribution of malaria risk in the MARC region. Malaria diagnostic records were collected from government and non-governmental supported health facilities, cleaned, processed and combined, along with demographic and health system information. Statistical analyses were performed to describe spatial and temporal variation in malaria incidence. The density of health delivery units by area was calculated to allow comparison of malaria incidence with access to diagnosis and treatment. The MARC Data Repository increased the quantity of available data on malaria diagnostic test results from 759,692 to 2,054,464 for the years 2012 to 2014. Resulting in up to a 7.2-fold increase in incidence of *Pf* incidence in some townships. While the burden is higher with a different relative distribution than

previously reported, the MARC Data Repository provides much stronger evidence that P. falciparum transmission is declining in the MARC region.

6.2 Background

Understanding the burden of disease is foundational to any policy for malaria control or elimination. Moreover, as outlined in Chapter 5, understanding the geographic distribution of malaria burden allows resources to be directed to where they will have the most impact; providing prevention and treatment services to the people who need them most. High quality disease surveillance (207) to obtain reliable, relevant and timely information on malaria burden is essential. This is equally true for the analyses in this thesis; any modelling results are only as good as the quality of the data going in and predictions of cost-effectiveness are likely to depend substantially on local estimates of disease burden.

In Myanmar, the National Malaria Control Programme (NMCP) collects data on patients tested for malaria with the support of the World Health Organization (WHO). Prior to 2011 routine malaria surveillance principally comprised aggregated case data provided by the Health Management Information System. 2011 saw the introduction of a vertical reporting system to collate individual test results from government facilities. Later, in 2012, this was expanded to include a standardized paper reporting form for non-governmental implementing partners (IPs) (208). However, the provision of malaria services in Myanmar is fragmented across several sectors (public, private, military and civil society) and myriad organisations presenting additional challenges to the efficient collection of disease surveillance data. Malaria diagnosis and treatment services in the MARC region are provided through MOH run hospitals, clinics and rural health posts; MOH and civil society malaria CHWs; regulated and unregulated private sector clinics and drug shops and; military

medical services. The central malaria case database is held by WHO country office on behalf of the NMCP.

In 2014 the MARC region data was shared with the University of Oxford. Following examination of the database and discussion with stakeholders it became clear that, while malaria surveillance systems were improving, the database primarily consisted of case data from MOH health facilities and CHWs and did not include malaria case data from several other sources. Standardised forms had been developed and were used by most civil society organisations in the MARC region to collect case data from CHW programmes, but these data were not entered into the central WHO/MOH database. The steps required to achieve this are:

- Hard copies of the data are shared with the Township Medical Office by government health facilities and non-governmental organisations
- Data are entered into a local database by the Township Medical Office
- The electronic version of the township data is sent to the central database managers
- Township data are added to the central database

Many implementing organisations collected malaria case data for monitoring and evaluation purposes, however prior to initiatives to standardise least data collection formats, each organisation digitised and stored data according to their own requirements. The result of this was that substantial amount of malaria data was fragmented and held by many different organisations. In response to these challenges, as part of the University of Oxford's modelling work and in collaboration with the NMCP, WHO and the Department for Medical Research (DMR), the MARC Malaria Data Repository was established and an office opened in the DMR compound in Yangon.

6.3 Methods

The MARC Malaria Data repository was established in 2013 as a collaboration between the National Malaria Control Programme, the Department of Medical Research and the WHO Country Office and the University of Oxford. The aim of the repository was to collate available data from civil society organisations and combine with the WHO/NMCP central database. The inclusion criteria for data were:

- Village level or individual level records
- Species specific (at a minimum *Pf* and non-*Pf*)
- Monthly aggregation (not quarterly or annual summaries)

Preferable but not essential:

- Patient age
- Patient sex

Subsequently, township aggregate data was included in the data repository, if supporting information on CHW count by township was available. Data received was cross-checked against summary reports to funding organisations where available. To maximize engagement with the initiative organisations were not asked to undertake any reformatting; data could be provided in any form where the inclusion criteria were met.

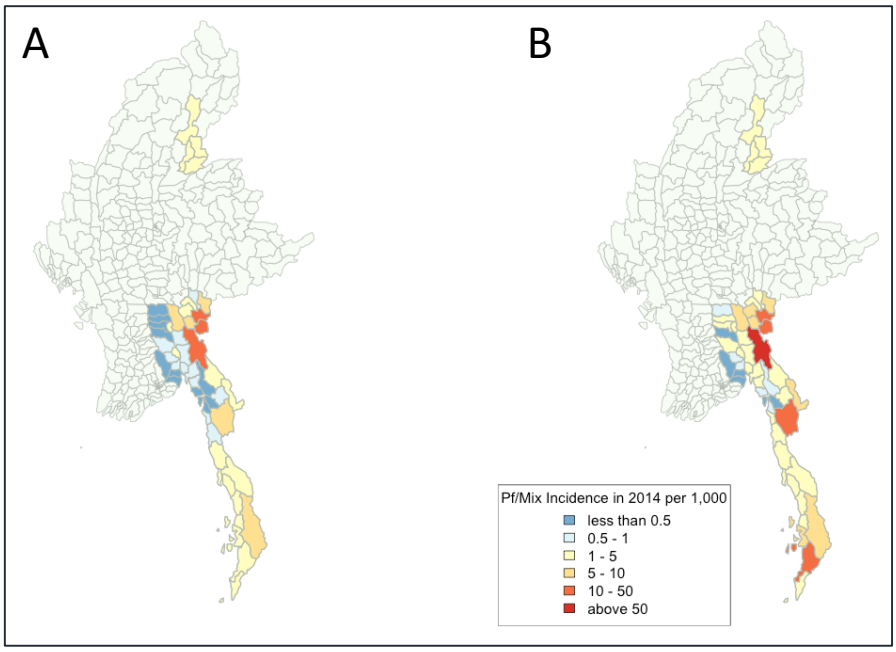
Extensive data cleaning and processing was required to aggregate datasets. Location fields including State/Region, Township, Village Tract and Village were translated from Myanmar language where necessary and where possible place codes (PCodes) were assigned according to an independent registry (57). As the registry of village level PCodes is not comprehensive the village name was used to count the number of unique villages with CHWs. Each township was reviewed in

turn to clean and standardize village name spelling and counting was disaggregated by township so that villages with the same name in different parts of the country are counted separately.

Year, Month and test result fields were standardized. Additional fields were added to track the parent organization and to categorize data by the type of treatment provider (CHW, clinic, screening point etc). The original Access database was expanded to include various data formats linked by key common fields. Finally, additional relevant datasets were integrated including population by village tract and number of health facilities (from health posts to tertiary hospitals) per township (57).

Descriptive statistical analysis was performed using R statistical software. The township was the lowest administrative unit of aggregation as no catchment areas to link government health facilities with the surrounding villages were available. Before and after spatial summaries by number of test results and number of malaria cases were mapped. Shape files, to graph data by administrative geographic units, were obtained from the Myanmar Information Management Unit (MIMU) (209). Annual parasite incidence (API) was calculated by township for 2014 and presented alongside the density of healthcare delivery units by area, a measure of likely remoteness of the township population from access to malaria treatment, and the number of malaria CHWs by township. Time series trends are presented as the number of malaria cases per month, split by species and source, and the number of malaria diagnostic tests per month, split by test result. All analysis excludes active case detection (ACD), whereby individuals without symptoms are screened for malaria. The quantity of ACD data is relatively small but would be a potential source of bias since active case detection is not performed in all townships nor is it performed consistently over time.

Figure 9: Confirmed *Plasmodium falciparum* incidence by township for the MARC region, 2014



* A: Without top-up data. B: Including all collected data.

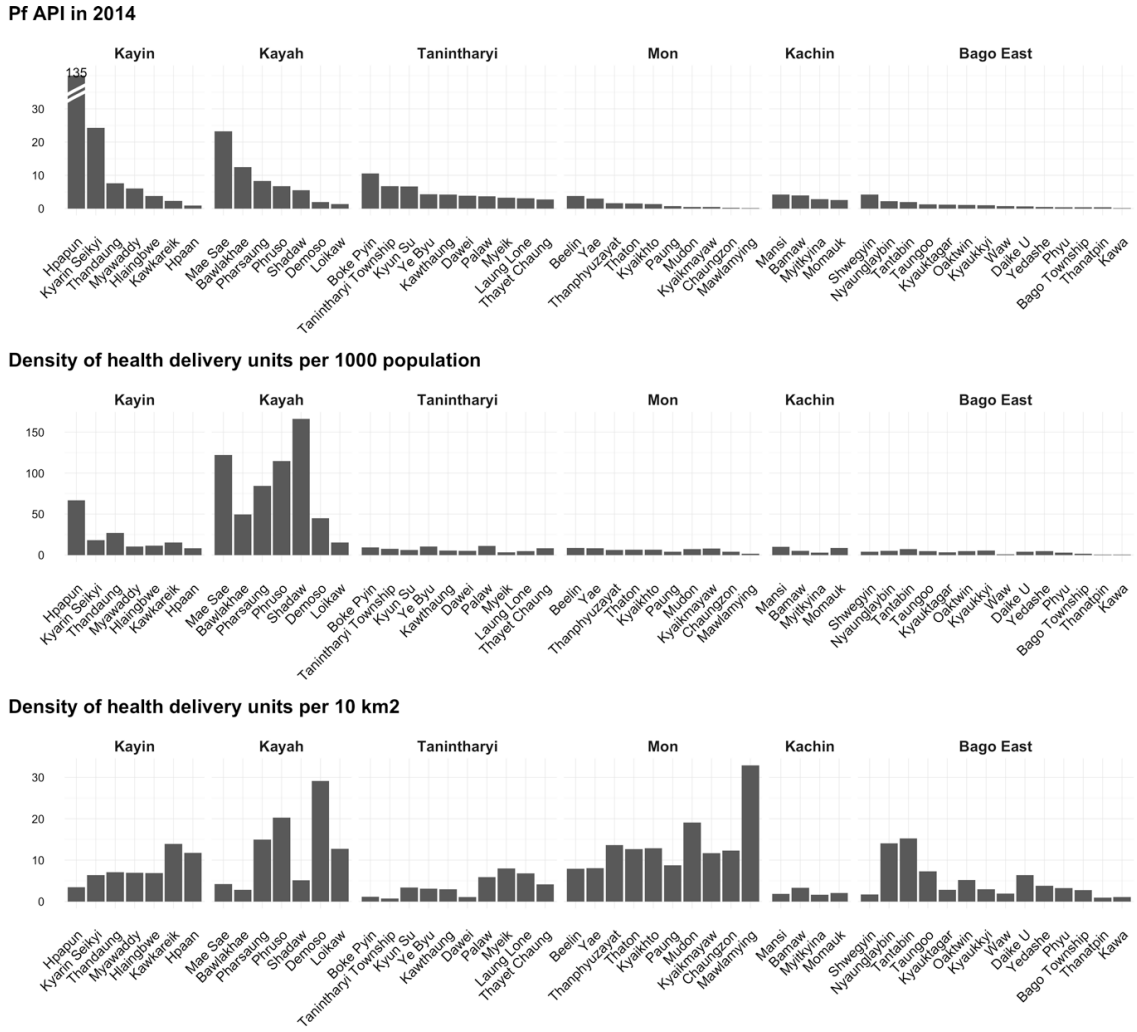
6.4 Results

For the years 2012 to 2014 in the 52 MARC Townships the quantity of data on malaria diagnostic test results increased from 759,692 to 2,054,464. The number of confirmed *Pf* cases increased from 102,290 to 175,376. Overall 60.7% of cases were *Pf* or mixed species. The geographic distribution of these data by township can be seen in Figure 9. The townships that saw the greatest increase in the number of malaria cases were Kawkareik (Kayin) (725 to 6203 cases) and Boke Pyin (Tanintharyi) (1655 to 10938 cases).

Unless stated otherwise, epidemiological results reported here are based on the expanded database, including data from non-governmental organisations. The annual parasite incidence for the MARC region in 2014 was 3.4 cases per 1000 population (range by township 0.09 to 134 *Pf*

cases per 1000 population). Townships with high API typically also had low density (by area) of health delivery units (Figure 10).

Figure 10: *Plasmodium falciparum* incidence and access to treatment by township, 2014



Time series analysis of all malaria diagnostic results for the MARC region shows malaria diagnostic testing increasing over time as access to treatment is expanded, along with expected seasonal variation (Figure 12). Though testing volume rises over time the proportion of tests that are *Pf* positive declines suggesting a decline in malaria transmission. Figure 12 panel B shows the number of malaria cases over time split by source and species. There is a notable unseasonal spike in

malaria cases in January 2013. The spike is observable in the *Pf* and Basic Health System (BHS) data and to a lesser extent in the Non-*Pf* cases. There is no concomitant increase in the number of malaria tests as might be expected if the increase was due to an artefact of reporting.

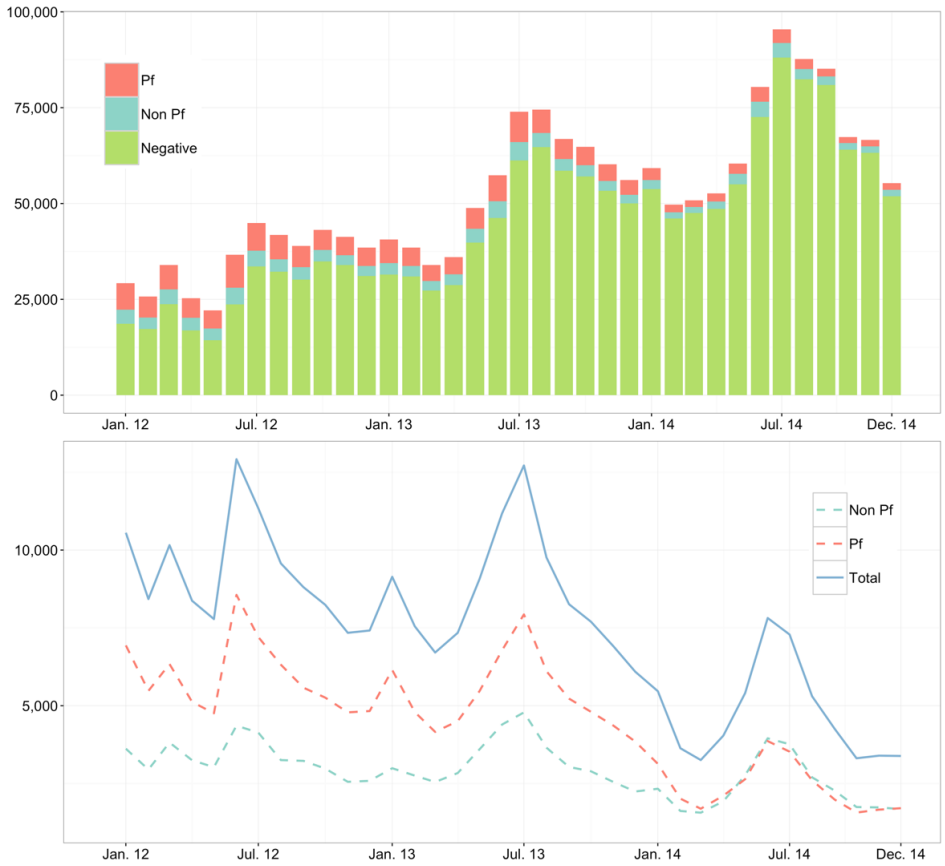
6.5 Discussion

The MARC Data Repository has almost tripled the amount of malaria data available for the MARC region in the years 2012-2014 and changed the understanding of the malaria landscape in these parts of Myanmar. The true burden of malaria is likely to be higher than previously reported with a different geographical distribution. The differences observed here highlight the need for quality malaria surveillance. This has been identified as a priority by NMCP which in collaboration with various partners has continually sought to strengthen malaria surveillance. Further malaria surveillance improvements are planned in the coming years.

From the updated dataset it is clear that malaria risk within the MARC region, an area identified as a priority for malaria control and elimination, is highly heterogeneous. The townships with the highest incidence of malaria are in many cases also the townships with the lowest density of public or civil society malaria diagnosis and treatment points. That is, the populations in these townships are, on average, at greater risk of malaria and likely to have further to travel to receive care. This underlines the importance of reaching marginal populations, which is already a priority for many organizations. To maximise their effectiveness malaria CHWs should therefore be targeted to areas where i) malaria risk is relatively high and ii) existing access to diagnosis and treatment is relatively low.

The MARC Data Repository is the strongest evidence to-date that *Pf* malaria transmission is in the MARC region is declining. Several organisations, including the VBDC, have observed such trends in their own data (*personal communnication*). The consolidated data in the MARC Data Repository show the number confirmed *Pf* cases is falling year on year, even as the volume of malaria diagnostic tests conducted rises considerably.

Figure 11: Malaria diagnostic tests and cases by month, 2012-2014



There are several limitations to this initiative. A small number of IPs could not provide data in a format that could be used in the data repository and the amount of missing data resulting from this is not known. In addition, data were not obtained from the Ministry of Defence and data collection systems do not currently exist for the private sector, although Population Services International

plan to introduce this. The private sector is likely to be a very substantial source of malaria treatment and, to a lesser but increasing extent, malaria diagnosis. Differences in the availability of malaria diagnosis and treatment and differences in the locations where individuals are exposed to, and then seek treatment for, malaria, may bias the picture on geographic distribution of malaria risk. Indeed, the scale up of malaria diagnosis and treatment in a township may in itself lead to an increase in reported malaria cases. Nevertheless, the MARC Data Repository constitutes a substantial increase on the previously available data.

The data repository is not intended to be a sustainable system for malaria surveillance, rather it was intended as a one-time initiative to strengthen malaria data for the years 2012-2014 that would support the economic-epidemiological models to guide future implementation of interventions. Data was gathered in a wide range of formats and considerable work was required to process. Going forward, standardized systems for data entry and digital storage will remove the need for this. NMCP continue to work on strengthening malaria surveillance to establish systems for receiving, processing and responding to routine malaria case data.

Finally, an interactive dashboard has been developed to allow users better access to information on malaria in the MARC region. The dashboard can be found at www.myanmarmalaria.net and has also been developed as a standalone offline.

Chapter 7 Cost-effectiveness and resource allocation of Plasmodium falciparum malaria control in Myanmar: A static modelling analysis of bed nets and community health workers

7.1 Chapter summary

Two interventions receive the majority of malaria control funding in Myanmar i) insecticide treated bed nets and ii) early diagnosis and treatment through malaria community health workers. This chapter aims to provide practical recommendations on how to maximise impact from investment in these interventions. A simple decision tree is used to model intervention costs and effects in terms of Years of Life Lost. The evaluation is from the perspective of the service provider and costs and effects are calculated in line with standard methodology. Sensitivity and scenario analysis are undertaken to identify key drivers of cost-effectiveness. Standard cost-effectiveness analysis is then extended via a spatially explicit resource allocation model.

Community health workers have the potential for high impact on malaria, particularly when baseline access to treatment is low and community health worker use is high, but are relatively costly, therefore efficient targeting is important. Insecticide treated bed nets are relatively inexpensive and moderately effective in the Myanmar settings, representing a low risk but modest return intervention. It is crucial to note that unlike many healthcare interventions, bed nets and community health workers are not mutually exclusive nor are they necessarily at their most efficient when universally applied. Modelled resource allocation scenarios highlight that in this case there is no “one size fits all” cost-effectiveness result. Health gains will be maximised by effective targeting of both interventions.

7.2 Background

The motivation for this analysis was, at the request of the funders 3MDG and the Bill and Melinda Gates Foundation, to provide timely inputs into discussions on the prioritisation of malaria spending in the MARC region. The study uses a simple decision tree model to estimate the cost-effectiveness of insecticide treated bed nets (now so-called long lasting insecticide treated bed nets) and malaria community health workers. The study emphasises sensitivity and scenario analysis rather than a generalised cost-effectiveness result. Targeted allocation of these resources is illustrated by an allocation model for the MARC region in Myanmar.

7.3 Methods

7.3.1 Costing

Financial costs are included from the perspective of the National Malaria Control Programme or other malaria intervention funders. In this analysis ITN distribution is assumed to be conducted though a dedicated distribution campaign. ITN cost is comprised of procurement cost (c_p), direct distribution costs (c_d) and programme management (c_m). Cost data were obtained from Three Millennium Development Goal (3MDG), a funding organisation in Myanmar, with crosschecking of components against private sector quotations. ITN coverage is defined as 2 nets per household with 10% wastage (w) and a mean household size of 5.2 people. The primary time horizon is one year and as such the per person ITN cost is annualised according to the lifespan of the net (l), assumed to be 3 years, using a discount rate of 5% (r) (23).

$$c_{ITN} = \frac{(c_p + c_d + c_m)(1 + w)}{r^{-1}(1 - (1 + r)^{-l})}$$

CHW costs are derived from separate detailed cost analysis reported in full elsewhere (165). To briefly summarise, CHW costs are estimated using an ingredients based micro costing of six cost centres: patient services; training; monitoring and supervision, programme management; incentives and overheads. For this cost-effectiveness analysis the cost of treatment (c_{ACT}) is separated from the remaining CHW cost per person covered (c_{CHW}). In addition to intervention costs, diagnosis and treatment direct costs for malaria cases treated by the basic health system are included (c_{ACT}).

Table 5: Parameter list and values for decision tree models

	Model parameter	Symbol	Default Value	Lower Estimate	Upper Estimate	Source
Setting	Baseline access to treatment (% of cases receiving ACT)	a	30%	1%	95%	2011 MARC survey indicates low availability, but recently survey by PSI indicates a substantial increase (210). Agreed in consultation with stakeholders.
	Cost of treatment	c_{ACT}	$3	1	10	Wholesale price of diagnosis and treatment, consumables only. Obtained from 3MDG procurement receipts.
	Proportion of malaria cases that die in absence of treatment	μ	1%	0.1%	10%	Expert opinion (211).
	Malaria risk	m	5%	0.1%	30%	Probability of malaria is highly variable but changes do not affect comparative analysis between intervention options.
	Probability that a person with malaria uses a CHW (where available)	q	30%	1%	95%	Community survey by Department of Medical Research in Myanmar finds 19% of surveyed first seek treatment at CHW (unpublished). Community survey in Cambodia finds low utilisation of CHW in villages with a CHW (Yeung et al. unpublished)
	Mean number of Years of Life Lost per death	d	30	15	45	Assumed based on life expectancy of 65 years and knowing that most malaria deaths in Myanmar are adults.
	Village population	v	500	-	-	Village size is based on unpublished unicef data. At the time of the study the village level census data was unavailable.
	Discount rate	r	5%	0%		
Intervention	Annual cost of ITN per person	c_{ITN}	$0.70	$0.50	$1.5	Estimated
	Annual cost of CHW per person	c_{CHW}	$2	$1.10	$4.50	(165)
	ITN protective efficacy	p	30%	0%	50%	A Cochrane review finds ITN are associated with a 50% reduction in infection. However, this includes a substantial amount of evidence from settings with mosquitoes likely to be more susceptible to ITNs (70,78,212,213)
	Reduction in mortality after treatment with ACT or ACT + PQ	r_1	90%	50%	99%	Expert opinion.

7.3.2 Model

CHW are an extension of the health system and therefore marginal utility will depend on locally specific access to treatment. The model must define a common metric to quantify the effects of ITN and CHW. The model calculates the number of Years of Life Lost (YLL), a widely used metric for health impact, through treatment of cases or cases directly averted by bed nets. In this case YLL are likely to be similar to Disability Adjusted Life Years (DALYs) as the contribution of morbidity will be negligible compared with mortality. The model was developed in both R (version 3.1.2) and TreeAge (TreeAge Pro 2014, USA) (211).

The probability tree (Figure 13) traces an individual through a chronological series of event possibilities beginning with an annual probability of contracting malaria (m) adjusted by the protective effect of ITN (p), if applicable. Individuals with malaria have a probability they will receive treatment from a provider other than a CHW (a). If a CHW is available in the village there is a probability (q) that a malaria case will seek treatment from the CHW, from both those who would have received treatment elsewhere and from those who would not have received any treatment. Each case of malaria has a probability of death in absence of treatment (μ) and a mean number of YLLs per death (d). We assume that treatment is with an ACT. The direct reduction in mortality is assumed to be the same for ACT (r_1). The terminal payoffs are scaled by population (v) and calculate the net cost and net effects for each intervention arm for one village (or one township when applied in the resource allocation model, see below). Parameter values can be found in Table 5.

Parameters are grouped by setting-related and intervention-related inputs and there is a substantial degree of uncertainty in many of the estimates. Wide ranges for sensitivity analysis are used where this is the case. Malaria risk in the MARC region is highly variable and the available data are limited, as shown in Chapter 6. In this analysis, an annual probability of illness of 5% is used for the general cost-effectiveness analysis with township-specific estimates used in the resource allocation model. While uncertainty in the true level of malaria risk may affect the ICER, it would not be expected to affect the relative prioritisation of interventions. While empirical data on the case fatality of untreated malaria are not available for practical reasons, results from a Delphi study of expert opinion by Lubell et al. are commonly used to defined this parameter in malaria outcome models (211). The malaria data repository reported in Chapter 6 did not include mortality data, so the mean age at death was unknown. However, since malaria in Myanmar commonly affects adults (rather than children, as is the case in many other settings) an average of 30 years of life lost was assumed for each death. While this assumption affects the ICER estimate, it would not be expected to change the rank order of intervention cost-effectiveness.

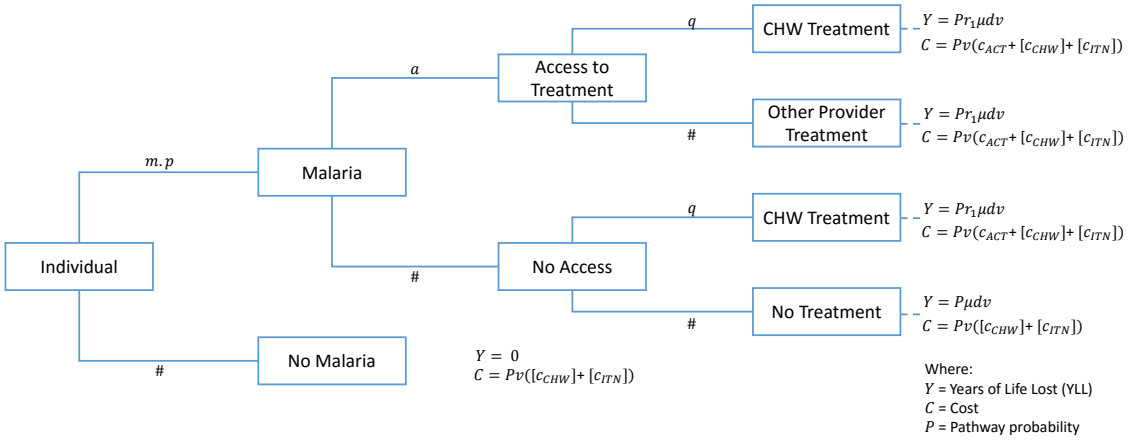
Access to treatment was an essential parameter to include in the model since one of the key mechanisms in how the roll out of CHW programmes impact malaria outcomes is through improved access to treatment. Baseline access to treatment in the MARC area is poorly understood and difficult to characterise since it will be highly heterogeneous. The best available evidence identified is the MARC baseline survey, which is several years out of date, and unpublished surveys by PSI. In consultation with implementing stakeholders, and taking these surveys in to account, it was assumed that 30% of individuals with malaria would access quality diagnosis and treatment at baseline, but to explore a wide range of possibilities (1-95%) in the sensitivity analysis. The cost of treatment was assumed to be $3 per course based on 3MDG procurement receipts. This

assumption does not reflect the variation in treatment used and cost differences for adults and children. Data on treatment seeking at a CHW, when one is present in the village, were not available for Myanmar. Unpublished MOH documents report 19% CHW uptake, however, stakeholders in implementing organisations considered likely uptake for good quality CHW for areas with substantial malaria risk would be much greater. A 30% CHW uptake was assumed with 1-95% sensitivity range. In this model, only one provider is attended per person, individuals may seek treatment from a CHW instead of their previous provider. This is intended to reflect the greater marginal utility is areas with poor access to treatment, even when uptake at the CHW is equal.

ITN efficacy was decided through discussion with several local stakeholders. As described in Chapter 2 mosquito anthropophilic biting in Myanmar occurs more commonly at dusk and dawn than during sleeping hours, which is likely to reduce ITN effectiveness. A 30% protective effect was assumed for ITN use with a sensitivity range of 0 to 50%. As with evidence for the untreated case-fatality rate, empirical estimates of impact on mortality from treatment with an ACT compared to no treatment are unavailable. However, the effectiveness is thought to be very high in discussion with leading researchers a 90% protective effect against mortality was assumed.

The model was developed as the simplest structure that incorporates the key relevant data and provides the desired output metrics of cost and years of life lost. The advantages of a simple model are ease of communication to end users, speed of development and flexibility of application.

Figure 12: Probability tree model of cost and impact for malaria community health workers and bed nets



7.3.3 Analysis

Bed nets and community health workers are not universally applied interventions and a general estimate of intervention costs and effects misses important variation, particularly with respect to the sometimes extreme remoteness of different populations in Myanmar. Instead, here intervention cost-effectiveness is calculated in four illustrative accessibility or remoteness scenarios, whereby more remote settings are characterised by increased cost of programme delivery, increased CHW uptake and decreased baseline access to treatment (Table 7). Data are not available to support specific parameterisations for these assumptions but the direction of trends are intuitive and supported by policy makers at the national malarial control programme and programme managers at an affiliated non-governmental organisation, Medical Action Myanmar. In addition to the scenario analysis, univariate sensitivity analysis is undertaken to identify key determinants of intervention cost-effectiveness. Probabilistic Sensitivity Analysis (PSA) can be found in the supporting documentation. We summarise quantified and non-quantified costs and

consequences in Table 8 to aid interpretation and to highlight potentially important factors that are not included in the quantitative analysis, as recommended for economic evaluations of public health interventions by Weatherly and colleagues (11).

Cost-effectiveness ratios are calculated for each intervention against a common null comparator or "no additional intervention" baseline, which includes the number of YLLs expected in absence of intervention and the cost of treatment for patients who receive it. The marginal benefit of each in the presence of the other is not equal to the marginal benefit of each in isolation. A CHW in a village with good bed net coverage has lower impact than in the same village without bed net coverage because there are fewer cases to treat, and vice versa. For this reason, the combined intervention arm is included explicitly as a model output rather than as a sum of separate interventions. Estimates are per year and reflect a village of 500 people with 25 malaria cases per year in absence of interventions.

Table 6: Parameter values for four remoteness scenarios

		Remoteness Scenario			
Parameter		*Easily Accessible*	*Accessible*	*Difficult to Access*	*Very Difficult to Access*
Annual cost of VHW per person	c_{CHW}	1.10	2.00	3.20	4.50
Annual cost of LLIN per person	c_{ITN}	0.5	0.70	1.2	1.5
Probability that a person with malaria utilises a VHW (where available)	q	0.15	0.3	0.45	0.6
Baseline access to treatment (% of cases receiving ACT)	a	0.5	0.3	0.15	0

7.3.4 Resource allocation

An extension to standard cost-effectiveness analysis, the second stage of this study applies a spatially explicit resource allocation model for a given budget (see Chapter 5). The model is applied to the Tier 1 or MARC region of Myanmar. There are 52 townships in Tier 1 to which a fixed budget of US$ 10 million is allocated. US$ 10 million is a ballpark figure for *annual* budget of ITN and CHW for the MARC region. This figure arose through discussion with the National Malaria Control Programme and 3MDG, a major fund for malaria programmes in Myanmar managed by UNOPS. It was agreed that analysis with more precise budget could be undertaken in the future if useful.

Township specific data on population is from the 2014 census (57) and malaria incidence is based on routine health system surveillance records, currently managed by WHO Myanmar on behalf of the Ministry of Health (2013, unpublished). The malaria surveillance system in Myanmar is undergoing systemic improvements and data capture is not complete. All other parameter values are as reported in Table 6.

The allocation model uses the decision tree in Figure 13 to calculate cost-effectiveness ratios for all intervention options for each geographic patch, in this case a township. Once all scenario cost-effectiveness ratios are calculated the model allocates the available budget starting with the most cost-effective intervention. As the budget is allocated, the most cost-effective intervention in a particular township may be replaced by a less cost-effective, but more effective intervention. Dominated intervention scenarios, those where any increase in effect can be achieved by a more cost-effective alternative, are excluded. The allocation process ceases when the remaining budget is less than the marginal cost of the next most cost-effective intervention (see Chapter 5). It is worth noting that the optimal allocation of resources is not identified through sequential iteration

and improvement of budget allocation options since the cost-effectiveness ratios provide sufficient information to identify the allocation result directly. This is more accurate and computationally efficient than identification of a distribution of resources through iterative optimisation or "brute-force" calculation of all or a large number of possible distribution scenarios. The resource allocation analysis is repeated to examine the impact of variations in bed net protective effectiveness, CHW uptake and cost sharing for integrated CHW programmes.

Table 7: Costs and effects of malaria interventions in four remoteness scenarios

		Remoteness: Easily Accessible	**Accessible**	**Difficult to Access**	**Very Difficult to Access**
ITN	Cost (US$)	238	343	596	750
	Effect (YLLs Averted)	1.24	1.64	1.95	2.25
	CER	193	209	306	333
CHW	Cost (US$)	556	1016	1629	2295
	Effect (YLLs Averted)	0.51	1.42	2.58	4.05
	CER	1089	715	631	567
	ICER	Abs Dominated	Abs Dominated	Ext Dominated	Ext Dominated
CHW & ITN	Cost (US$)	792	1354	2216	3031
	Effect (YLLs Averted)	1.59	2.63	3.75	5.08
	CER	499	515	591	597
	ICER	1583	1021	503	715

*CER here compares costs and effects of an intervention compared with no intervention

** ICER compares costs and effects of an intervention compared with the next most effective undominated option

Figure 13: Costs and effects of malaria control in different accessibility scenarios

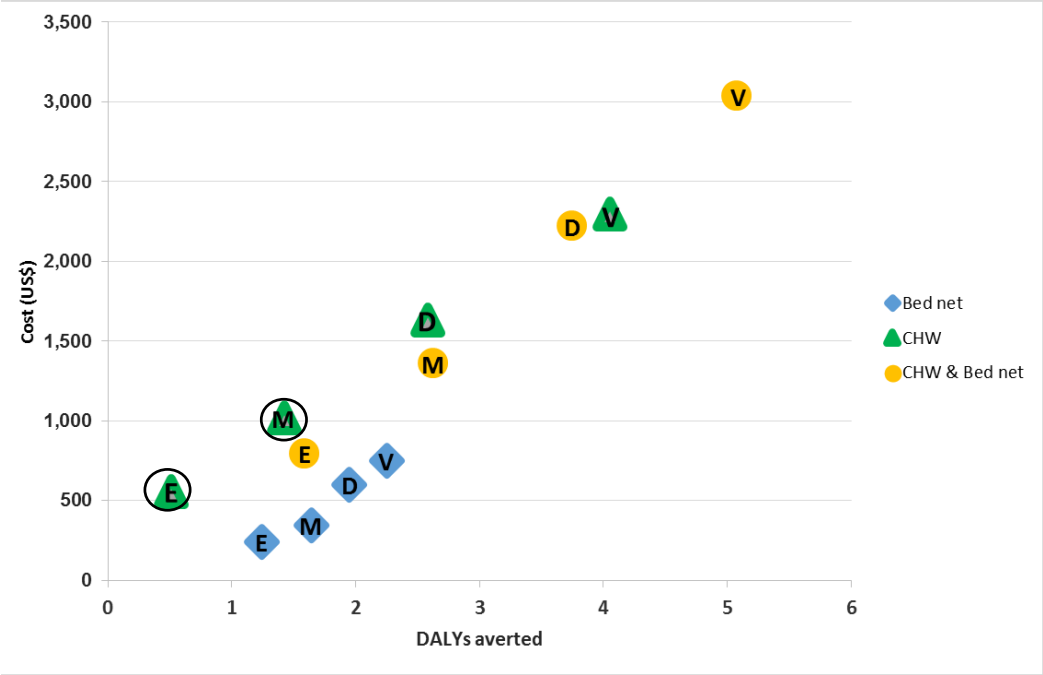


Figure Legend: Circle indicates a dominated intervention. E: Easily accessible; M: Moderately accessible; D: Difficult to access; V: Very difficult to access.

7.4 Results

The cost-effectiveness of malaria control in Myanmar is context dependent. CHW have greater potential effects, particularly in more remote settings, but are also more costly. In the scenario analysis, easily accessible village setting CHW avert 0.51 YLLs per year at a cost of US$ 556 (US$ 1089 per YLL averted). This rises in the very difficult to reach villages to 4.05 YLLs averted at a cost of US$ 2295 (US$ 567 per YLL averted), a higher cost but a more cost-effective use of CHWs. Bed nets were consistently less costly and a modestly effective intervention. In the easily accessible village setting bed nets avert 1.24 YLLs at a cost of US$ 238 (US$ 193 per YLL averted), rising to 2.25YLL averted for US$ 750 (US$ 333 per YLL averted). In the very difficult to access village setting, a combination of both bed nets and CHW gives the greatest impact of 5.08 YLLs averted for a cost

of US$ 3031 (US$ 597 per YLL averted). The above results are summarised in Table 8 and Figure 14 and assume that CHW only provide malaria services (this assumption is relaxed in the resource allocation analysis).

Figure 14: Change in CHW cost-effectiveness: univariate sensitivity analysis of all relevant parameters

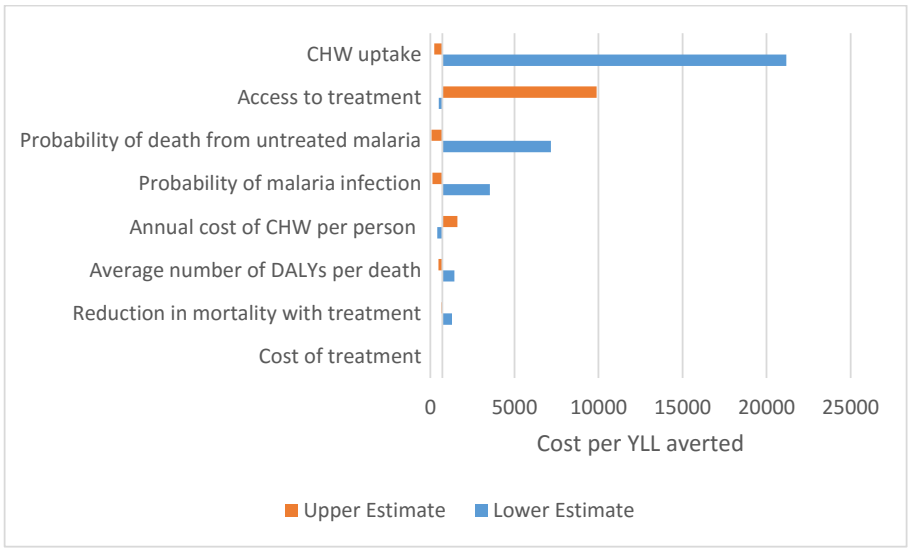
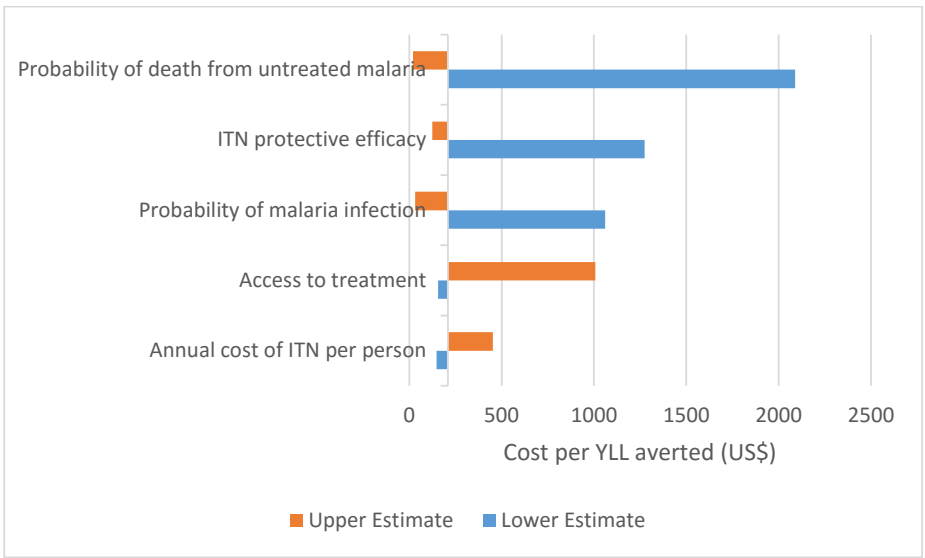


Figure 15: Change in bed net cost-effectiveness: univariate sensitivity analysis of all relevant parameters



7.4.1 Sensitivity analysis

Univariate sensitivity analysis was conducted for the cost-effectiveness of CHW (Figure 15) and bed nets (Figure 16) using the wide uncertainty ranges in Table 6. The key determinants of cost-effectiveness for CHW are baseline access to treatment with an ACT and the likelihood that a person with malaria seeks treatment from the CHW. In reality, these two factors may be related; low baseline access to treatment might be expected to increase treatment seeking at a CHW. Univariate sensitivity analysis treats these values as independent. The key determinants of bed net cost-effectiveness are the untreated malaria mortality risk and the protective effect of the net. Changes in malaria incidence and mortality affect the magnitude of effects substantially but proportionally for all intervention options, and therefore do not affect intervention comparison.

7.4.2 Resource allocation

Figure 17, panel A presents an illustrative optimal allocation of an annual budget of US$ 10 million to CHW and ITN roll out in the 52 townships of the MARC region, Myanmar. Almost half of the townships are allocated both CHW and ITN, 12 townships receive ITN only and 15 townships are allocated to provide standard health services without CHW or ITN. Figure 17 panels B to D present the scenario variations where key assumptions are varied in order to observe the effect on resource allocation. Panel B assumes a low ITN protective effect of 5%, rather than the default 30%. Panel C presents resource distribution assuming 95% uptake of CHW by individuals with malaria, rather than 30%. Panels B and C find that at the margin, CHW rather than ITN should be prioritised. The specific townships receiving these marginal interventions is likely to be an artefact of population size and the residual budget amount at the end of the allocation process. Panel D presents a cost-sharing scenario, where the benefits of an integrated CHW programme are represented by an assumption that funds allocated for malaria control need only fund 50% of the total programme

cost. Notably, the allocation of both CHW and ITN to the majority of Southern, and Western township and to the Kachin townships in the North, is robust to these scenario variations.

Figure 16: Township allocation of malaria interventions in the MARC region, Myanmar

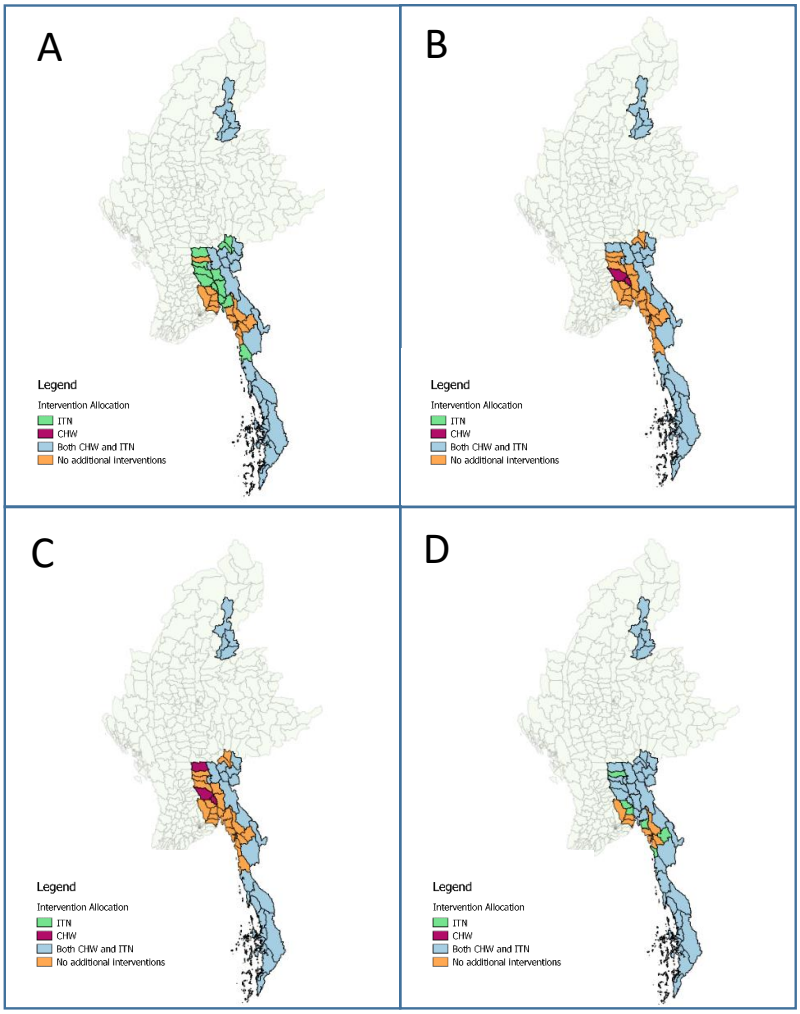


Figure Legend: Maps indicate allocation of US$ 10 million to bed nets and malaria community health workers in the MARC region, Myanmar. A: Allocation using default parameter values detailed in Table 6. B: Allocation assuming a lower bed net protective effect of 5%. C: Allocation assuming a higher uptake of community health workers; 95% of malaria infections. D: Allocation assuming 50% cost-sharing for community health workers. For panels B-D all parameters other than the specified variation are the default values outlined in Table 6.

7.5 Discussion

Malaria intervention decisions in Myanmar are based on judgement supported by the limited available evidence. The average and incremental cost-effectiveness ratios give decision makers a sense of “bang for buck” to inform these judgements while the resource allocation modelling highlights the importance of targeting both interventions to where they can have the greatest impact. This study finds that CHW have the potential for high impact on malaria, particularly in difficult to access areas, where availability of other services may be low and if CHW use is good. However, CHW are more costly and, if only delivering malaria services, are associated with higher cost-effectiveness ratios. ITN are a robustly cost-effective intervention but the total health impact is expected to be lower in Myanmar due to the biting habits of the of the main mosquito vector species. The annualisation of the ITN cost over the lifespan of the net, conservatively assumed to be three years, means the comparative cost is lower. Although the cost of health gains is low with ITN, in the context of planning for malaria elimination more impactful interventions will need to be considered.

Table 8: Cost-consequence summary of insecticide treated nets and malaria community health workers in Myanmar

	ITN	CHW
Direct Costs	One off purchase and distribution costs are annualised over the lifespan of the net Annual equivalent cost per village in modelled scenarios: US$ 240 - 750	Annual costs include: training, patient services, monitoring and supervision, programme management and CHW remuneration or incentives. Annual cost range in modelled scenarios (excluding variable drug costs): US$ 560 – 2300 Although the effective cost for malaria funds could be reduced through cost sharing.
Direct Consequences	Modest impact on malaria disease in Myanmar due to crepuscular and exophagic biting.	High impact on malaria disease if there is good utilisation of the CHW by people who have malaria.
Indirect Consequences	Modest impact on malaria transmission in Myanmar due to crepuscular and exophagic biting	High impact on malaria transmission if there is good utilisation of the CHW by people who have malaria.
	Direct effects of ITN result in use of fewer diagnostics and treatment and therefore save some costs (included in analysis).	CHW can be used to provide other health services, feedback valuable information on malaria burden, provide information and educational messages to the community (not included in analysis).

The cost-effectiveness of both CHW and ITN is sensitive to the baseline availability of treatment, indicating that services will be most cost-effective when targeted to areas with poor access to malaria diagnosis and treatment. The utilisation of CHW is also very important and investment in quality training, CHW supervision and community engagement may be important to implementing

a cost-effective CHW programme (214). A further option available to planners seeking to improve the cost-effectiveness of CHW programmes is to expand the package of services offered by CHW. This is already happening and many CHW are now also providing a basic health care package or providing additional services such as tuberculosis detection and treatment. Measures to improve the cost-effectiveness of CHWs include expanding the scope of available services; strategies to improve the likelihood that community members seek treatment from the community health worker when they have fever; and targeting community health workers to where they will be most cost-effective.

For several reasons the main analysis does not apply a cost-effectiveness threshold. It is difficult to define an appropriate threshold for the cost per YLL or DALY averted; the budget context in Myanmar is complex with modest NMCP funds being supplemented by international aid, moreover in the context of a drive towards elimination all interventions will cease to appear cost-effective as the malaria burden decreases (in absence of a model for long term benefits). The use of measures such as cost-per YLL averted are therefore less relevant and highly uncertain. The most immediate question is how to maximise impact from malaria funds available in Myanmar and for this no threshold is necessary.

An extension of standard cost-effectiveness analysis to spatially (in this case township-wise) specific resource allocation modelling highlights the need for a paradigm shift in policy discussion from prioritising universal coverage of the “most cost-effective” intervention to targeting of both interventions and presents illustrative township specific recommendations. In this analysis, malaria burden and to a lesser extent population numbers determine the optimal distribution of resources. Future work will seek to include additional data specific to each township.

7.5.1 Limitations

This analysis has several limitations. Firstly, many of the model parameters were unable to be grounded in clear empirical evidence. Rather specified parameter values are assumptions based on the best available evidence and the opinions of several experts on malaria in Myanmar. Notably some key areas of uncertainty, such as overall malaria risk and case fatality rate in untreated malaria, may affect the absolute ICER values but have less effect on the rank order of intervention prioritisation. The model does not include human population movement or malaria transmission dynamics. A malaria transmission model, incorporated into the cost-effectiveness model, would be a useful extension. This would allow indirect effects to be incorporated into the analysis and provide projections of the impact on malaria transmission going forward. The analysis does not include benefits to the patient beyond malaria impact, such as reduced costs to access care nor are issues of service quality examined here. There is a strong interest in extending the scope of CHWs to diagnose and treat other causes of illness and therefore higher health gains than accounted for here. The model considers malaria control in the general population and does not specifically include high risk groups such as migrant or mobile populations. Resource allocation modelling is applied at the township level whereas in Myanmar townships make decisions to allocate malaria interventions on a village by village basis. Finally, township variation here is characterised by population and malaria burden. Costs, baseline access to treatment and treatment seeking behaviour are not assumed to vary between townships.

Chapter 8 Geographic resource allocation of Plasmodium falciparum malaria control in Myanmar: A dynamic modelling analysis of bed nets and community health workers

8.1 Chapter summary

This chapter is a synthesis of the work described in the previous chapters and aims to address the efficient allocation of insecticide treated bed nets and malaria community health workers in the MARC region, Myanmar, for an illustrative budget of US$10m. A dynamic deterministic compartmental model of malaria transmission is used in combination with post-simulation calculation of economic and clinical outcomes. Township-wise estimates of costs and effects are generated for all intervention options of interest and a geographic resource allocation algorithm is used to provide targeting recommendations that maximise health gains for the resources available.

Efficient geographic resource allocation results are presented, with an emphasis of variability and uncertainty. Probabilistic uncertainty analysis shows that, even with considerable prior parameter uncertainty, recommended interventions are remarkably consistent for some townships. The study illustrates the use of dynamic transmission cost-effectiveness modelling within a budget-based geographic resource allocation framework.

8.2 Background

This analysis aims to inform the geographic allocation of investment in the scale-up of core malaria interventions (insecticide treated bed nets and malaria community health workers) in the MARC

region in Myanmar. The analysis is a synthesis of the preceding Chapters; developing a dynamic transmission economic model to use within a geographic resource allocation framework and calibrated using the incidence data gathered as part of the MARC malaria data repository. The aim is to offer recommendations on malaria policy in the MARC region and serve as an illustration of how geographic resource allocation based on cost-effectiveness modelling can be applied.

8.3 Methods

To be able to inform geographic targeting of resources the dynamic transmission economic model must be able to estimate the cost and the health impact, including knock-on transmission effects, of ITN and CHW scale-up at a suitable geographic unit of programmatic implementation. The township was identified as the most appropriate administrative level to model geographic allocation. Essential data including population count were only available down to township level, which prevented village level analysis. While district level administrative boundaries were available, the district was not a commonly used administrative level for the MoH. Province level analysis was considered inferior to the Township level as the additional aggregation would mask heterogeneity that could practically be addressed in geographically targeted malaria programming.

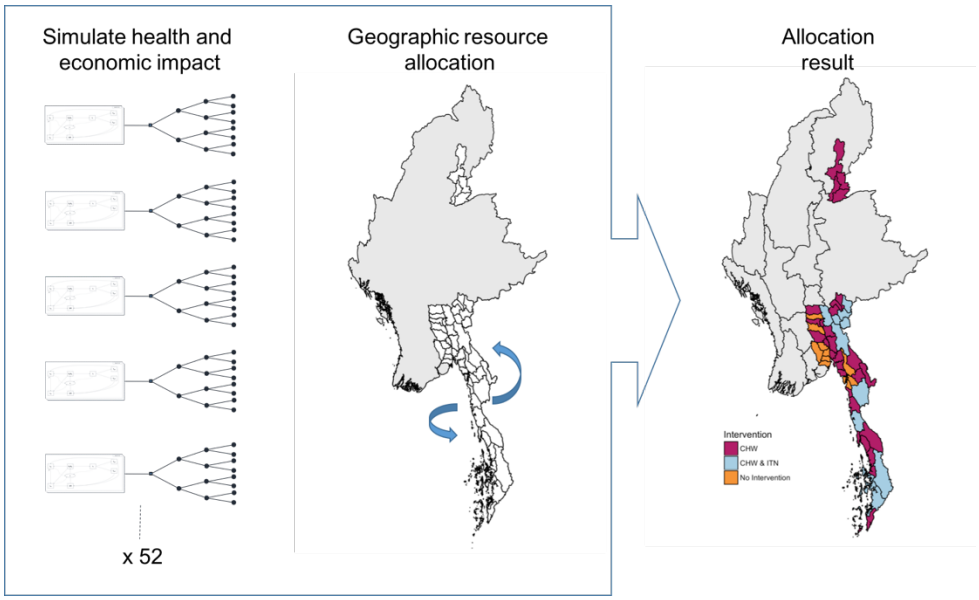
The overall model combines a dynamic model of malaria transmission combined with calculations of cost and health outcomes based on the transmission model outputs. The hybrid model system is replicated 52 times and each is assigned to simulate one township, forming a patchwork, spatially-defined model system. This patchwork of models is used to estimate costs and effects for all intervention options of interest in all townships. The resulting dataset of costs and effects of all intervention-township combinations is used to obtain an efficient allocation of these interventions

across the MARC region for a given annual budget (see Chapter 5 for further details on the resource allocation method) (Figure 18).

The evaluation period begins in 2013, as this is when the cost data was collected and is also the mid-point of the available incidence data. While dynamic models aim to extrapolate forward in time, the likely robustness of results decreases rapidly the further projections extend into the future. While some malaria transmission models aim to estimate the expected time to malaria elimination this is not necessary for the purposes of efficient geographic allocation. Even the most sophisticated forecasting models will struggle to accurately predict malaria incidence beyond the near future as it is very difficult to predict the effect of changes in ecology, climate, population behaviour and economic development on disease transmission. To strike a balance between the reliability of model outputs and the desire to capture all relevant costs and effects a 3-year time horizon was used for evaluation.

Except for a 2011 baseline survey in the MARC region, data on the coverage of interventions was not available. For this reason, the counterfactual for all allocation scenarios is no coverage of ITN or CHW.

Figure 17: Overview of geographic resource allocation with dynamic-transmission economic epidemiological model



8.3.1 Malaria transmission model

A deterministic compartmental model with an adapted Susceptible-Exposed-Infectious-Treated (SEIT) structure was developed to simulate the transmission of *Pf* malaria in each township as well as the effects of vector control and diagnosis and treatment (Figure 19).

Mathematical modelling begins with certain mechanistic assumptions about an outcome of interest, in contrast to statistical modelling which uses no information on underlying processes. There is extensive literature on mathematical modelling of malaria and other mosquito borne diseases (86,215,216), some of which are extremely complex. However, it is important to strike a balance between mechanistic complexity and model parsimony. By its nature, a model is a simplification of a more complex reality and each additional feature of the model should usefully contribute to a better estimate of the outcome of interest. In this case, the ability to characterise the interaction of interventions with the transmission cycle is just as important as characterisation

of transmission. It is also essential to distinguish between symptomatic and asymptomatic. Asymptomatic cases will not seek treatment and therefore constitute a reservoir of disease that case management interventions will not address. Similarly, it is necessary to distinguish between treatment seeking behaviour of symptomatic cases. Potential benefits of improved access to treatment include: better clinical outcomes for those who seek treatment but would not have without the intervention as well as reduced transmission resulting from the treatment of those same individuals. In addition, treatment quality and time-to-treatment are key and affect not only health outcomes but also disease transmission. These too are included in the model as described below.

The dynamic transmission model is comprised of a series of differential equations which determine the flow of individuals as described above and in Figure 19. Each equation below describes the inward and outward flows of each compartment of the model. Capital letters denote compartments and lower case letter denote model parameters.

$$\frac{dS}{dt} = -\lambda S + \frac{I_{ua}}{d_a} + \frac{qT_{oth}}{ph} + \frac{T_{ACT}}{ph}$$

$$\frac{dE}{dt} = \lambda S - \frac{E}{\gamma_h}$$

$$\frac{dI_{us}}{dt} = \frac{m(1 - v_{treat})E}{\gamma_h} + \frac{(1-q)T_{oth}}{ph} - \frac{I_{us}}{d_s}$$

$$\frac{dI_{ua}}{dt} = \frac{(1-m)E}{\gamma_h} + \frac{I_{us}}{d_s} - \frac{I_{ua}}{d_a}$$

$$\frac{dI_T}{dt} = \frac{mv_{treat}E}{\gamma_h} - \frac{I_T}{d_{treat}}$$

$$\frac{dT_{oth}}{dt} = \frac{(1 - v_{ACT})I_T}{d_{treat}} - \frac{T_{oth}}{ph}$$

$$\frac{dT_{ACT}}{dt} = \frac{v_{ACT}I_T}{d_{treat}} - \frac{T_{ACT}}{ph}$$

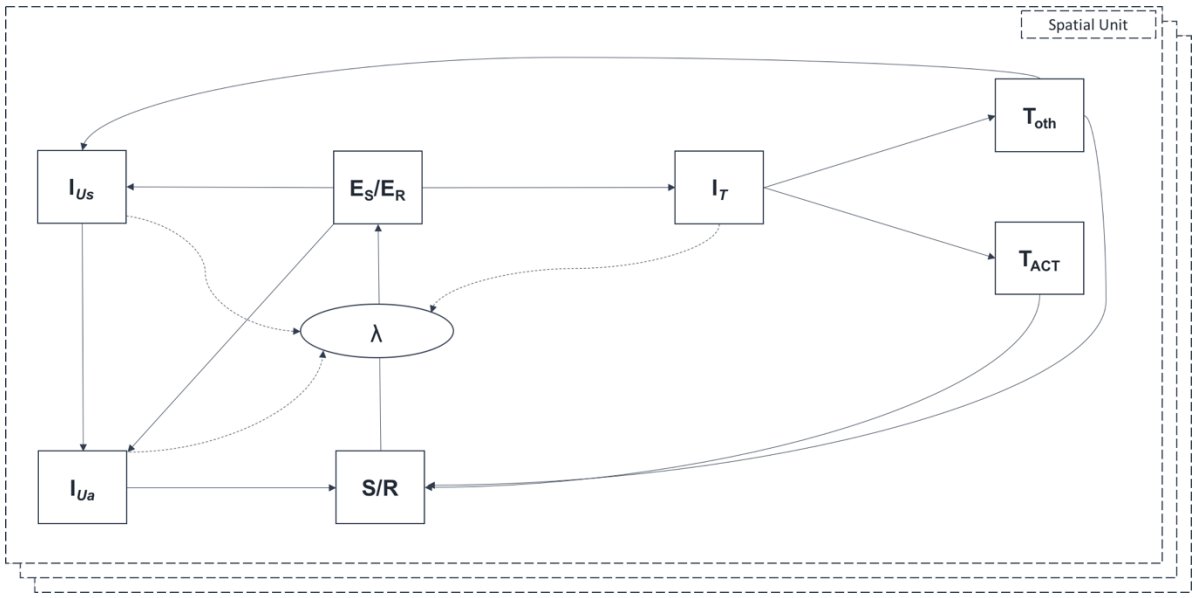
Susceptible individuals (S) are exposed to a force of infection (λ) that is a function of the number of infectious individuals in the population. Exposed individuals (E) become infectious at a rate which is the inverse of the intrinsic incubation period (γ_h). Infectious individuals fall into three categories symptomatic treatment-seeking (I_T), symptomatic but does not seek treatment (I_{us}) and asymptomatic (therefore also untreated) (I_{ua}), according to the likelihood of symptomatic infection (m) and baseline treatment seeking (v_{treat}). Symptomatic untreated infections become asymptomatic at a rate that is the inverse of the mean duration of clinical illness (d_s). Symptomatic treatment-seeking individuals receive treatment at a rate that is the inverse of the mean time-to-treatment (d_{treat}) and receive either quality (T_{ACT}) or sub-standard diagnosis and treatment (T_{oth}), according to the baseline availability of quality care (v_{ACT}). A proportion ($1 - q$) of individuals receiving sub-standard care are reallocated to the untreated compartment while treated individuals return to susceptible at a rate which is the inverse of the period of prophylaxis (ph). Asymptomatic infections resolve at a rate which is the inverse of the duration of asymptomatic infection (d_a).

Only events involved in transmission are calculated in the dynamic model; costs and clinical outcomes including mortality are calculated post-hoc. It is computationally more efficient to have the fewest calculations possible in the dynamic model where calculations are repeated each time step of the simulation. It is assumed that the number of deaths is small and does not substantially

influence (S) or transmission dynamics. The parameters used in the dynamic model and the post-simulation calculations are described in Table 10.

It is common to run transmission models to equilibrium before introducing interventions. For repeated simulation, this would involve substantial wasted computation as each run simulates the same burn-in period. Instead we obtain the steady state conditions once using the "steadystate" function within the rootSolve package (217), and retained for future simulations.

Figure 18: Malaria transmission model diagram



Force of infection

A standard SI compartmental model has the following equation for the force of infection (λ):

$$\lambda = \frac{\beta I}{N}$$

Where I is the number of infectious individuals, N is the total population and β is the effective contact rate. That is, β is the "rate at which two specific individuals come into effective contact per unit time" (218), an effective contact in this context meaning the transmission of infection from one to another. $\beta$is often derived by fitting a transmission model to data.

Malaria transmission occurs not by direct contact with another person but via a mosquito vector. This can be modelled explicitly by incorporating mosquito populations into the model.

$$\lambda = \frac{\beta_{mh} I_m}{N_m}$$

However, it is not possible to obtain data on the total number of mosquitos and other related parameters such as the mosquito biting rate, birth rate and mortality rate are not easily defined with precision.

An alternative to explicit modelling of the mosquito vector transmission is implicit modelling by i) adjusting the definition of β to represent the receptivity of malaria transmission in that population; ii) Introducing a time delay to reflect the extrinsic incubation period, that is, the time it takes for a mosquito to become infectious to humans after ingesting a blood meal containing *Pf* parasites; and iii) Applying an oscillating function to reflect seasonality in the abundance of mosquitos and therefore in the ecological receptivity of malaria transmission. Therefore, in this model the force of infection is the function:

$$\lambda(t) = \frac{I_{all}(t-\gamma_m)}{N} \beta \left(1 + \varphi cos\big(2\pi(t-\phi)\big)\right)$$

Where

$I_{all} = (I_{us} + I_{ua} + I_T)$ (Total number of infectious individuals)

The transmission receptivity (β) as well as the amplitude (φ) and phase angle (ϕ) (or timing of peaks and troughs) of the seasonality are fitted using data on malaria incidence (see Model Fitting).

Table 9: Dynamic transmission economic epidemiological model parameters

Parameter	*Symbol*	*Unit*	*Value*	*Uncertainty*	*Comments*
Epidemiology					
Transmissibility	β	-	-	MCMC posterior	Fitted by township
Amplitude (seasonal forcing)	φ	-	-	MCMC posterior	Fitted by township
Phase angle (seasonal forcing)	ϕ	-	0.428	Fixed*	Fitted for MARC region
Intrinsic incubation period (human)	γ_h	days	15	Fixed*	(219)
Extrinsic incubation period (mosquito)	γ_m	days	14	Fixed*	(220,221)
Duration of clinical illness in untreated cases	d_s	days	9	Fixed*	(222,223)
Duration of infectiousness in asymptomatic carriage	d_a	days	160	Fixed*	(224–226)
Severity: Proportion of untreated cases that progress to severe disease	s	-	0.25	Triangular (0.18-0.30)	(211)
Fatality in severe untreated cases	μ	-	0.6	Triangular (0.5, 0.6, 0.85)	(211)
Proportion of new infections that are symptomatic	m	-	0.9	Fixed*	Originally estimated to be 0.713 for MARC region as a whole using function derived from Aguas et al. and taking beta and probability of treatment as inputs (227). Experts familiar with clinical malaria in Myanmar believe >0.9 is more likely (pers comm.).

Township population Interventions	$N_{township}$	population	Township specific	Fixed	(57)
Treatment seeking (prior to intervention)	v_{treat}	-	0.718	Beta ($\alpha = 92.35, \beta = 36.59$) Where 95CI (0.649, 0.779)	Proportion of malaria cases that seek treatment, prior to modelled interventions (210)
Time to treatment	d_t	days	3	Triangular (1, 3, 5)	(210)
Availability of artemisinin combination therapies: Proportion of treated cases receiving an ACT	v_{ACT}	-	0.25	Triangular (0.15 0.25, 0.5)	PSI surveys show ACT availability in private sector in 2012 was negligible (228). Availability in the public sector and civil society services may be better but the overall availability was low.
Non-ACT treatment quality: Effectiveness in comparison with ACT.	q	-	0.2	Beta ($\alpha = 2.522, \beta = 7.635$) Where 95CI(0.1, 0.6)	Assumed Taking into account drug cocktails and imperfect adherence.
Reporting rate: Proportion of all treated cases captured by incidence database used for this study	g	-	0.4	Triangular (0.2, 0.4, 0.7)	Public sector and civil society data systems are partial. MARC Baseline reports 37% of patient sought treatment in the private sector (210) (See Chapter 6)
Use of insecticide treated bed nets where available	u_{ITN}	-	0.846	Beta ($\alpha = 393.8, \beta = 72.38$) 95CI (0.816 to 0.871)	MARC baseline survey. Usage among those with 'sufficient access' to nets (210).
Protective efficacy of insecticide treated bed net	p_{ITN}	-	0.3	Triangular (0.05, 0.3, 0.5)	Cochrane review reports 50% reduction in incidence however ITNs thought to be

					less effective in Myanmar and other South East Asian countries than other settings dues to mosquito biting behavior (78,229).
[Protective effectiveness of insecticide treated bed net]		-	$p_{ITN} \times u_{ITN} = 0.258$		Produced in situ
Improved access 1: CHW treatment seeking, where available	u_{CHW}	-	0.7	Triangular (0.1, 0.7, 0.9)	Assumed MARC baseline reports low CHW treatment seeking but does not break down by population with and without access to a CHW. (210) Likely to be considerable variation among CHWs – we are concerned with the mean characteristics and uncertainty in that mean.
[Illustrative Total treatment seeking with CHW]			$v_{treat} + (1 - v_{treat}) \times u_{CHW} = 0.915$		Produced in situ
Improved access 2: Reduction in time to treatment due to CHW in village	d_{CHW}		2/3	Triangular (1/3, 2/3, 1)	We assume that on average time to treatment is reduced from 3 days to 1 day or by 2/3rds Assumed
Protective efficacy of ACT treatment against progression to severe disease	p_{ACT}	-	0.95	Triangular (0.85, 0.95, 0.99)	No trials comparing ACT with no treatment, but we know that ACTs are highly effective, even compared with other antimalarials. Once treated with ACT

					(+PQ) we assume contribution to transmission is negligible.
Duration of prophylaxis (outpatient)	ph	days	12	Gamma ($\alpha = 13.62, \beta = 1$) Where 95CI (9, 20.6)	Lumefantrine 90% protective for 12 days Piperaquine for 26 days (126) We conservatively use the AL estimate.
Economics					
Discount rate	r	-	0.03	Triangular (0, 0.03, 0.05)	Assumed
Cost of diagnosis and treatment per malaria case (commodities only)	$\mathrm{c_{treat}}$	USD (2013) per *Pf* case	1.5	Gamma ($\alpha = 2.418, \beta = 1.104$) Where 95CI(1, 5)	(165,166)
Cost of ITN per person per year in a sufficiently provided for population	$\mathrm{c_{ITN}}$	USD (2013) per capita per year	1.05	Gamma ($\alpha = 2.53, \beta = 2.39$) Where With quantiles (0.5, 0.7, 1.2, 1.5)	(166)
[Illustrative cost to maintain ITN coverage per village]		US$ per year	840		Annual equivalent cost assuming distribution campaign every three years. Illustrated for village of 800 population.
Cost of malaria CHW programme (excluding treatment costs) per person per year in a sufficiently provided for population	$\mathrm{c_{CHW}}$	USD (2013) per capita per year	2	Gamma ($\alpha = 7.263, \beta = 3.466$) With quantiles (1.1, 2, 3.2, 4.5)	(165,166)
CHW cost sharing coefficient	$\mathrm{c_{copay}}$		1/3	Uniform (0, 2/3)	Assumed

[Illustrative cost of CHW per village (without cost sharing)]		US$ per year	1087 (1630)		Illustrated with village of 800 and 20 malaria cases.
Cost of hospitalisation	c_{hosp}	US$ per admission	190.3	Triangular (150, 190, 230)	A study of the cost of inpatient hospitalization due to *Pf malaria* on the Thai-Myanmar border (230). While this hospital and others on the Thai side of the border serve a substantial catchment area within Myanmar costs may be higher than in Myanmar hospitals.
DALY weighting for moderate malaria illness	w_m	-	0.0053	Beta ($\alpha = 0.0383, \beta = 2.580$) Where 95CI (0.033, 0081)	(231)
DALY weighting for severe malaria	w_s	-	0.21	Beta ($\alpha = 15.03, \beta = 55.37$) Where 95CI (0.139, 0.298)	(231)
Life expectancy	l	years	65.65	Triangular (60, 65.65, 70)	(232)
Mean age at death	a_μ	years	35	Triangular (20, 35, 45)	Assumed. Unlike other parts of the world malaria in Myanmar is more common in adults.

* These epidemiological parameters were fixed during beta MCMC fitting process. Sampling a new value would require refitting beta and therefore several days of computation time for each Monte Carlo sample. However, variation in transmission intensity would be captured by assessing the impact of variation in β.

8.3.2 Interventions

The developed model can be used to estimate the impact of interventions on population health, both in terms of direct effects of the prevention or treatment of cases and the reduction in the transmission of disease. Malaria community health workers improve diagnosis and treatment of malaria in three ways: access to treatment, time to treatment and quality of treatment. Where available, a mean proportion of the population chooses to seek treatment from the CHW (u_{CHW}). Treatment seeking for this population is assumed to be faster (d_{CHW}) and is assumed to provide an ACT to confirmed cases. In the transmission model these are governed by the following adjustments:

Treatment seeking:

$$v_{treat} = v_{treat} + \omega_{CHW} u_{CHW} (1 - v_{treat})$$

Where ω_{CHW} is CHW coverage (typically one or zero by township in this analysis but the model has the option for partial coverage scenarios).

Reduced time to seeking treatment:

$$d_{treat} = d_{treat} - \omega_{CHW} u_{CHW} d_{treat} d_{CHW}$$

Likelihood the treatment is an ACT:

$$v_{ACT} = v_{ACT} + \omega_{CHW} u_{CHW} (1 - v_{ACT})$$

The coverage parameters are in fact functions of time i.e. $\omega_{CHW}(t)$ and $\omega_{ITN}(t)$. A linear approximation is used to smooth expected intervention coverage between data or assumptions on coverage by year.

The structure of these adjustments accounts for both new treatment seeking and displacement of those who would have sought treatment elsewhere. That is, the total number of cases seeking treatment from a CHW is:

$$Community\ heath\ worker\ cases = \frac{\omega_{CHW} u_{CHW} mE}{\gamma_h}$$

In other words, the rate of new clinical infections ($\frac{mE}{\gamma_h}$), where E is the compartment recording the current number of exposed individuals, m is the proportion of infections that are clinical and γ_h is the human incubation period, multiplied by CHW coverage and uptake ($\omega_{CHW} u_{CHW}$).

Multiplying the previous calculation by the proportion of new cases who would ordinarily go untreated, the total number of new treatments due to the introduction of the CHW is:

$$New\ treatments = \frac{\omega_{CHW} u_{CHW} (1 - v_{treat}) mE}{\gamma_h}$$

In other words, $\frac{(1 - v_{treat}) mE}{\gamma_h}$ is the number of new infections that would go untreated and the CHW coverage and uptake coefficients are applied to this to obtain the new treatments. This reflects that

some of the cases treated by a CHW would have sought treatment elsewhere. However, of cases that would have sought treatment elsewhere, an increased proportion receive more timely and better quality treatment.

$$Improved\ treatments = \frac{\omega_{CHW} u_{CHW} v_{treat}(1 - v_{ACT})mE}{\gamma_h}$$

Again where $\frac{v_{treat}(1-v_{ACT})mE}{\gamma_h}$ is the number of treated cases not receiving an ACT, to which CHW coverage and uptake coefficients are applied.

The improved time to treatment is simply d_{CHW} and is applied to all CHW cases. On successful treatment, it is assumed that individuals no longer contribute to the force of infection. In addition, treated individuals expect improved clinical outcomes (see 8.3.3).

Insecticide treated bed nets protect individuals from malaria by preventing biting from an infectious mosquito, preventing a mosquito becoming infected by biting an infectious human and by killing mosquitos and reducing local transmissibility. Available data on ITN effectiveness from randomised controlled trials is assumed to reflect all mechanisms of effectiveness (70,78) and is reflected in the model through an adjustment to the force of infection:

$$\lambda^*(t) = \frac{(t - \gamma_m)I_{all}}{N}\beta\overline{\boldsymbol{p}}_{\boldsymbol{ITN}}\left(1 + \varphi Cos\left(2\pi(t - \phi - \gamma_m)\right)\right)$$

Where

$\bar{p}_{ITN} = 1 - \omega_{ITN} u_{ITN} p_{ITN}$ (Complement of bed net protective effectiveness)

8.3.3 Clinical Outcomes

For reasons of model parsimony and computational efficiency, clinical severity and mortality are calculated post hoc rather than as part of the transmission model. Untreated individuals (including those returned to the untreated compartment due to poor treatment) have a probability of severe disease (s) and severe cases have a risk of mortality μ. For treated individuals, the probability of severe disease (and thus mortality) is adjusted by the protective effect of ACT equivalent treatment (p_{ACT}).

$$Severe\ cases = s((1 - p_{ACT})\left(\frac{T_{oth} q}{ph_{oth}} + \frac{T_{ACT}}{ph_{ACT}}\right) + \frac{I_{us}}{d_s})$$

$$Mortality = s\boldsymbol{\mu}((1 - p_{ACT})\left(\frac{T_{oth} q}{ph_{oth}} + \frac{T_{ACT}}{ph_{ACT}}\right) + \frac{I_{us}}{d_s})$$

Disability adjusted life years (DALYs) a measure of aggregate health utility (or in the case of DALYs disutility) combine both years of life lost (YLL) and the impact of clinical illness or years lived with disability (YLD). In this model the YLL total is the number of deaths multiplied by the life expectancy (l) minus the mean age at death (a_{μ}). The YLD total is the number of symptomatic cases multiplied by the disutility weighting for moderate infectious disease illness (w_m) added to the number of severe cases multiplied by weighting for severe illness (w_s).

$$DALY = YLL + YLD$$

In terms of the model parameters:

$$YLL = s\mu((1 - p_{ACT})\left(\frac{T_{oth}q}{ph_{oth}} + \frac{T_{ACT}}{ph_{ACT}}\right) + \frac{I_{us}}{d_s})(l - a_{\mu})$$

$$YLD = \frac{w_m mE}{\gamma_h} + w_s s((1 - p_{ACT})\left(\frac{T_{oth}q}{ph_{oth}} + \frac{T_{ACT}}{ph_{ACT}}\right) + \frac{I_{us}}{d_s})$$

To simplify the above equations:

$$YLL = \boldsymbol{mortality}.(l - a_{\mu})$$

$$YLD = \boldsymbol{symptomatic\ cases}.w_m + \boldsymbol{severe\ cases}.w_s$$

8.3.4 Costing

Approximate annualised unit cost estimates per person for malaria community health workers and bed net distribution are available from ingredients based intervention costings (165,166). These are multiplied by the township populations and discounted as appropriate if the evaluation timespan extends past 1 year. The cost of treatments for community health workers will depend on the incidence of malaria. For this reason, estimates of the commodity costs of malaria treatment are separated from the remaining programme cost, that is, in order to allow these costs to track expected changes in malaria transmission.

$$ITN\ cost = \frac{c_{ITN} y N_{township}}{r^{-1}(1-(1+r)^{-y}}$$

$$CHW\ cost = \frac{c_{CHW} c_{copay} y N_{township}}{r^{-1}(1-(1+r)^{-y}}$$

$$Cost\ of\ illness\ (CHW) = \frac{\omega_{CHW} u_{CHW} mE}{\gamma_h} c_{treat}$$

To reflect not only the financial cost of scaling up interventions we also include crude estimate of the cost of illness from outpatients and hospitalisations. It is important to track total spending on malaria cases, not only those associated with the intervention programmes. All cost of illness estimates are also grouped by year and discounted at rate (d).

$$Cost\ of\ illness\ (all\ outpatients) = \frac{v_{treat} mE}{\gamma_h} c_{treat}$$

$$Cost\ of\ illness\ (all\ hospitalisations) = sv_{hosp} c_{hosp}((1-p_{ACT})\left(\frac{T_{oth} q}{ph_{oth}} + \frac{T_{ACT}}{ph_{ACT}}\right) + \frac{I_{us}}{d_s})$$

The treatment compartments in the transmission model refer to outpatient treatment seeking. We apply the cost of inpatient treatment seeking to all severe cases, assuming that most severe cases do receive inpatient treatment at some point. This allows for cases where individuals do not initially seek treatment for mild or moderate illness but are later present at a hospital when illness has worsened.

8.3.5 Parameterisation

Epidemiological parameters

Parameters on the intrinsic and extrinsic incubation periods of *Plasmodium falciparum*, durations of infectiousness and clinical illness, the proportion of cases which progress to severe disease and the rate of fatality in these severe cases if untreated, are all defined using standard literature sources (see Table 9 for details). In this sense, *Pf* malaria in Myanmar is not assumed to be biologically different from elsewhere. The key epidemiological parameter is malaria transmissibility (β). This is fitted to incidence data from each township and reflects the differences in the potential for malaria transmission in each locality. The MCMC fitting process provides an uncertainty distribution and while the other epidemiological parameters must be fixed during model fitting, variation in β captures general epidemiological variation. That is, variation in say duration of extrinsic incubation period would affect the expected β to influence model transmission. Seasonality is governed by two parameters, the amplitude (φ) and phase angle (ϕ) of the seasonal peak (see Section 8.3.6 for further details and a description of parameter fitting).

Intervention Parameters

According to the MARC baseline survey, baseline treatment seeking for fever was 71.8% and time to treatment was three days. Availability of ACTs was thought to be low and set at 25%; private sector surveys found very low ACT availability, though ACTs could be obtained through the public sector. To include the benefit of providing ACT treatment to individuals (through CHWs) compared with non-ACT treatment it is necessary to estimate the effectiveness of non-ACT treatment compared with ACTs. Treatment in the informal private sector in Myanmar often includes drug cocktails that may contain some antimalarials (at sub-therapeutic doses) or none at all (233). In

consultation with local experts it was conservatively estimated that non-ACT treatment in Myanmar was one fifth as effective as an ACT.

Despite the significant achievements made by the MARC Data Repository initiative in collating data on malaria incidence from government and civil society organisations, the results are nevertheless very likely to be an under estimate. Some civil society data was not shared, data from Myanmar military health services in the region were unavailable and the MARC baseline survey indicates that 37% of patients sought treatment in the private sector (210), again, for which no case data could be retrieved. It was assumed that a case of malaria in the MARC region had a 40% of being recorded in the MARC Data Repository. In other words, we assume the true burden of malaria in all townships is 2.5 times greater than reported.

Baseline ITN usage when available was 84.6% according to the MARC baseline survey (210). As discussed previously in this thesis, the differences in biting behaviour in many mosquito species found in Myanmar mean that ITN are likely to be less effective than elsewhere. Therefore while the Cochrane review reports a 50% protective effect against infection (78) this analysis uses a reduced estimate of 30%. While the MARC baseline survey reports low CHW treatment seeking it does not breakdown by populations with and without access to a CHW. There is likely to be considerable variation in uptake between CHW according to how that individual is perceived by the community. Further discussions with key stakeholders led to a revised estimate (compared with Chapter 7) that average CHW uptake would be at least 70% among new CHW programmes. Time to treatment in the areas where CHWs are introduced would be reduced from three days to one day. ACTs are the most effective antimalarial therapy available and while evidence comparing ACT treatment to untreated malaria cannot be produced 95% efficacy is assumed. Once the individual is treated with

an ACT (in many cases the transmission blocking drug primaquine is also administered) transmission is assumed to be negligible. In addition to direct treatment and onward transmission effects, ACT treatment also has a prophylaxis effect due to the artemisinin partner therapy. In Myanmar lumefantrine is the most common partner drug and therefore a 12-day period of protection due to prophylaxis is used (176).

Economic and Outcomes Parameters

A discount rate of 3% was used to adjust for time preferences. The variable costs of diagnosis and treatment were estimated at $1.5 based on the approximate cost of the consumables required including the ACT and a rapid diagnostic test. While the annual per person cost of CHW provision excluding treatment consumable costs was estimated to be US$ 2 (165,166). It also became clear that some integrated CHW programmes were replacing malaria-specific programmes. To reflect this a cost-sharing coefficient was introduced to adjust CHWs programme costs (excluding treatment consumables but including all CHW time). This is set at 1/3 in the base case analysis meaning that programme costs are reduced by 1/3 with respect to the malaria budget. The cost of ITN provision per person per year in a sufficiently provided for population was estimated to be US$ 1.05. A study on the Thai-Myanmar border found the cost of inpatient hospitalization due to *Pf* malaria to be US$ 190 per case (230). While this hospital and others on the Thai side of the border serve a substantial catchment area within Myanmar costs may be higher than in Myanmar hospitals.

Health outcomes were modelled as disability adjusted life years using standard weightings for moderate and severe illness (231). Mean age at death was assumed to be 35 years and life expectancy 65.65 years (232).

8.3.6 Model fitting

To characterise the differences in malaria transmission between townships in the MARC region the model is fitted to data on the monthly incidence of *Pf* cases recorded separately for each township. Chapter 3 describes the initiative to gather this data from the numerous organisations implementing malaria programmes in the MARC region.

The key model parameter to fit to this data is the transmissibility parameter beta (β). This describes the degree to which infections can be spread from one person to another and can be thought to reflect a combination of factors but principally the ecology of the mosquito population and their ability to act as a disease vector. In addition to beta the two parameters that characterise malaria seasonality amplitude (φ) and phase angle (ϕ) (the relative height and timing of seasonal peaks in malaria incidence respectively) are also fitted. Since the timing of interventions is not evaluated in this study seasonality is unlikely to be an important driver of results but seasonality is included for completeness and to aid the fitting of beta. For some townships, the incidence data do not show clear seasonal trends, however we believe this is due to the relatively low number of cases and quality of reporting timeliness and therefore apply seasonal forcing in all townships. The phase angle was assumed to be consistent for the 52 townships and fitted to the MARC region as a whole, while amplitude was allowed to vary between townships and fitted simultaneously with beta, applying a floor value of 0.1.

The data collected comprises the NMCP/WHO database as well as additional data collected from other organisations providing malaria diagnosis and treatment services in the region of interest (see Chapter 6). Despite the efforts made to collect additional incidence data the recorded cases will nevertheless reflect a proportion of the true number of cases. A reporting rate (g) that reflects the

probability a case of malaria in the MARC region in 2012-14 is recorded in the MARC Data Repository, is assumed. This takes into account the roles of the private sector, the military and traditional medicine in providing malaria case management in the MARC region, as well as further civil society organisations not included in the available dataset and cases where the individuals do not seek treatment. Variation in reporting rates between townships may be an important source of error in priority setting and systematic bias is plausible whereby remote townships have both weaker surveillance systems and greater true burden of malaria. However, in absence of a rationale with which to apply different reporting rates to townships, the same rate is applied to all.

The available data show a marked decline in the incidence of *Pf* cases during 2012-14. While investment in interventions including the distribution of bed nets and the expansion of diagnosis and treatment services through community health workers increased during these years, data on intervention coverage are scarce. The MARC baseline survey finds that 11.6% of individuals with fever sought treatment from a community health worker and 35.1% of households owned an insecticide treated bed net (210). For the purposes of fitting to declining incidence data we assumed arbitrary annual increases in intervention coverage in 2013 and 2014. For the economic evaluation 2013 is the first year of intervention.

Two approaches are taken to model fitting. First, an iterative Nelder-Mead or downhill simplex optimisation algorithm is used to obtain initial parameter estimates with relatively low computational cost (234). Second, a Markov Chain Monte Carlo (MCMC) method using an adaptive Metropolis-Hastings algorithm (235,236) is applied to achieve a more robust estimate and a sampling distribution. In both Nelder-Mead and MCMC methods the objective function is a minimisation of the negative log-likelihood of the data given the model, assuming a Poisson

likelihood distribution. The township-wise fitted parameter estimates were used as the starting initial values for the MCMC method.

Some infectious disease transmission models are subjected to a model validation procedure (237), this was not undertaken in this study but could be a useful extension in future work.

8.3.7 Geographic resource allocation

The evaluation takes a provider perspective as the aim is to inform budget allocation. The common comparator scenario is that of no further investment, i.e. no sustained ITN coverage and no CHWs. The allocation algorithm makes allocation decisions using incremental intervention comparisons, as described in detail in Chapter 5, so this is not consequential in terms of the allocation result. The township is the unit of allocation as this is the administrative geographic planning unit most commonly used by stakeholders in planning and implementing malaria programmes.

Malaria transmission is simulated for three years from the time of intervention (1 year and 5 years also evaluated). For simplicity, it is assumed that intervention coverage is maintained for the three years and all intervention costs either track simulation events or are annualised (as appropriate, with fixed costs being annualised and variable costs for diagnosis and treatment applied per simulated event). The time horizon with respect to the economic evaluation is life course, meaning that years of life lost are calculated with respect to life expectancy. The fitted dynamic-transmission economic model is used to estimate the incremental cost and health impact of each intervention in each township compared with a common “no additional intervention” scenario. From this information, an efficient geographic allocation of resources is obtained for a budget of US$ 10

million. In this process intervention costs are used to track the remaining budget while net cost, including differences in the cost of illness between scenarios is used to assess cost-effectiveness.

Given the degree of uncertainty in model inputs, scenario and uncertainty analysis are central to the presentation of results. The default allocation result, using the values described in Table 10, is presented as part of a panel of allocation scenarios given different parameter assumptions. Further, a probabilistic sensitivity analysis (PSA) is conducted by sampling from the parameter distributions described in Table 10 and repeating the geographic resource allocation analysis. Parameters are assigned beta, gamma or triangular sampling distributions according to the supported range of the parameters and the prior belief about the parameter uncertainty. Triangular distributions allow a clear communication of the expected value and specified range and are well suited to parameters with little prior data to fit a sampling distribution to. However, the distribution density is clustered around the central estimate so may not be sufficiently 'loose' a prior in some cases. The Beta distribution is bound between zero and one and therefore is suitable for parameters that describe proportions. Gamma distribution is bound between zero and positive infinity and can be used for parameters that can take values in this range. Beta and Gamma distributions are fitted to prior data or beliefs (including 95% CI or quantiles) using a Nelder-Mead linear optimisation.

In standard cost-effectiveness analysis, PSA results report the number of times a particular intervention option is the optimal choice. Presenting the results of the geographic allocation is somewhat different as the result of each simulation includes, in this case, 52 intervention selections. To summarise and present the PSA results, the number of times each intervention is selected in each township is presented in both bar plot and heat maps.

Table 10:Township-wise transmissibility (β) estimates

Township	Population (2014)	*Pf* cases (2013-14)	API ($\mathbf{10^{-3}}$) (mean 2013-14)	Nelder-Mead	MCMC		
				Transmissibility Parameter ($\boldsymbol{\beta}$) ($\mathbf{10^{-3}}$)	Transmissibility Parameter ($\boldsymbol{\beta}$) ($\mathbf{10^{-3}}$)	Lower 95 CI	Upper 95 CI
Myitkyina	317604	3193	10.1	7.983	8.044	8.032	8.057
Bamaw	135877	2291	16.9	7.961	8.000	7.984	8.016
Momauk	62914	796	12.7	8.039	8.162	8.129	8.196
Mansi	52945	791	14.9	8.104	8.305	8.266	8.344
Loikaw	128401	1036	8.1	7.857	7.754	7.745	7.764
Demoso	79201	550	6.9	7.863	7.764	7.746	7.783
Phruso	29374	654	22.3	8.022	8.143	8.103	8.184
Shadaw	6742	473	70.2	8.565	9.521	9.328	9.715
Bawlakhae	10996	513	46.7	8.311	8.857	8.752	8.963
Pharsaung	25594	929	36.3	8.165	8.490	8.434	8.545
Mae Sae	6319	1144	181.0	9.980	13.867	13.332	14.402
Hpaan	421575	1102	2.6	7.803	7.622	7.620	7.625
Hlaingbwe	265883	3036	11.4	7.874	7.795	7.788	7.802
Hpapun	35085	7497	213.7	9.988	14.930	14.661	15.198
Thandaung	96052	3102	32.3	8.108	8.351	8.326	8.376
Myawaddy	210540	4272	20.3	8.015	8.128	8.112	8.143
Kawkareik	220342	2417	11.0	7.888	7.829	7.820	7.837
Kyarin Seikyi	254849	9576	37.6	8.094	8.330	8.315	8.344
Dawei	146964	2585	17.6	8.034	8.169	8.150	8.187
Laung Lone	118317	2042	17.3	8.011	8.122	8.105	8.138
Thayet Chaung	105662	1397	13.2	7.907	7.873	7.857	7.889
Ye Byu	122633	1976	16.1	8.073	8.262	8.240	8.283
Myeik	284489	4035	14.2	7.971	8.026	8.016	8.036
Kyun Su	171753	5634	32.8	8.276	8.782	8.761	8.804
Palaw	129992	1896	14.6	7.951	7.977	7.962	7.993
Tanintharyi	106853	3228	30.2	8.286	8.793	8.764	8.821
Kawthaung	140020	2227	15.9	7.966	8.013	7.998	8.028
Boke Pyin	81718	3679	45.0	8.337	8.942	8.909	8.976
Bago	491434	839	1.7	7.820	7.662	7.659	7.665
Thanatpin	145287	126	0.9	7.792	7.595	7.592	7.598
Kawa	197363	43	0.2	7.785	7.579	7.577	7.581
Waw	176014	355	2.0	7.806	7.630	7.625	7.635
Nyaunglaybin	199483	1232	6.2	7.857	7.753	7.745	7.760
Kyauktagar	251212	1397	5.6	7.869	7.782	7.775	7.789
Daike U	202530	476	2.4	7.820	7.662	7.657	7.668

Shwegyin	107462	1348	12.5	7.964	8.008	7.991	8.025
Taungoo	262056	980	3.7	7.827	7.680	7.675	7.685
Yedashe	213593	1137	5.3	7.868	7.780	7.772	7.787
Kyaukkyi	113329	441	3.9	7.856	7.748	7.736	7.761
Phyu	257273	728	2.8	7.819	7.661	7.656	7.666
Oaktwin	159828	593	3.7	7.845	7.723	7.716	7.731
Tantabin	117276	936	8.0	7.882	7.814	7.803	7.826
Mawlamying	289388	260	0.9	7.797	7.607	7.604	7.610
Kyaikmayaw	195810	379	1.9	7.823	7.671	7.665	7.678
Chaungzon	122126	158	1.3	7.813	7.648	7.640	7.656
Thanphyuzayat	170536	966	5.7	7.846	7.725	7.718	7.733
Mudon	190737	461	2.4	7.817	7.657	7.651	7.662
Yae	263624	2018	7.7	7.882	7.813	7.805	7.821
Thaton	238106	1096	4.6	7.858	7.755	7.748	7.762
Paung	218459	653	3.0	7.833	7.694	7.689	7.700
Kyaikhto	184532	1446	7.8	7.887	7.825	7.815	7.834
Beelin	181075	2510	13.9	7.967	8.015	8.004	8.027

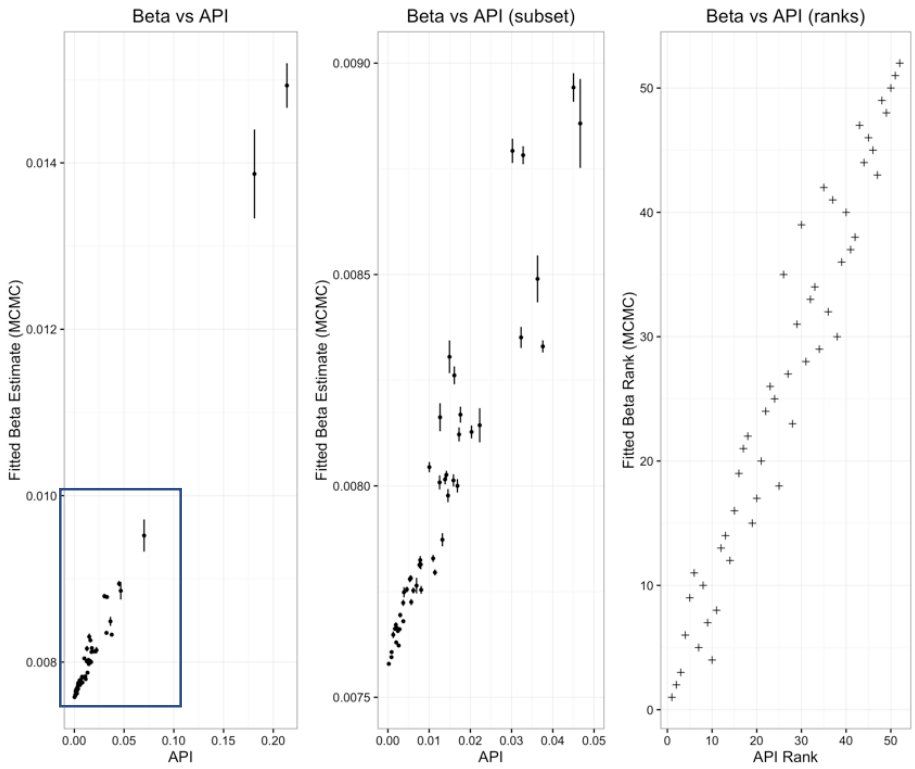
8.4 Results

8.4.1 Model fitting

Township-wise estimates of beta from both the Nelder-Mead and the MCMC methods can be found in Table 11 along with 95% confidence intervals from the MCMC method. The MCMC traces for beta and amplitude for each township can be found in the Appendix.

The observed cases predicted by the model for each township given the fitted MCMC results for malaria transmissibility and seasonality are presented in Figure 19. Not all townships' incidence data shows clear seasonality; however, the most important outcome is that the estimate for transmissibility (β) reaonably reflects the expected burden of disease. There is good agreement between API and beta and the 95% confidence intervals only overlap between townships where the beta estimates and API are similar.

Figure 19: Comparison of fitted township transmissibility (β) with API



8.4.2 Resource allocation

Given the substantial uncertainty in the model inputs we emphasise scenario and sensitivity analysis in the reporting of results. Figure 20 presents a panel of results for the allocation of US$ 10m to ITN and CHW within the 52 MARC townships. The panel includes the base case result (A) given the parameter values detailed in Table 10 as well as a series of alternative scenarios with single or multiple parameter changes. All scenarios recommend a mixture of interventions including with no additional interventions in some, low burden, townships and implementation of both interventions in other, high burden, townships. All scenarios except D (Low ITN protective effect, p_{ITN} = 0.05) recommend using both ITN and CHW in the townships with the highest burden of malaria. Scenarios B, F and G are notable in that ITN are the first choice intervention with CHW

added in high burden townships, whereas in the other scenarios CHW are the first choice. A low value for CHW uptake is assumed in all parameters.

Figure 20: Scenario analyses of geographic resource allocation of ITN and CHW in the MARC region

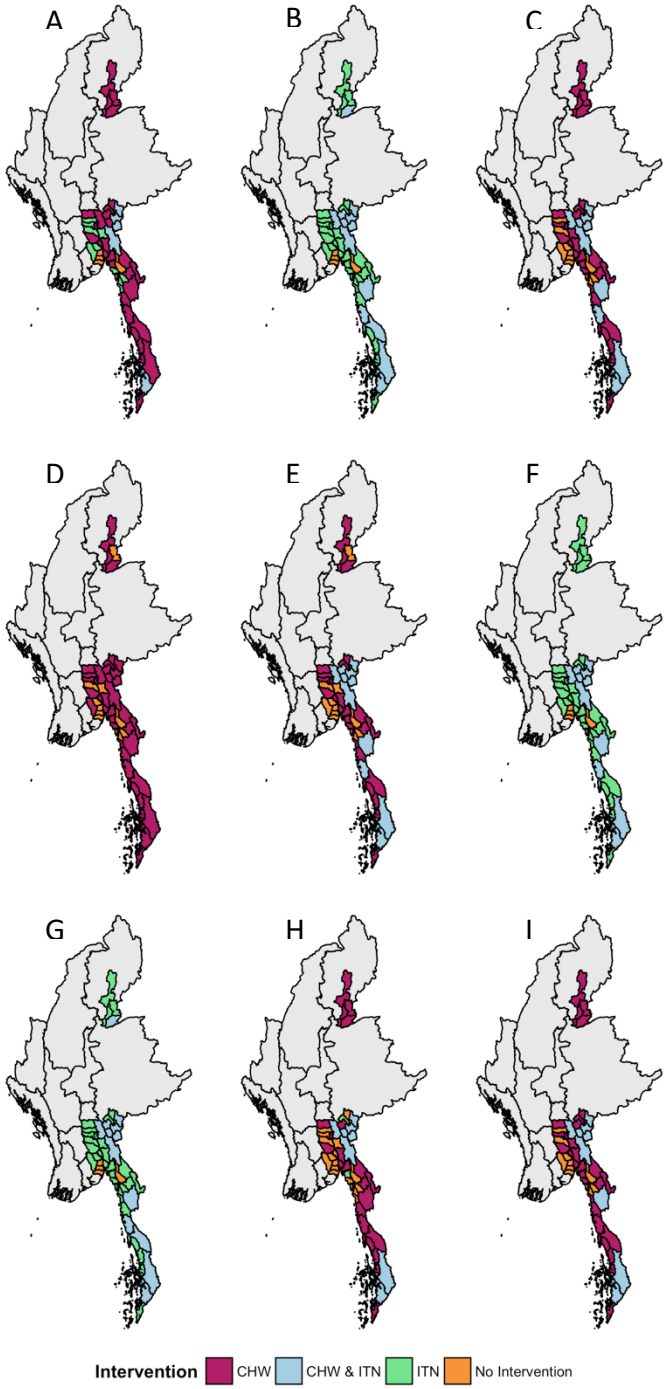


Figure Legend:
A: Default parameter values as described in Table 10. B: Low CHW uptake (u_{CHW} = 0.1). C: Low cost of illness (c_{treat} = 1). D: Low ITN protective effect (p_{ITN} = 0.05). E: Low CHW uptake AND Low ITN protective effect (u_{CHW} = 0.1, p_{ITN} = 0.05). F: Low CHW uptake AND No CHW cost sharing (u_{CHW} = 0.1, c_{copay} = 0). G: Low CHW uptake AND Low ITN protective effect AND No CHW cost sharing (u_{CHW} = 0.1, p_{ITN} = 0.05, c_{copay} = 0). H: No CHW cost sharing (c_{copay} = 0). I: Provider perspective

Probabilistic sensitivity analysis (PSA) results are expressed as the likelihood that an intervention is the optimal allocation in a particular township, given the parameter uncertainty specified in Table 10. Figure 22 presents the mapped results separately for each intervention and combined. The intensity of the colour is determined by the proportion of simulations where that intervention option is selected. White colour means a low likelihood that the intervention is a cost-effective choice with higher colour saturation indicates that the intervention is likely to be a cost-effective choice. In the left most panel, the separate intervention plots are combined into a single map. The colour of the township is determined by the most likely optimal choice with the intensity reflecting the likelihood of that option on the same scale as the single-intervention plots. Figure 23 presents the same results as a bar plot, allowing the likelihood score to be read with greater precision.

Figure 21: Geographic resource allocation of ITN and CHW in the MARC region: Mapped Probabilistic sensitivity analysis

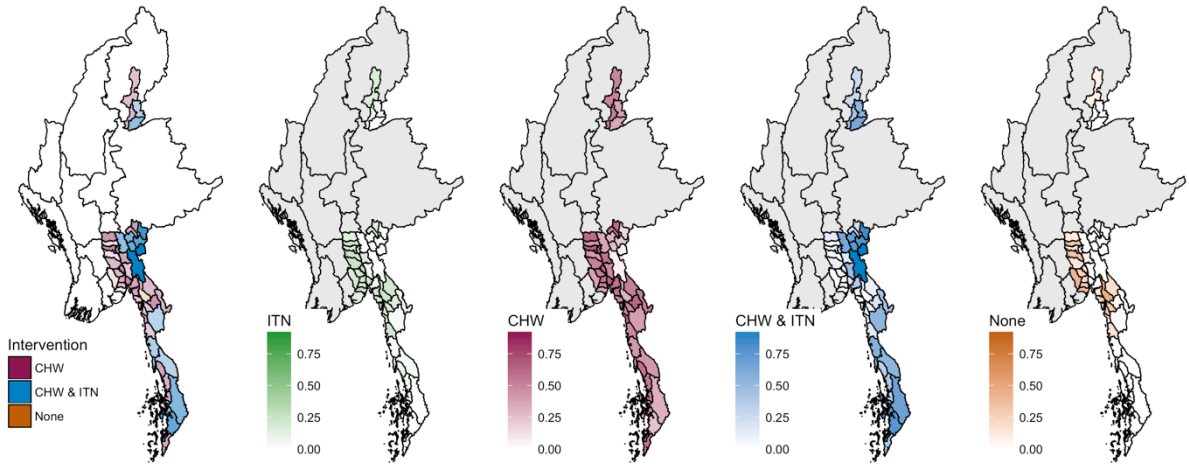
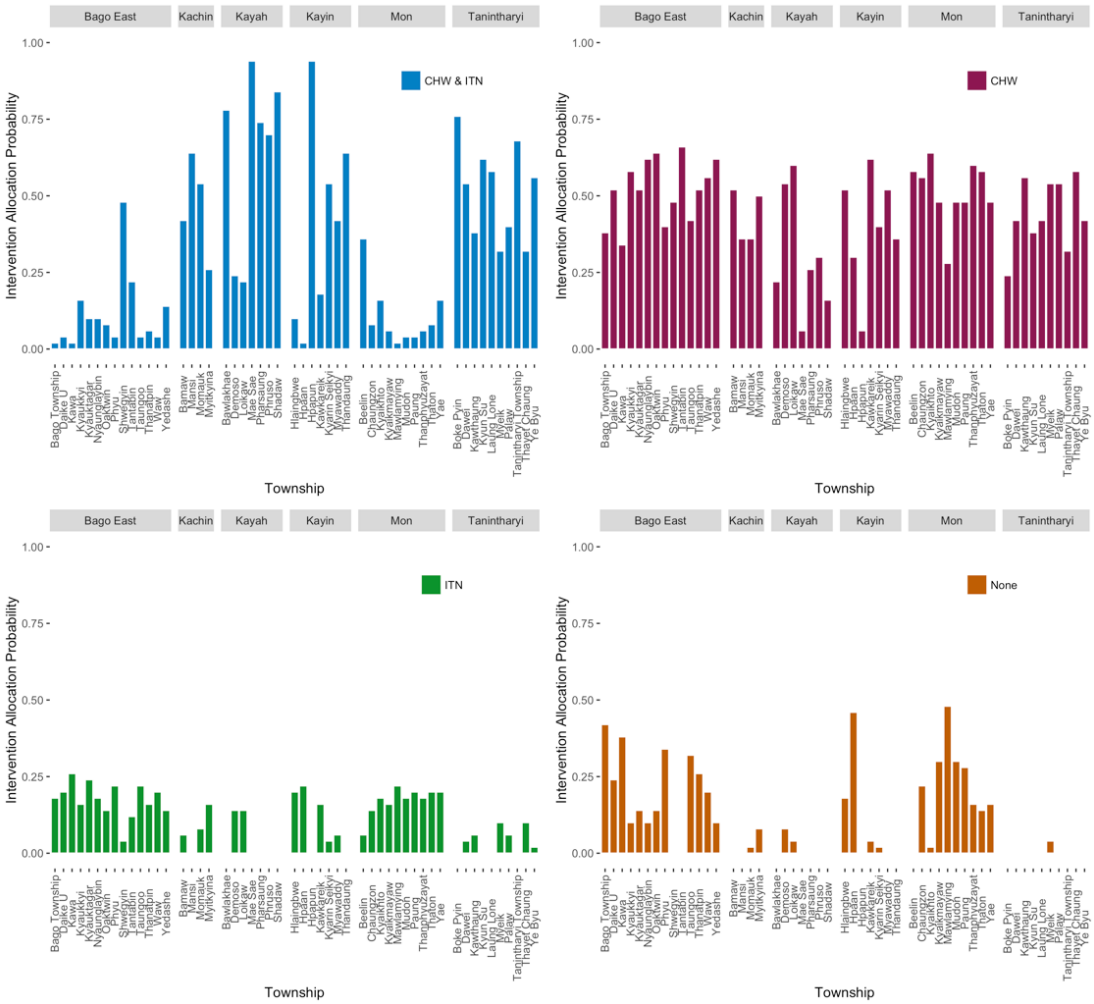


Figure 22: Geographic resource allocation of ITN and CHW in the MARC region: Bar plot probabilistic sensitivity analysis



8.5 Discussion

In this analysis, a dynamic transmission economic evaluation model was used to assess the scale-up of core malaria interventions in the MARC region in Myanmar. Specifically, efficient investment scenarios of US$10m in ITN or malaria CHWs were identified using a geographic resource allocation algorithm to synthesise information on expected costs and effects of each intervention option, including intervention combinations, in each Township.

Standard cost-effectiveness analysis was not well suited to inform priority setting of malaria spending on ITN or CHW in the MARC region. There is no clear cost-effectiveness threshold (CET) defined for the Myanmar health sector by the Ministry of Health or other national institution and there is increasing consensus that the WHO recommended threshold of 1x and 3x GDP per capita are too high (34,238). Moreover, even if a health sector CET were available there are several further complications to the use of CET for priority setting within a malaria elimination campaign (see Chapter 4). Moreover, there are two dimensions to the priority setting problem; which intervention to choose (though they are not mutually exclusive) and where to implement. As such an alternative framework on geographic targeting is applied (see Chapter 5).

The analysis provides an illustration of the application of a geographic resource allocation framework as well as tentative policy recommendations for malaria planning in the MARC region. All sensitivity and scenario analyses recommend a mixture of interventions, geographically targeted to maximise impact. Moreover, there is clear guidance on the optimal approach for some townships. For example, in Mae Sae, Hpapun and several others, greater investment and implementation of both interventions was consistently the recommended course of action.

8.5.1 Model choices

While some modelling groups develop a single all-purpose model of malaria transmission, the approach within the modelling group in MORU is that junior staff develop bespoke models for the studies they are working on. While the disadvantage of this approach is that more time is spent on model development, the advantages are that models are designed specifically for the study in question and can therefore, in principle, be simpler and more parsimonious with enough complexity to address the question at hand but without characteristics that might be needed to

answer another question. In this model mosquito populations are not included explicitly. While early versions of the model did include mosquito compartments it was found that no data were available to support the additional parameters required to define mosquito population numbers, birth rates, death rates and biting rates and there was no additional benefit compared with describing the force of infection in terms of transmissibility, extrinsic incubation and seasonality, whereby the characteristics of mosquito populations are implicitly incorporated into these parameters. Moreover, evidence of the effectiveness of interventions does not disaggregate effect by the life cycle stages of mosquitos or plasmodia and so evidence from randomised controlled trials on the effectiveness of bed nets can more easily be applied to a single transmissibility parameter.

Stochastic versions of the compartmental model were developed by recasting compartment transition rates a probability that an event occurs in a particular period of time, as described in the Reed-Frost equation (described subsequently by Abbey (239) and then Fine (240)). However, stochastic model behaviour is particularly important when modelling disease elimination. Since the evaluation does not aim to evaluate elimination model stochastic was not considered a priority. An alternative to compartmental modelling (whether deterministic or stochastic) is the individual or agent based model. The permitted states of an individual based model might be equivalent to a compartmental (or Markov) model, however instead of tracking aggregated groups, each individual is defined explicitly. An individual-based model would be impractical to simulate transmission in the MARC region, comprising a population of 8.71 million.

Malaria transmission is simulated for three years post-intervention. This is shorter than some other analyses, as we can see in Table 3, Chapter 3. Transmission models can be used to forecast time to

elimination and, in this case, long time horizons are necessary. However, the accuracy of any transmission model declines rapidly the further into the future the model is used to forecast (particularly if secular trends are considered). The purpose of the transmission model here, compared with the static model, is not to project further into the future but to quantitatively include indirect impact that occurs because of the effect of the interventions on malaria transmission in addition to direct health benefits. This can be achieved with a relatively short time horizon, avoiding the uncertainty associated with long-run forecasting.

Early versions of the model featured inter-township malaria transmission. That is, each township has a force of infection due to transmission within the township and an additional force of infection from other townships due to human population movement and, to a lesser extent, mosquito population movement at the township boundaries. In this case the transmissibility parameter is disaggregated into a transmissibility matrix that characterises between-township transmission. However, this model was not compatible with the geographic resource allocation framework. The algorithm sequentially selects intervention-township options to identify an efficient allocation of interventions, however with inter-township connectivity each intervention selection in each township would require explicit simulation of new cost and effect results for all townships. Rather than 208 transmission simulations required for a single allocation result (interventions by 52 townships) 10,816 transmission simulations would be required for a single result. Removing inter-township transmission will underweight the impact of intervening in so-called “source” populations, where areas of high malaria transmission export cases and sustain transmission elsewhere. However, the framework already prioritises intervention in high burden populations. Nevertheless, nuanced geographic targeting could be supported by analysis of likely sources and sinks (241).

8.5.2 Limitations

There are several limitations to this analysis. Despite efforts to improve the quality of data on monthly incidence of *Pf* cases by township described in Chapter 6, there is likely to be considerable difference between the recorded incidence of *Pf* cases and the true burden of malaria in the MARC region. While the empirical incidence was inflated by a reporting rate this was applied uniformly to all townships; consequential error will lie in heterogeneous differences in reporting between townships. Also, the year of evaluation is 2013 since this is the year under consideration at the outset of this work, it also the year cost data collection took place and falls within the period for which we have collected improved incidence data. Results can still be informative to contemporary policy making with respect the kinds of strategies that are likely to be effective, that is, targeting resource to where impact will be greatest, but are not reliable township specific recommendations.

The analysis only considered two interventions as these were considered the most relevant by policymakers. However other malaria priority setting analyses (136,179,183,242) have considered a wider range of interventions. Incorporating the full range of interventions may find that application of multiple interventions to the highest burden disease areas is the most efficient strategy or, conversely, could predict that the marginal impact of several interventions in one township is less than wider application of fewer interventions.

With some structural adaptations of the model, better locally specific data could be harnessed. The township-wise quantification of access-to-treatment and existing deployment of malaria prevention interventions could improve estimates of the marginal impact of further investment. For example, if a township has relatively good coverage of bed nets but fewer options for quality diagnosis and

treatment then malaria CHWs are likely to have a greater marginal impact. Similarly, recent initiatives support the use of variable cost functions instead of flat rate intervention unit costs (199,243–245). Incorporating geographic heterogeneity in intervention cost, if such data were available, could be usefully incorporated into the analysis within the geographic resource allocation framework.

There is considerable quantified and unquantified uncertainty in the analysis. However, to some extent this reflects the uncertainty in the decision problem facing policy makers. Policy makers also synthesise the available evidence and make a judgement about the allocation of ITN and CHW in the MARC region. Where geographic priority setting plays a role and relies on heuristics such as risk stratification of villages or townships as well as the knowledge of local medical officers and communities. Among some key stakeholders the malaria policy discourse centres on “universal coverage” of what are perceived to be the best interventions. In one respect, universal coverage is a rigorous, comprehensive goal; leaving no group behind. However, in malaria policy universal coverage often does not mean the country as a whole but defined areas considered to be more of a priority for malaria interventions than elsewhere, such as the MARC region. This geographic priority setting could be both more nuanced and better supported by a systematic synthesis of the available evidence. This study illustrates application of a framework for this analysis.

Discussion

Chapter 9 Discussion

9.1 Summary

This thesis describes a programme of research aimed at informing priority setting in malaria control and elimination in Myanmar. Specifically, it addresses the geographic targeting of insecticide treated bed nets and improved diagnosis and treatment at the village level through community health workers.

Malaria in Myanmar is a public health priority due to both the health burden caused by the disease and the threat posed by the spread or emergence of Plasmodium parasites resistant to artemisinin-based therapies. At the outset of this DPhil official malaria policy focused on malaria *control* and *containment* of drug resistance. During the course of the DPhil, as well as significant changes in wider political and economic conditions in Myanmar, official malaria policy shifted from control and containment to elimination. This shift took place in the context of wider regional momentum toward malaria elimination with major funders of malaria programmes advocating for elimination. In late 2014 heads of state convening in Nay Pyi Taw, Myanmar for the 9th East Asia Summit, pledged to eliminate malaria from the Asia-Pacific region by 2030, an ambitious and unprecedented political commitment. While the pivot towards elimination does have important consequences for malaria policy and investment decisions, it did not affect the relevance of the DPhil research question. Investment in ITN distribution and CHW programmes would remain a foundational component to any malaria elimination strategy.

The original question posed at the outset of the DPhil was “which is more cost-effective in Myanmar, insecticide treated bed nets or diagnosis and treatment of clinical malaria through community health workers?”. Standard cost-effectiveness analysis would aim to report a best-estimate cost-effectiveness ratio along with an exploration of how this could be expected to change under different conditions or assumptions. This analysis goes further in mainstreaming heterogeneity between populations into the primary analysis; presenting township-wise geographic allocations of these interventions, for a given budget. Additional outputs from the thesis include the first literature review of dynamic-transmission economic evaluations in low and middle income countries; a critical review of economic evaluation methods in the context of malaria policy making and; a data repository that tripled the available data on malaria burden in the MARC region.

The impact of interventions on the transmission of disease, as well as direct health gains from treatment or prevention, played an important role in the discourse surrounding prioritisation of bed nets or malaria community health workers in Myanmar. Mathematical modelling of infectious disease transmission may be combined with health economics methods to incorporate transmission effects into the assessment of intervention cost-effectiveness. At the outset of this DPhil, dynamic transmission economic evaluation was, and to some extent remains, an emerging cross-disciplinary method. It was decided to undertake a literature review to understand the state-of-the-art, particularly with respect to its application in low and middle income countries. The review (described in Chapter 3) found that most studies concerned well-funded disease areas, particularly HIV/AIDS, and that methodological practice and reporting from the perspective of healthcare economic evaluation, could be improved. Conducting the review supported the thesis in several ways. In addition to a greater awareness of the methodological and reporting challenges specific to DT-EE studies such as taking care not to separate sensitivity analysis by economic and

epidemiological parameters, the review also led to connections being made with other researchers working in this space.

Within the first year of the research it was realised that a generalised results and recommendations on intervention cost-effectiveness, as often reported by cost-effectiveness analysis, may be inconsistent with the capacity for implementation of bed nets and community health workers in some areas and not others. As a result, development of an approach to geographic resource allocation based on cost-effectiveness became an important part of the DPhil research (Chapter 5). An algorithm was developed that efficiently allocates a budget to interventions in particular townships (or other geographic units) according to their expected costs and health impact. A budget was used as the resource constraint since malaria funding in Myanmar is largely driven by international aid and therefore typically ring-fenced for malaria spending. This too, is a departure from standard practice where ordinarily a cost-effectiveness threshold (CET) represents the relevant resource constraints. A critical appraisal of the application of cost-effectiveness methods to malaria policy making, including the CET, also became an important component of this work (Chapter 4).

The MARC data repository, an initiative to collate existing data on malaria burden in the MARC region described in Chapter 6, resulted in a tripling of the available data on malaria incidence with the number of confirmed *Pf* cases rising by 50%. The repository was established in collaboration with the National Malaria Control Programme, the Department of Medical Research and the WHO Country Office and collected village or township level data from 15 separate implementing organisations. As the collected data were not available in a standardised format, considerable efforts were required to process and aggregate these data. However once complete, the resulting

data provided a fuller picture of the malaria burden in the MARC region, and found that *Plasmodium falciparum* transmission is likely to be in decline.

Lastly, the static and dynamic analyses of the cost-effectiveness and geographic resource allocation of bed nets and community health workers (Chapters 7 and 8) bring the methodological and data collection components of the research into applied analysis. Below these two analyses are compared with each other and against the most relevant standard of best practice for economic evaluation in low and middle income countries, the Reference Case recently published by the International Decision Support Initiative (243). The take-away message of the applied economic evaluation could be summarised as a recommendation that, in the case of malaria planning in the MARC region, geographic priority setting is equally as important as prioritising between interventions. That is, discussion and indeed evaluation of both the effectiveness and cost of bed nets and community health workers is important, but universal application of whichever is considered the most cost-effective intervention, could result in the roll-out of interventions in areas where they would have comparatively little impact and therefore be an inefficient use of resources. The applied analysis does offer township-specific recommendations, some of which are remarkably robust to parameter uncertainty. However, likely incompleteness of incidence data, the lack of information on existing intervention coverage and that the evaluation window begins in 2013, now several years in the past, means that township specific model results are not directly applicable to malaria control and elimination planning in Myanmar today.

9.2 Static versus dynamic analyses

The static analysis and the dynamic analysis both model the cost-effectiveness of insecticide treated bed nets and malaria community health workers in the MARC region and apply geographic

allocation of a US$10m annual budget. While the analyses are differentiated through reference the model's characterisation of malaria risk over time, there are several further differences in both model and evaluation design as summarised in Table 12. The dynamic model analysis is more comprehensive and includes additional cost of illness sources, the inclusion of morbidity in disease burden, accounting for under reporting in the burden of disease and the inclusion of the effect of interventions on disease transmission. Most changes between the models result in either a greater estimate of the burden of disease, a greater estimate of the impact interventions have on this burden or a greater estimate of the costs of illness averted by reduced transmission. For this reason, the ICERs reported in the dynamic analysis are consistently lower than in the static analysis.

Table 11: Differences between static and dynamic economic analyses of malaria investment in the MARC region

Analysis Characteristic	**Static**	**Dynamic**
Costs	Intervention costs and commodity costs for treatment	Intervention costs, commodity treatment costs for outpatient care and hospitalisation costs for severe cases
Outcome metric	Years of life lost	DALYs
Disease Transmission	Excluded	Included
Perspective	Provider	Provider
Time horizon	1 year primary, lifetime secondary	3-year primary, lifetime secondary
Malaria burden	Incidence taken at face value	Inflation factor of 2.5 applied to incidence reports
Treatment quality	Excluded	Included

In addition, a new consensus was reached on the expected treatment seeking at CHWs where available. When parameterising the dynamic model, it was agreed that quality CHW programmes in

areas where alternative access to treatment was poor could expect very high uptake among the local community. Sensitivity and scenario analysis highlights the importance of this assumption to investment decisions, for example Figure 21, panel B shows the low CHW uptake scenario and the investment allocation is much closer to the static model results. The importance of understanding CHW uptake was fed back to decision makers. Surveys to better understand uptake would be straight forward and with the relevant data, a variable function to reflect differences in uptake in different townships could be a useful advancement to the model.

9.2.1 Reference Case for economic evaluation in global health

The International Decision Support Initiative's (IDSI) Reference Case for Economic Evaluation was published in final peer reviewed form in late 2016 (earlier versions were available though not at the design stage of the static or dynamic analyses) (243). The stated aim of the Reference case is to "improve the usefulness of information produced through economic evaluation" by guiding the "planning, conduct and reporting of economic evaluation so that both the approach to the analysis and the reporting of results are coherent, transparent and consistent". At the same time the Reference Case also explicitly recognises the need for methodological development and aims to create space for this by defining 11 guiding principles as the foundation of its recommendations (Table 13). Alongside these principles are more prescriptive methodological specifications and reporting standards, however, the principles themselves leave space for innovation while highlighting the goals economic evaluations should strive for.

Overall the final dynamic analysis aligns well with the Reference Case principles and meets almost all the methodological specifications. The Reference Case calls for interventions to be compared against a comparator scenario that describes the interventions that are currently on offer.

However, the comparator used for the dynamic analysis is a null scenario with respect to the interventions of interest. This aligns with the null comparator defined by WHO CHOICE's Generalised Cost Effectiveness Analysis (GCEA) framework (See Chapter 1). In this case, no coverage of insecticide treated bed nets and no existing networks of community health workers are accounted for because no data on intervention coverage was available.

Secondly the Reference Case calls for a societal perspective. However, the budget-based geographic framework implies a goal of efficient allocation of resources from a provider perspective and a provider perspective is used in this analysis. Lastly, the Reference Case calls for the inclusion of variable costs with scale. This would undoubtedly be a useful incorporation to a geographic resource allocation analysis but variable costs were not planned at the outset of the research and the necessary cost data were not collected. The recommendations of the Reference Case here highlights that the evaluation perspective for budget-based geographic resource allocation framework diverges from standard practice and two areas where the analysis could be improved though the collection of data on intervention coverage and characterisation of a variable cost function.

While there are some deviations from the specific methodological recommendations described in the Reference Case, the framework for budget-based geographic resource allocation notably goes beyond standard practice in addressing Reference Case fundamental principles eight and ten. Principle eight states that "The costs and effects of interventions on subpopulations within the decision problem should be explored and the implications properly characterised". This subpopulation heterogeneity, in this case defined by geographic regions, is very relevant to the decision problem of how to maximise health gains from spending on bed nets or community health

workers, yet is not well addressed by standard cost-effectiveness analysis. The geographic resource allocation algorithm constitutes a methodological development to address precisely this problem, incorporating heterogeneity between geographically defined subpopulations into the primary analysis rather than the sensitivity analysis, where there is a risk of conflation between heterogeneity and uncertainty. Principle ten states that “the impact of implementing the intervention on the health budget and on other constraints should be identified clearly and separately”. While standard practice is to use cost-effectiveness threshold to represent resource constraints it is difficult to identify an appropriate threshold. There is now growing consensus that the WHO CHOICE thresholds of x1 and x3 GDP per capita are too high, resulting in a proliferation of apparently “cost-effective” interventions that are not affordable to state healthcare providers. Moreover, even if an accurate cost-effectiveness threshold that reflected the opportunity cost of local healthcare spending were available, there are further challenges with the application of such threshold in the context of an elimination campaign and international financing. For this reason, the dynamic evaluation uses a budget as the resource constraint in the primary analysis rather than a separate analysis, going further than the Reference Case guidance.

Table 12: The IDSI economic evaluation Reference Case principles

1. Transparency	An economic evaluation should be communicated clearly and transparently to enable the decision- maker(s) to interpret the methods and results.
2. Comparator(s)	The comparator(s) against which costs and effects are measured should accurately reflect the decision problem.
3. Evidence	An economic evaluation should consider all available evidence relevant to the decision problem. The measure of health outcome should be appropriate to the decision problem, should capture positive and negative effects on length of life and quality of life, and should be generalizable across disease states.
4. Measure of health outcome	An economic evaluation should consider all available evidence relevant to the decision problem. The measure of health outcome should be appropriate to the decision problem, should capture positive and negative effects on length of life and quality of life, and should be generalizable across disease states.
5. Costs	All differences between the intervention and the comparator in expected resource use and costs of delivery to the target population(s) should be incorporated into the evaluation.
6. Time horizon and discount rate	The time horizon used in an economic evaluation should be of sufficient length to capture all costs and effects relevant to the decision problem; an appropriate discount rate should be used to discount costs and effects to present values.
7. Non-health effects and costs outside health budget (perspective)	Non-health effects and costs associated with gaining or providing access to health interventions that do not accrue to the health budget should be identified where relevant to the decision problem. All costs and effects should be disaggregated, either by sector of the economy or to whom they accrue.
8. Heterogeneity	The cost and effects of the intervention on sub- populations within the decision problem should be explored and the implications appropriately characterized.
9. Uncertainty	The uncertainty associated with an economic evaluation should be appropriately characterized.
10. Constraints	The impact of implementing the intervention on the health budget and on other constraints should be identified clearly and separately.
11. Equity considerations	An economic evaluation should explore the equity implications of implementing the intervention.

9.3 Malaria risk data and administrative level of allocation

Data on the geographic variation of disease risk is critical to both static and dynamic analyses. While significant improvements were made to the available data there are further opportunities to improve the understanding of malaria risk in the MARC region by collecting data through the private sector, cross-referencing routine case reports with prevalence surveys and improving cross-border surveillance to better understand risks in migrant and mobile populations. Moreover, there is a possibility that correlation between weaknesses in disease surveillance systems and malaria risk could further distort understanding of the geographic distribution of malaria risk. The importance of improved information on geographic resource allocation results may be assessable through adapted Value of Information Analysis, an approach to place a monetary value on the value of parameter uncertainty in economic evaluation.

The appropriate size of units of allocation, for example by province, district, township or village is an open question and one that could be the subject of further analysis. Here it will be important to consider cost variation across geographies and by scale (244,246) and, where relevant, the cost of obtaining data to inform geographically targeted strategies. It is possible that optimal resolutions for planning may differ between interventions, for example it is easy to imagine that CHWs could be best targeted by village while optimal ITN distribution might be less granular. Practical and political factors will be important drivers of the geographic unit of allocation. For example, Cambodian and Kenyan Ministries of Health have defined operational geographic units for the administration of healthcare services. In these cases, the administrative level for geographic allocation is defined and analysis has a clear allocation framework within which to operate. In Myanmar, the de facto level for MOH administration is the Township and this is therefore the level used in this thesis.

9.4 Equity Considerations

While the terms *inequality* and *inequity* are sometimes used interchangeably, not all inequalities are inequities. Health inequality is defined as "differences in health status or in the distribution of health determinants between different population groups" (247), whereas health inequity implies a (subjective) judgement about the fairness or justice of systematic differences in population health.

In general, economic evaluations aim to maximise total health gains for the resources available. That is, to maximise efficiency. However, efficiency is not the only criteria for consideration during the decision-making process and it may be necessary to consider the distributional effects that arise from resource allocation decisions on health, healthcare utilisation and healthcare financing. That is, does an action or policy affect inequalities and are these changes fair? This is reflected in Principle 11 in the Reference Case which recommends that *equity*, or the fairness in the distribution of costs and consequences, should be considered at all stages of an economic evaluation. While equity is an important consideration and methods for equity analysis alongside, or integrated into, economic evaluation are available (16,248) there is no consensus on best-practice, particularly with respect to dynamic-transmission economic evaluations.

In broad terms, geographic targeting of interventions is likely to promote vertical equity, that is, populations with greater needs are favoured over others. Whereas universal coverage strategies promote horizontal equity, all individuals at risk are provided the same services. Culyer summarises the difference between horizontal and vertical equity as horizontal equity being the like treatment of like individuals and horizontal treatment being the unlike treatment of unlike individuals (249). Preferences for vertical equity can be further integrated into the analysis using weighting coefficients to adjust how outcomes are values in difference populations. For example, if health

gains in lower socio-economic groups are to be given greater priority then information on the socio-economic differences between geographic units can be used to adjust outcome estimates, potentially yielding different resource allocation results. This approach tends towards an *egalitarian* position in terms of outcomes and an unequal distribution of resources to achieve this.

In terms of malaria policy in the MARC region, malaria is a disease of poverty and therefore malaria interventions that are maximally efficient are also likely to be broadly pro-equity in economic terms. It may also be important to consider equity in terms of ethnic group, gender, age or other characteristics. While among malaria stakeholders, discourse that is pro-poor or pro-marginalised-populations is not uncommon, there are longstanding disagreements between the many ethnic groups in the country and any explicit favouring of certain ethnic groups over others may cause tensions. Further work on the application of equity in malaria economic evaluation, both in Myanmar and elsewhere, is needed.

9.5 Evidence to Policy

During the DPhil research, regular communication was maintained with the National Malaria Control Programme, the Department of Medical Research, WHO Country Office and other stakeholders. For two years I was based in Yagon, where I helped to establish an office within the Department of Medical Research. I regularly participated in meetings of the malaria Technical Support Group, an advisory body of stakeholders that aims to support malaria policy making in Myanmar. I also participated in several special workshops and conferences intended to facilitate the development of the Myanmar malaria elimination strategy. The main message of the DPhil research, supporting planned geographic resource allocation instead of universal coverage of the

“best” intervention was disseminated at these fora as well as direct meetings with policy makers and donor organisations.

In addition, a website with an interactive interface was developed to allow users to explore the data available in the MARC data repository (www.myanmarmalaria.net). The website highlights the increase in the available data due to the initiative, allows users to see aggregate and township-wise malaria incidence trends and presents information on the coverage of public sector and civil society access points malaria diagnosis and treatment. An interactive interface for the geographic resource allocation analysis using the static decision tree model was also developed. Users can set the budget to be allocated as well as intervention unit costs, intervention effectiveness estimates and other parameters. Results are displayed as a colour coded map indicating the allocation of interventions with the greatest expected impact for the conditions define.

At the end of this DPhil research, malaria policy discourse had developed a stronger focus on geographically specific programming, though his work was far from the only view promoting such an approach. While the general discourse of “ITN vs CHW” had shifted to an approach of nuanced policy making, which became the primary goal of this work in the short-term, the results of the geographic targeting analysis were not used directly to inform policy making. There was a healthy degree of scepticism among some stakeholders about the quality and completeness of the data being fed into the model and the ability of models to replace detailed knowledge held by local health officers.

These concerns are more than understandable. There are several important areas where the analysis could be improved. Despite the achievements of the MARC Malaria Data Repository,

significant improvements to the quality of malaria surveillance systems are essential to understanding the true burden of disease and distribution of malaria transmission in Myanmar. Secondly, better systems for tracking the current distribution of interventions are essential for any practical analysis or tool to inform planning decisions. Thirdly, intervention costs are not likely to be consistent with geography or scale and more advanced cost functions would better reflect the likely costs of policy alternatives. Fourthly, a model validation exercise may improve confidence in the projections of the transmission model. Finally, as noted above, the priority setting process should reflect any equity preferences that are relevant to malaria policy making.

This analysis focuses on maximising impact from the core malaria interventions used in the MARC region, ITNs and malaria CHWs, rather than developing a comprehensive plan for malaria elimination. Nevertheless, efficiency in malaria control is an essential foundational step for any elimination campaign. Moreover, this analysis does take into account the expected decline in transmission due to allocation decisions, and in this sense priority setting recommendations should be in line with elimination strategy.

Overall, this DPhil research played a role in steering the policy discourse towards geographically specific malaria programming, a trend that is taking hold in NMCPs across the Mekong driven in part by modelling groups in MORU and elsewhere, with the leverage and support of large donors such as GFATM and BMGF. In trying to address questions of comparing intervention cost-effectiveness, a reframing of the question from a straight-forward comparison of interventions to an allocation of interventions in a way that would have most impact was developed. With further work, this approach has the potential to be a useful decision-tool to support policy-makers in the design of impactful strategies for malaria control and elimination.

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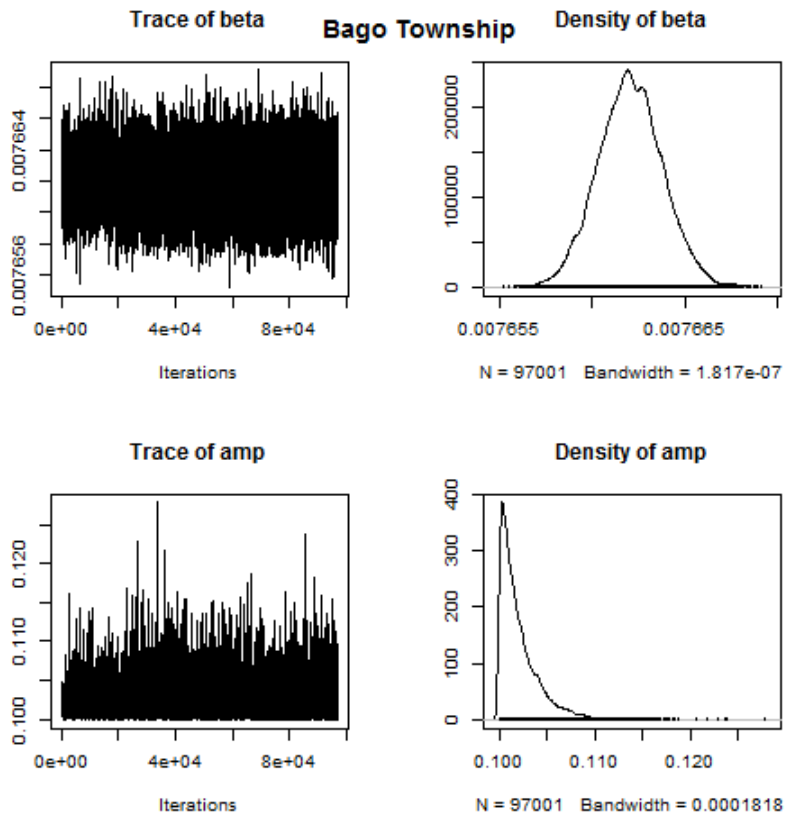
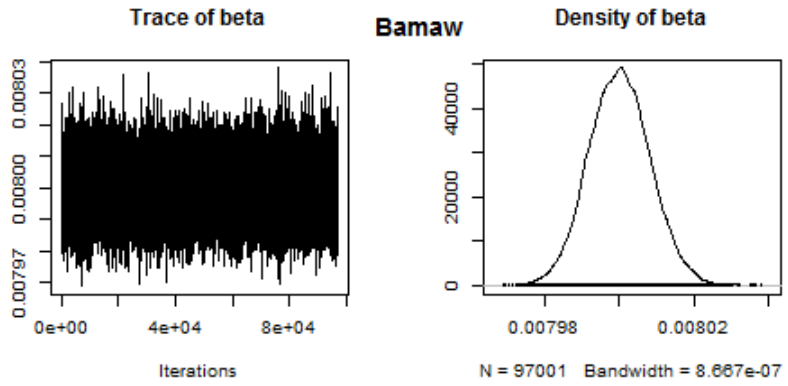
Appendix

A.1 Supporting figures for transmission model fitting

Included here are figures that show the Markov Chain Monte Carlo traces for fitting the transmissibility parameter (β).




Bamaw
Trace of beta
Density of beta
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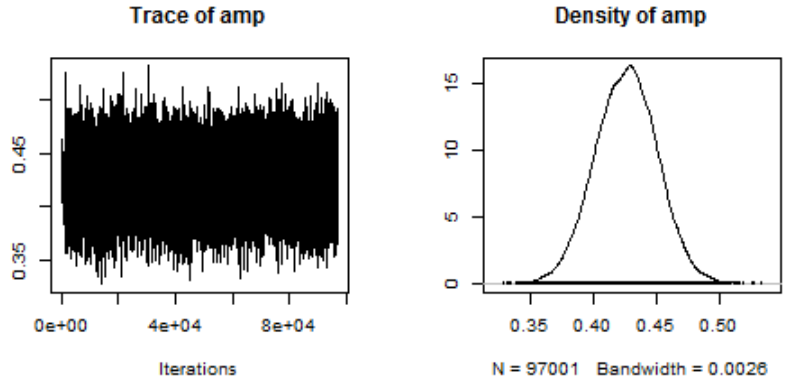
0.00800
0.00803
0e+00
4e+04
8e+04
Iterations
0
20000
40000
0.00798
0.00802
N = 97001 Bandwidth = 8.667e-07


Trace of amp
Density of amp
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0.45
0e+00
4e+04
8e+04
Iterations
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10
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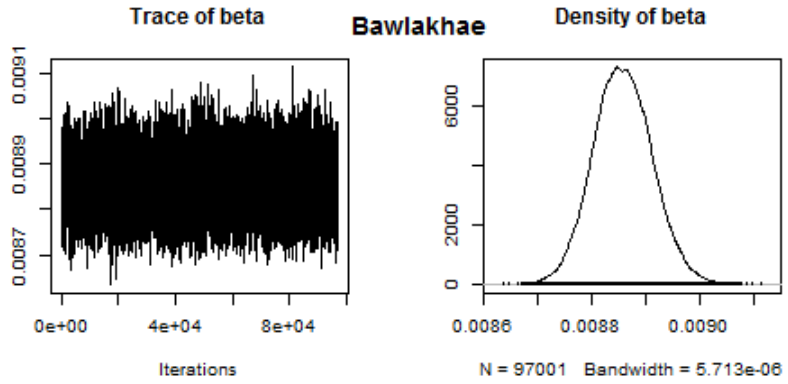
0.35
0.40
0.45
0.50
N = 97001 Bandwidth = 0.0026


Bawlakhae
Trace of beta
Density of beta
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0.0089
0.0091
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Iterations
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2000
6000
0.0086
0.0088
0.0090
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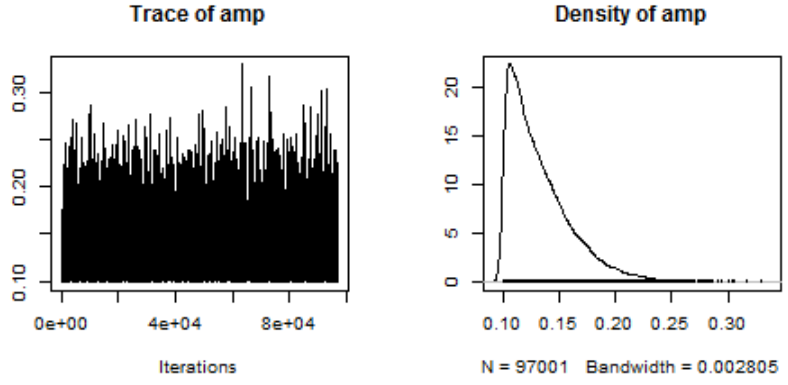
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Density of amp
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0.30
0e+00
4e+04
8e+04
Iterations
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15
20
0.10
0.15
0.20
0.25
0.30
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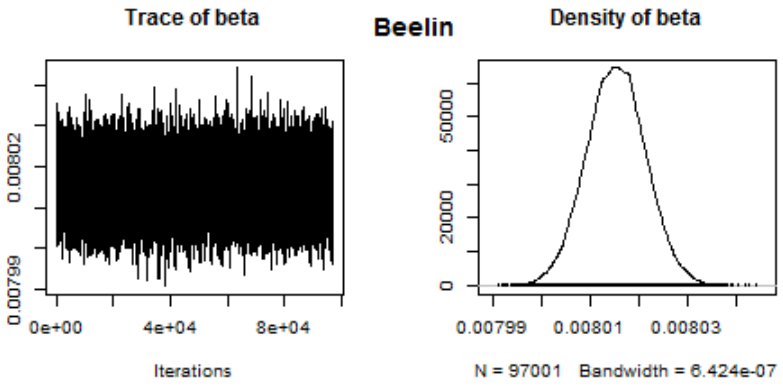
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Beelin
Density of beta
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0.00803
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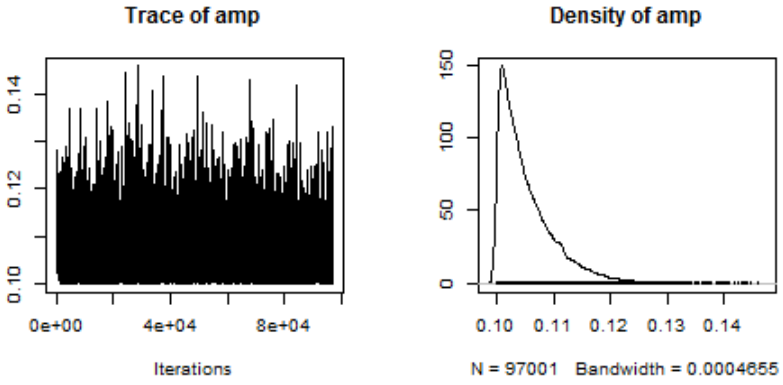
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Density of amp
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0.10
0.11
0.12
0.13
0.14
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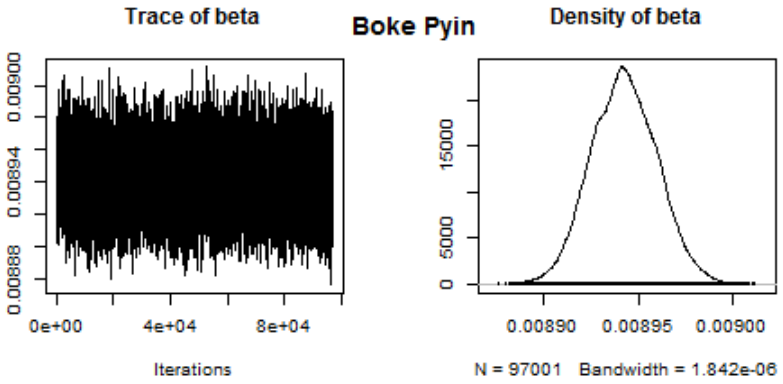
Trace of beta
Boke Pyin
Density of beta
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Iterations
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5000
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0.00890
0.00895
0.00900
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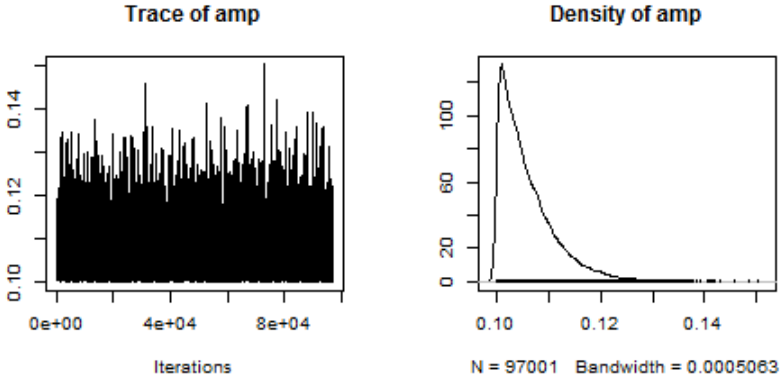
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Density of amp
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0.14
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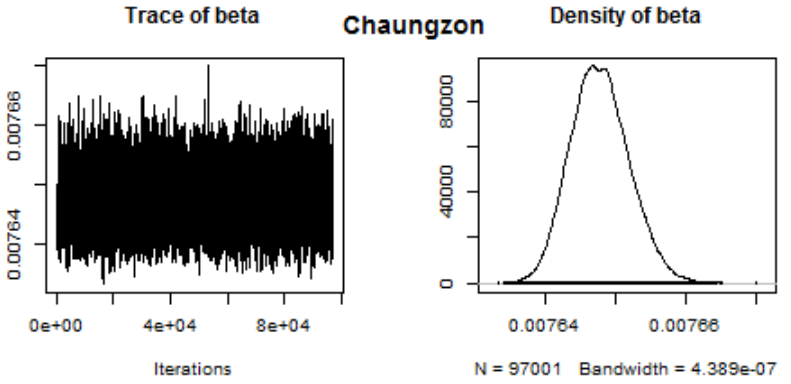
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Chaungzon
Density of beta
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0
0.00764
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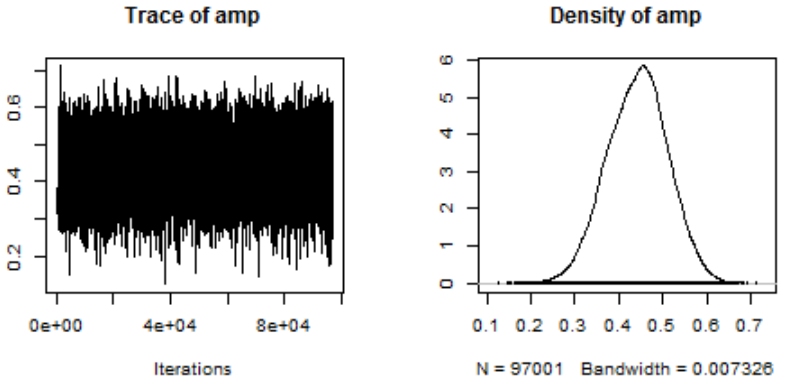
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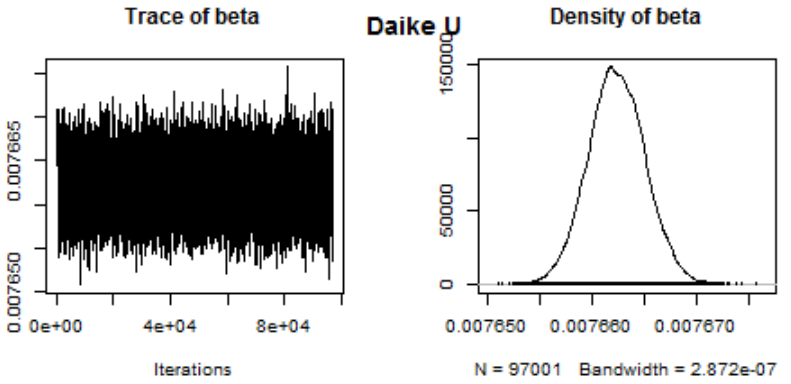
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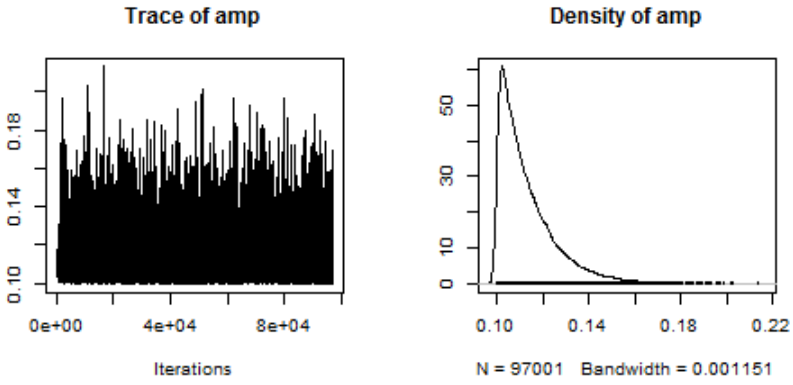
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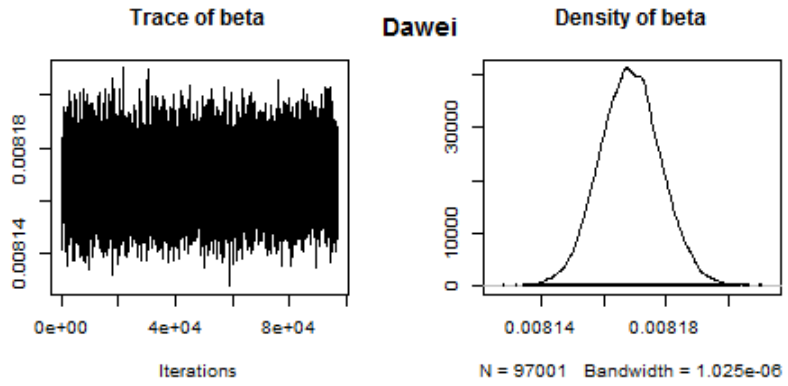
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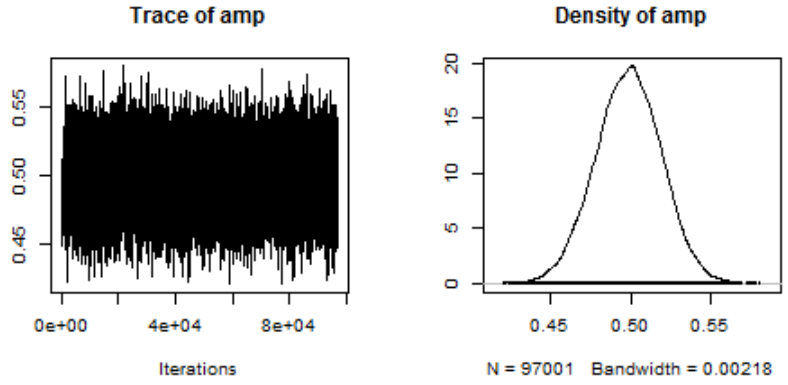
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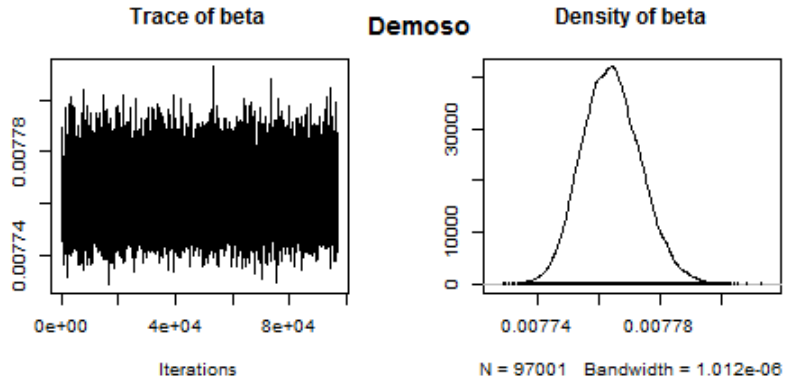
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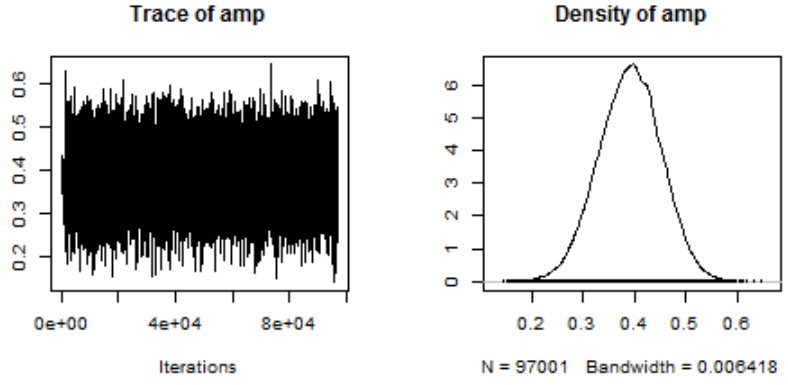
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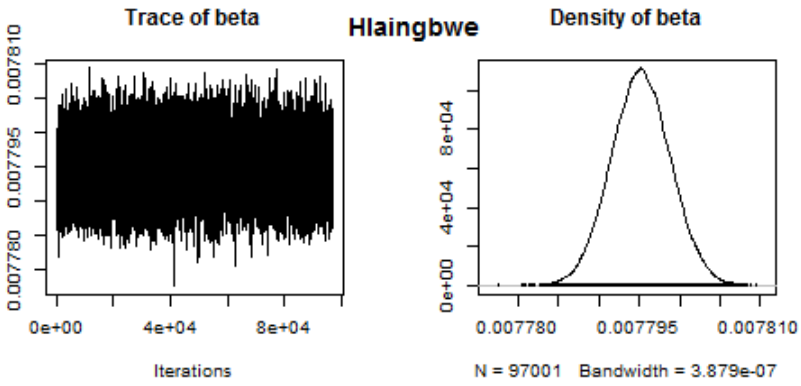
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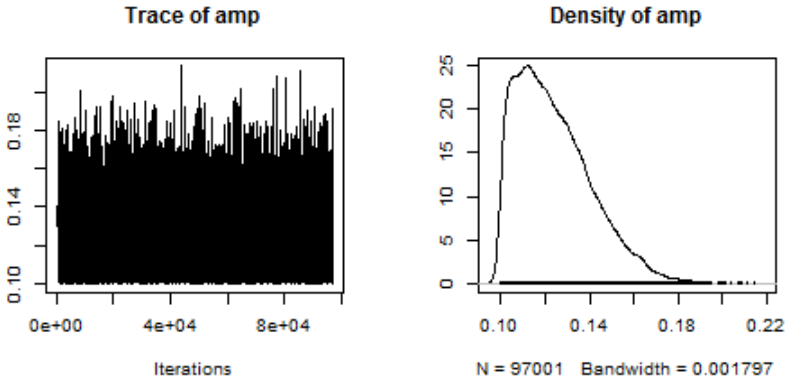
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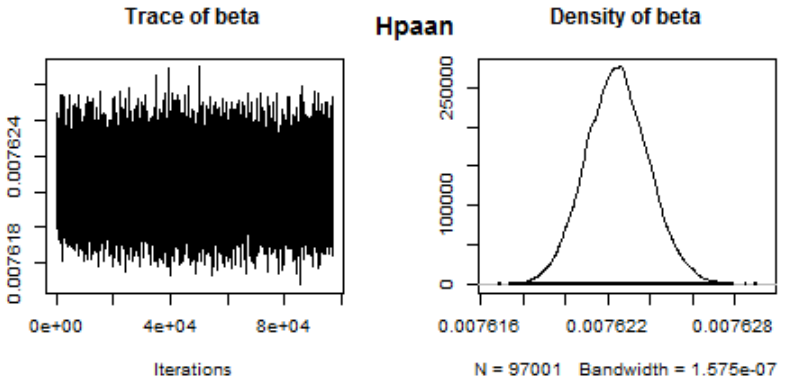
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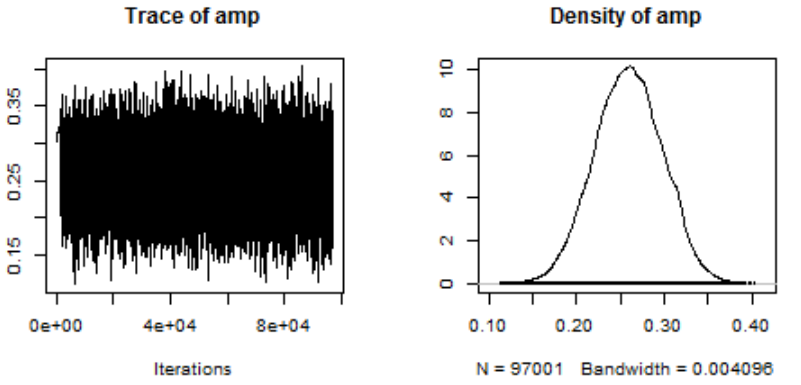
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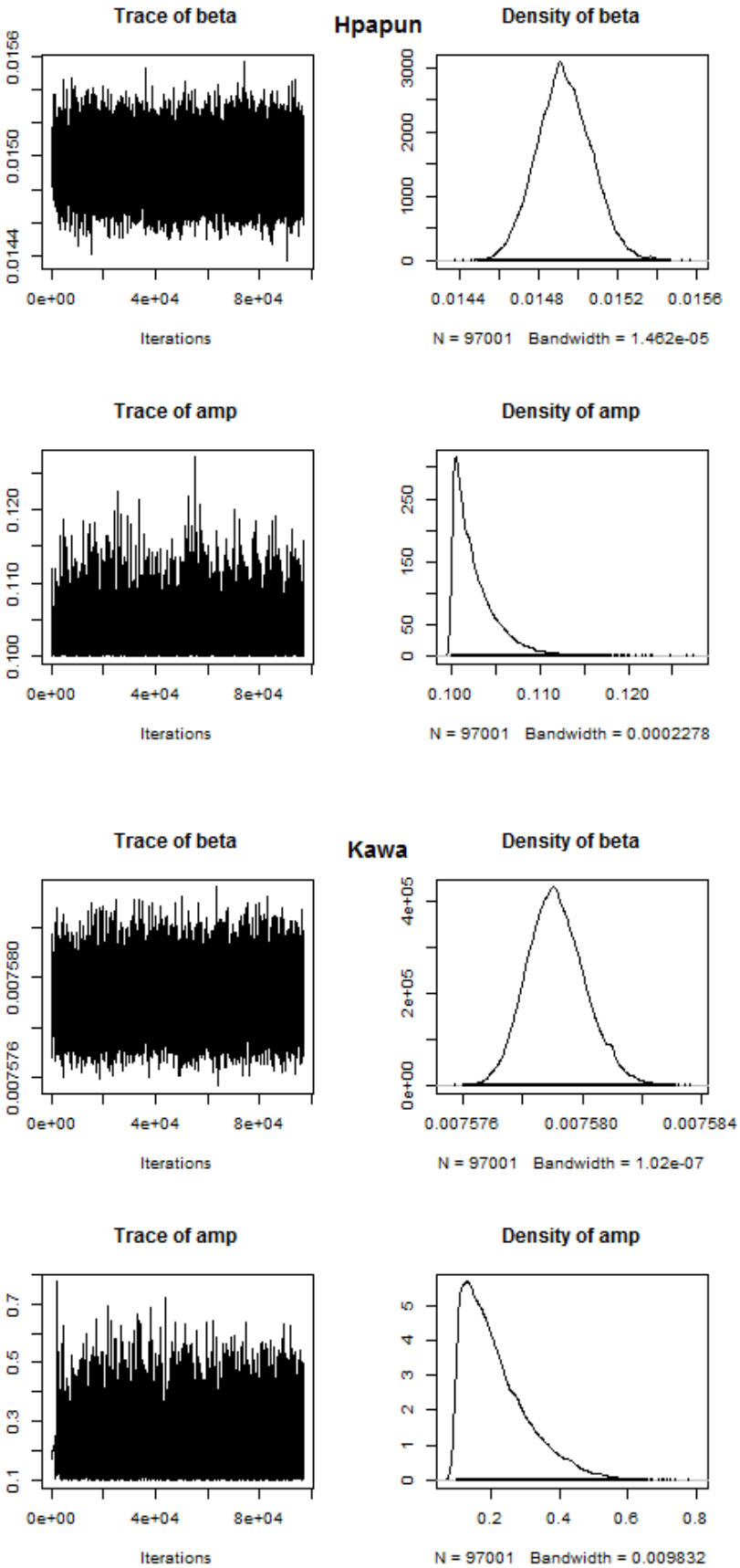
Hpapun
Trace of beta
Density of beta
Iterations
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Trace of amp
Density of amp
Iterations
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Kawa
Trace of beta
Density of beta
Iterations
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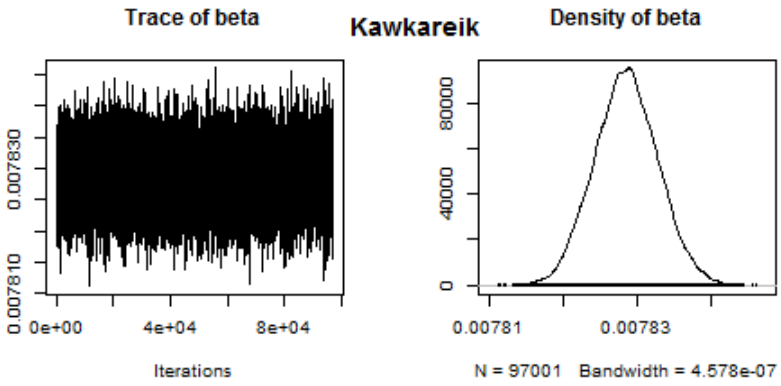
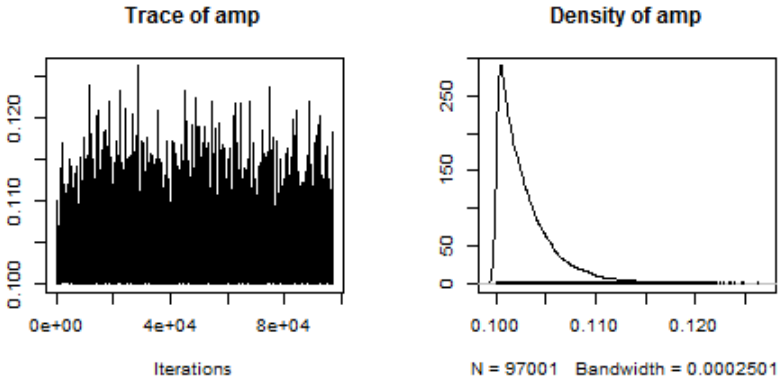
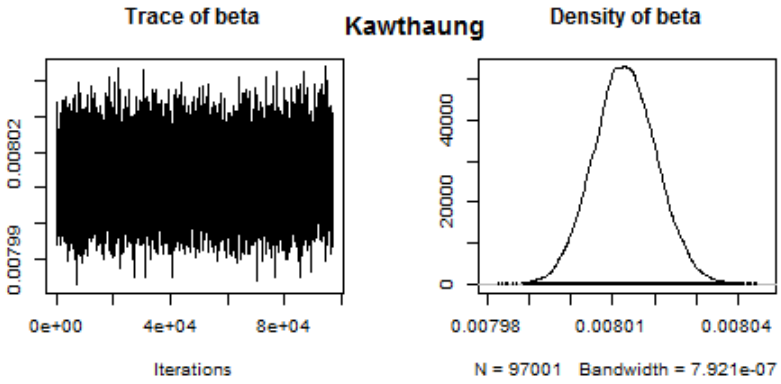
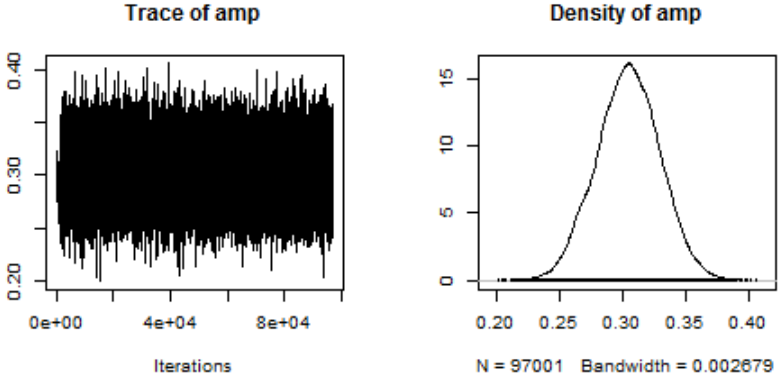
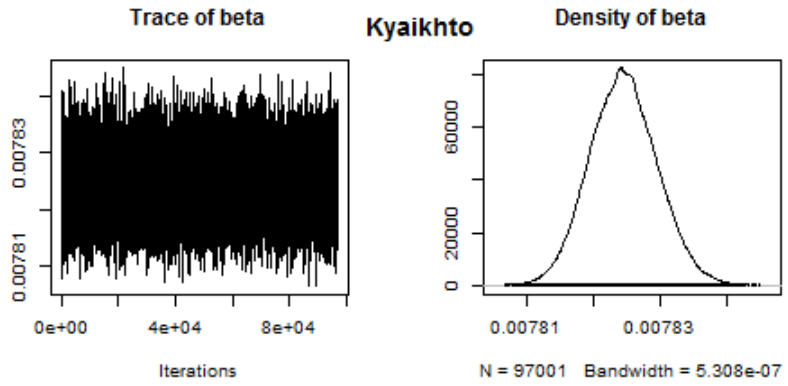
Trace of amp
Density of amp
Iterations
N = 97001 Bandwidth = 0.009832

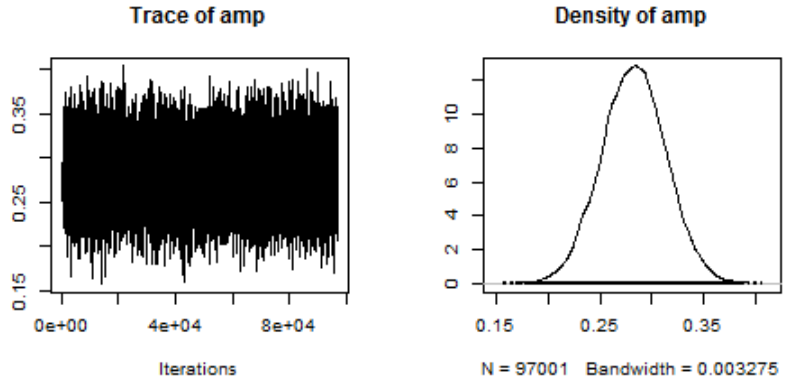

Kawkareik
Trace of beta
0.007810
0.007830
0e+00
4e+04
8e+04
Iterations
Density of beta
0
40000
80000
0.00781
0.00783
N = 97001 Bandwidth = 4.578e-07

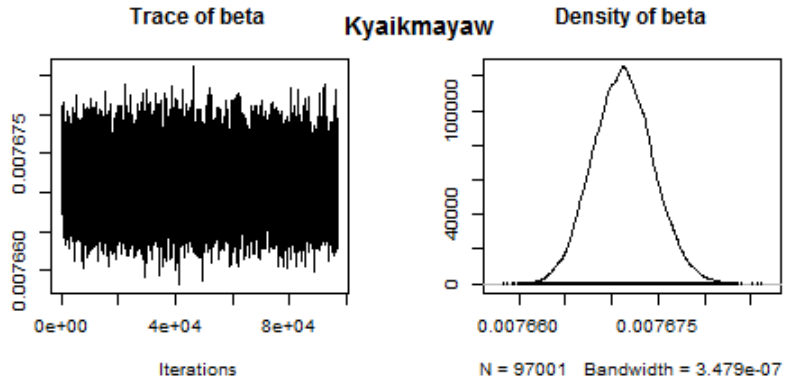

Trace of amp
0.100
0.110
0.120
0e+00
4e+04
8e+04
Iterations
Density of amp
0
50
150
250
0.100
0.110
0.120
N = 97001 Bandwidth = 0.0002501

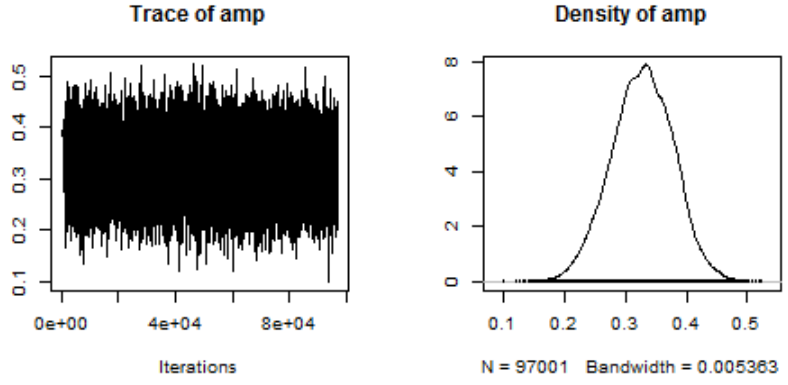

Kawthaung
Trace of beta
0.00799
0.00802
0e+00
4e+04
8e+04
Iterations
Density of beta
0
20000
40000
0.00798
0.00801
0.00804
N = 97001 Bandwidth = 7.921e-07

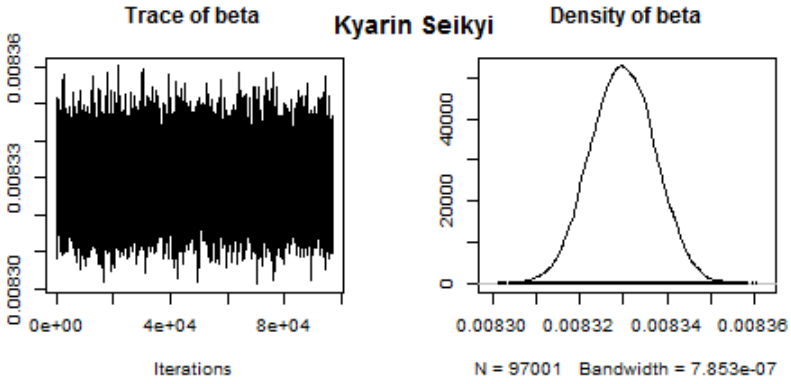

Trace of amp
0.20
0.30
0.40
0e+00
4e+04
8e+04
Iterations
Density of amp
0
5
10
15
0.20
0.25
0.30
0.35
0.40
N = 97001 Bandwidth = 0.002679

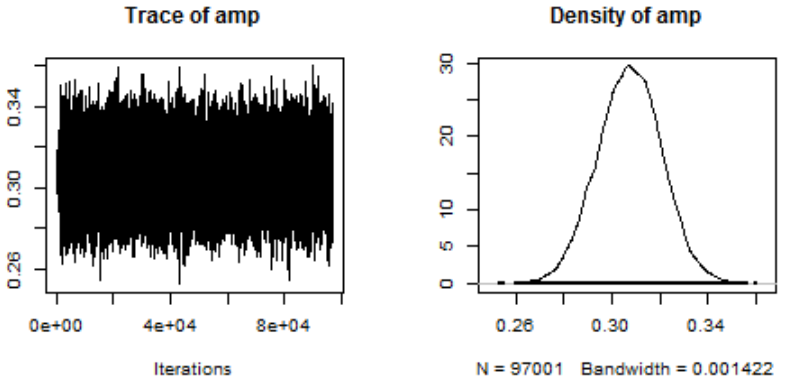

Kyaikhto
Trace of beta
Density of beta
0.00783
0.00781
0e+00
4e+04
8e+04
Iterations
60000
20000
0
0.00781
0.00783
N = 97001 Bandwidth = 5.308e-07

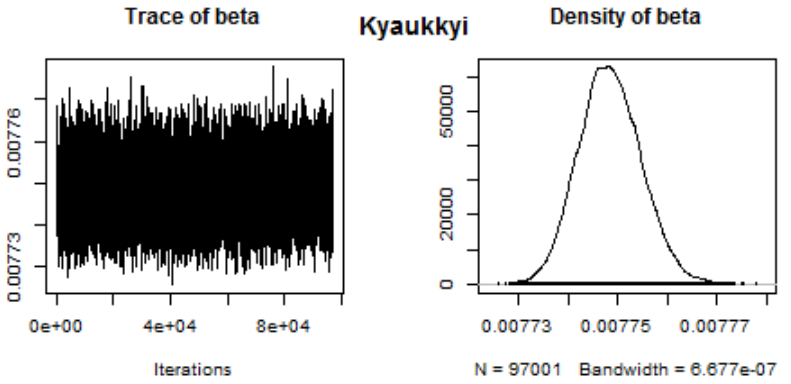

Trace of amp
Density of amp
0.35
0.25
0.15
0e+00
4e+04
8e+04
Iterations
10
8
6
4
2
0
0.15
0.25
0.35
N = 97001 Bandwidth = 0.003275

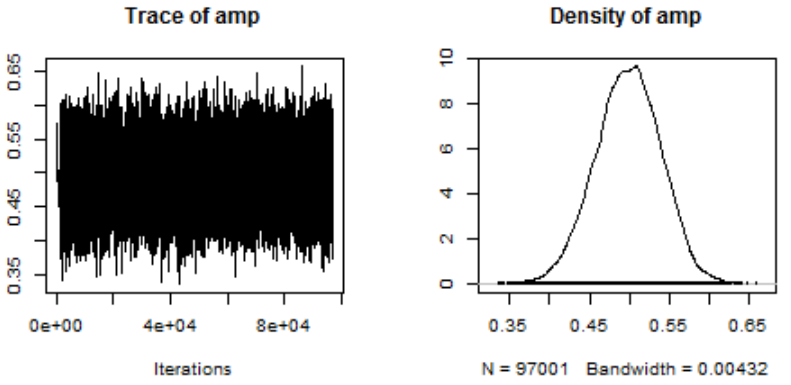

Kyaikmayaw
Trace of beta
Density of beta
0.007675
0.007660
0e+00
4e+04
8e+04
Iterations
100000
40000
0
0.007660
0.007675
N = 97001 Bandwidth = 3.479e-07

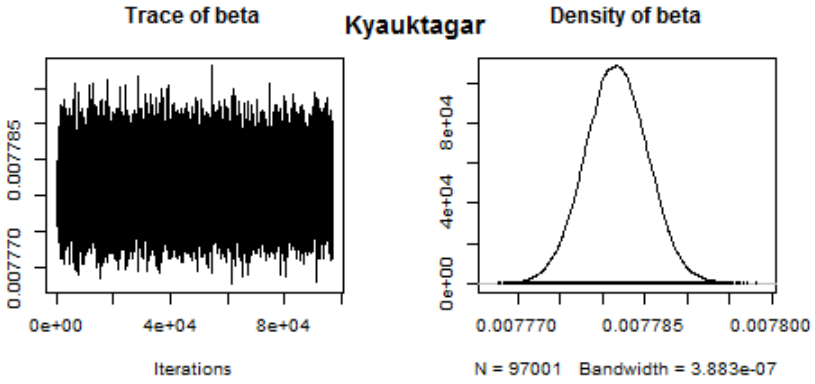

Trace of amp
Density of amp
0.5
0.4
0.3
0.2
0.1
0e+00
4e+04
8e+04
Iterations
8
6
4
2
0
0.1
0.2
0.3
0.4
0.5
N = 97001 Bandwidth = 0.005363

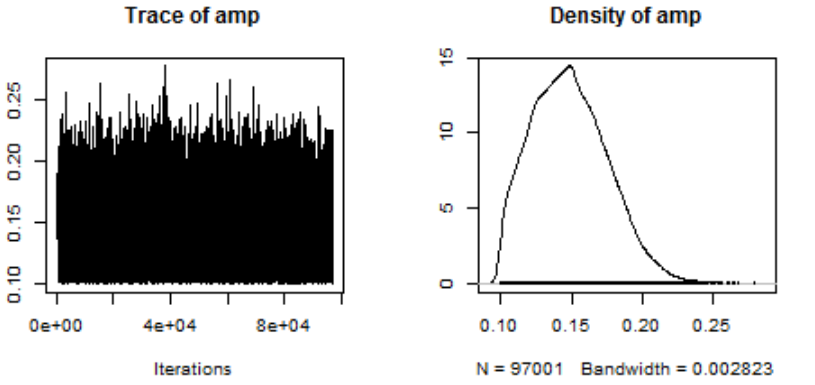

Kyarin Seikyi
Trace of beta
Density of beta
0.00836
0.00833
0.00830
0e+00
4e+04
8e+04
Iterations
40000
20000
0
0.00830
0.00832
0.00834
0.00836
N = 97001 Bandwidth = 7.853e-07

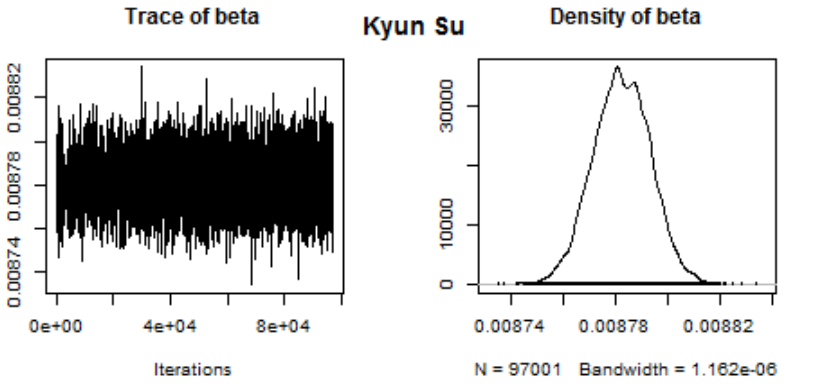

Trace of amp
Density of amp
0.34
0.30
0.26
0e+00
4e+04
8e+04
Iterations
30
20
10
5
0
0.26
0.30
0.34
N = 97001 Bandwidth = 0.001422

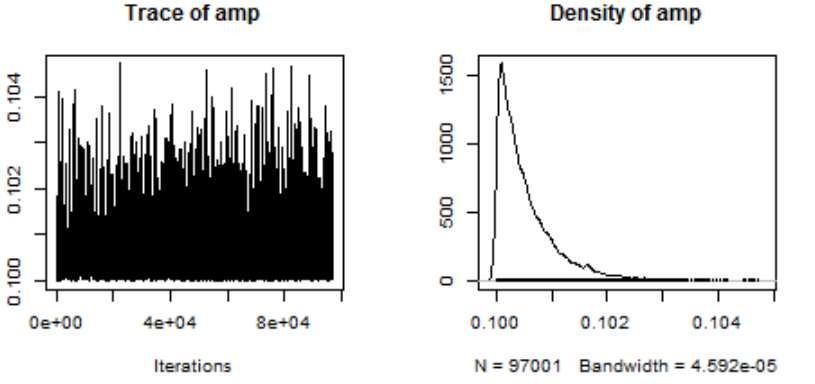

Kyaukkyi
Trace of beta
Density of beta
0.00776
0.00773
0e+00
4e+04
8e+04
Iterations
50000
20000
0
0.00773
0.00775
0.00777
N = 97001 Bandwidth = 6.677e-07

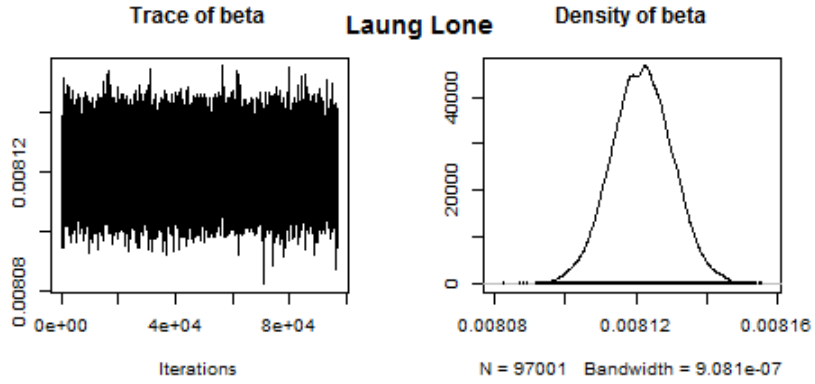

Trace of amp
Density of amp
0.65
0.55
0.45
0.35
0e+00
4e+04
8e+04
Iterations
10
8
6
4
2
0
0.35
0.45
0.55
0.65
N = 97001 Bandwidth = 0.00432

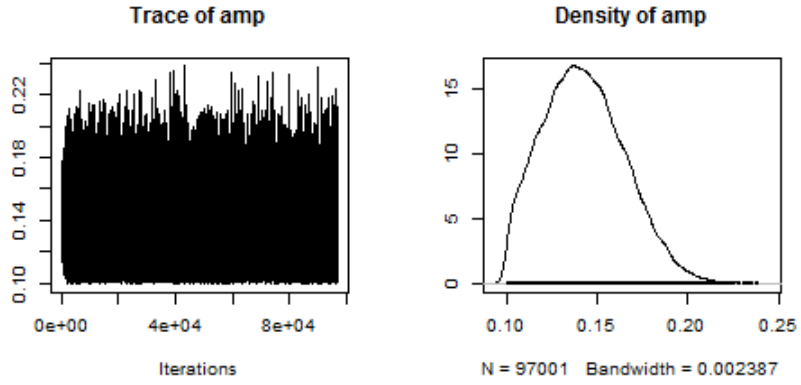

Trace of beta
Kyauktagar
Density of beta
0.007770
0.007785
0e+00
4e+04
8e+04
Iterations
0e+00
4e+04
8e+04
0.007770
0.007785
0.007800
N = 97001 Bandwidth = 3.883e-07

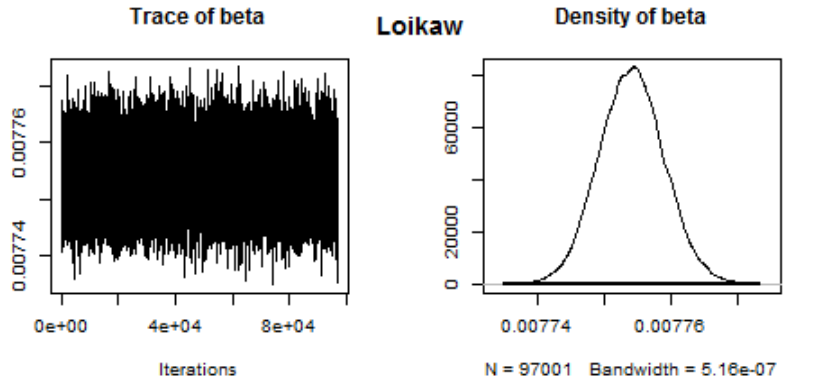

Trace of amp
Density of amp
0.10
0.15
0.20
0.25
Iterations
0
5
10
15
N = 97001 Bandwidth = 0.002823

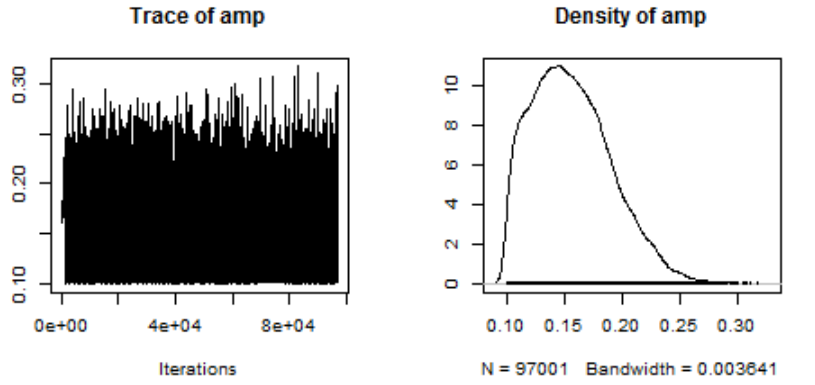

Trace of beta
Kyun Su
Density of beta
0.00874
0.00878
0.00882
Iterations
0
10000
30000
N = 97001 Bandwidth = 1.162e-06

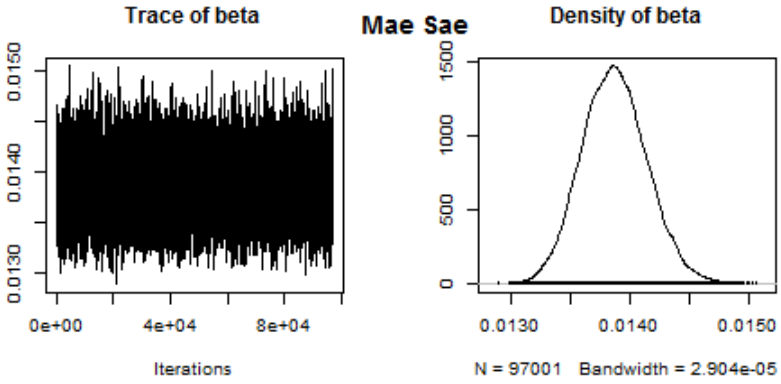

Trace of amp
Density of amp
0.100
0.102
0.104
Iterations
0
500
1000
1500
N = 97001 Bandwidth = 4.592e-05

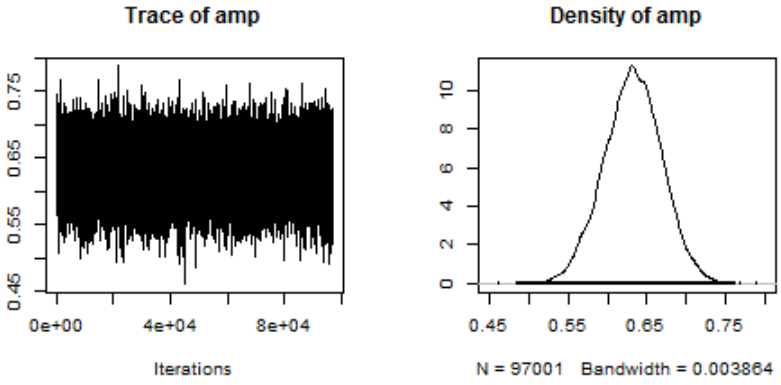

Laung Lone
Trace of beta
Density of beta
0.00808
0.00812
0e+00
4e+04
8e+04
Iterations
0
20000
40000
0.00808
0.00812
0.00816
N = 97001 Bandwidth = 9.081e-07

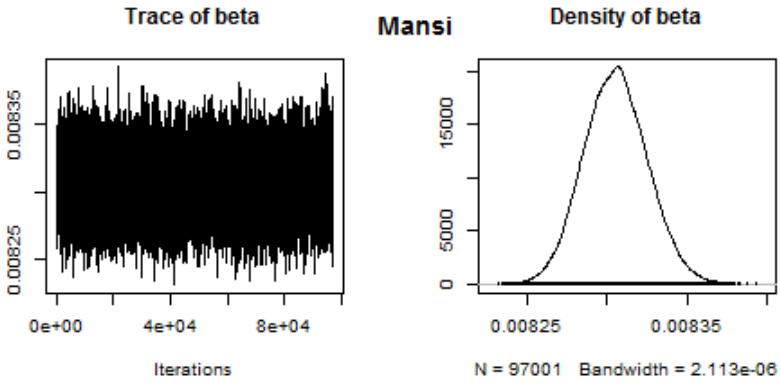

Trace of amp
Density of amp
0.10
0.14
0.18
0.22
0e+00
4e+04
8e+04
Iterations
0
5
10
15
0.10
0.15
0.20
0.25
N = 97001 Bandwidth = 0.002387

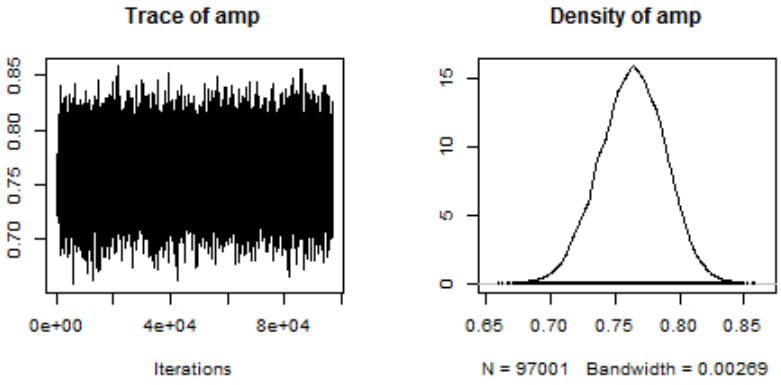

Loikaw
Trace of beta
Density of beta
0.00774
0.00776
0e+00
4e+04
8e+04
Iterations
0
20000
60000
0.00774
0.00776
N = 97001 Bandwidth = 5.16e-07

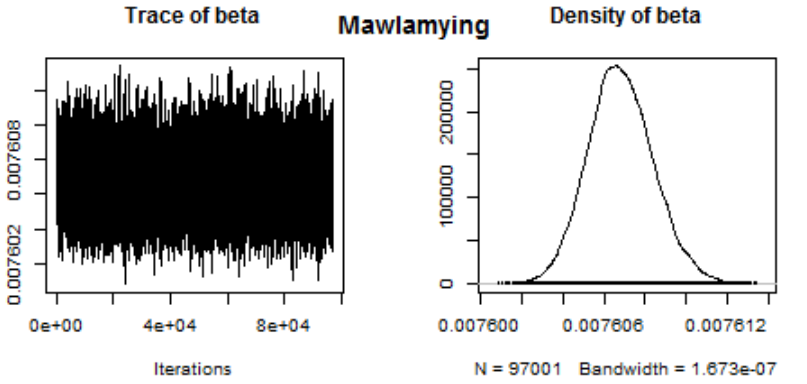

Trace of amp
Density of amp
0.10
0.20
0.30
0e+00
4e+04
8e+04
Iterations
0
2
4
6
8
10
0.10
0.15
0.20
0.25
0.30
N = 97001 Bandwidth = 0.003641

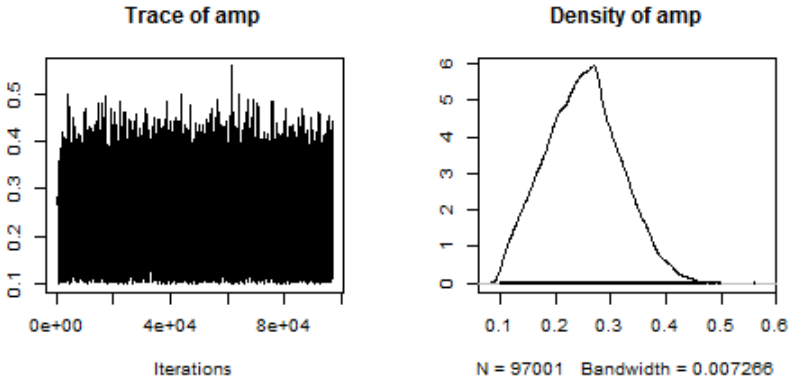

Mae Sae
Trace of beta
Density of beta
0.0130
0.0140
0.0150
0e+00
4e+04
8e+04
Iterations
0
500
1000
1500
0.0130
0.0140
0.0150
N = 97001 Bandwidth = 2.904e-05

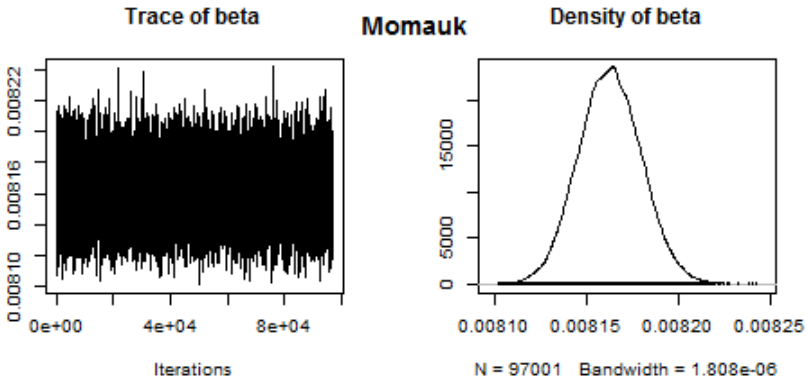

Trace of amp
Density of amp
0.45
0.55
0.65
0.75
0e+00
4e+04
8e+04
Iterations
0
2
4
6
8
10
0.45
0.55
0.65
0.75
N = 97001 Bandwidth = 0.003864

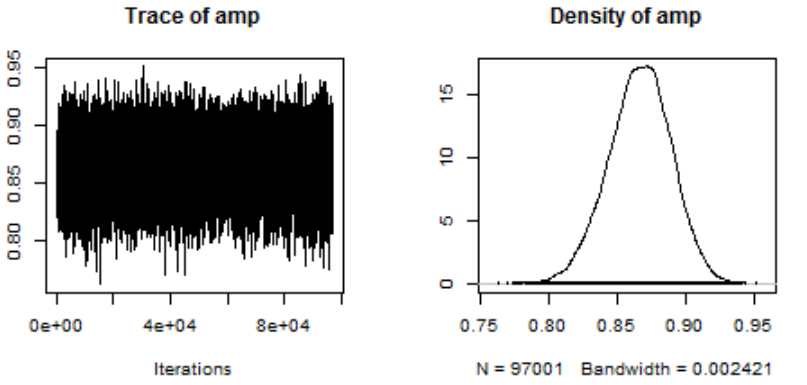

Mansi
Trace of beta
Density of beta
0.00825
0.00835
0e+00
4e+04
8e+04
Iterations
0
5000
15000
0.00825
0.00835
N = 97001 Bandwidth = 2.113e-06

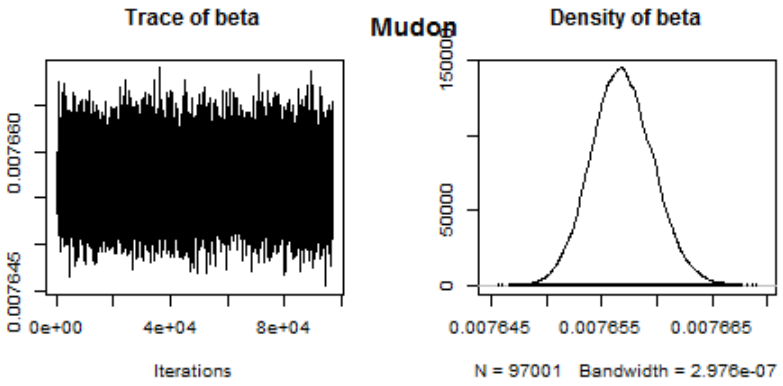

Trace of amp
Density of amp
0.70
0.75
0.80
0.85
0e+00
4e+04
8e+04
Iterations
0
5
10
15
0.65
0.70
0.75
0.80
0.85
N = 97001 Bandwidth = 0.00269


Mawlamying
Trace of beta
Density of beta
0.007602
0.007608
0e+00
4e+04
8e+04
Iterations
0
100000
200000
0.007600
0.007606
0.007612
N = 97001 Bandwidth = 1.673e-07


Trace of amp
Density of amp
0.1
0.2
0.3
0.4
0.5
0e+00
4e+04
8e+04
Iterations
0
1
2
3
4
5
6
0.1
0.2
0.3
0.4
0.5
0.6
N = 97001 Bandwidth = 0.007266

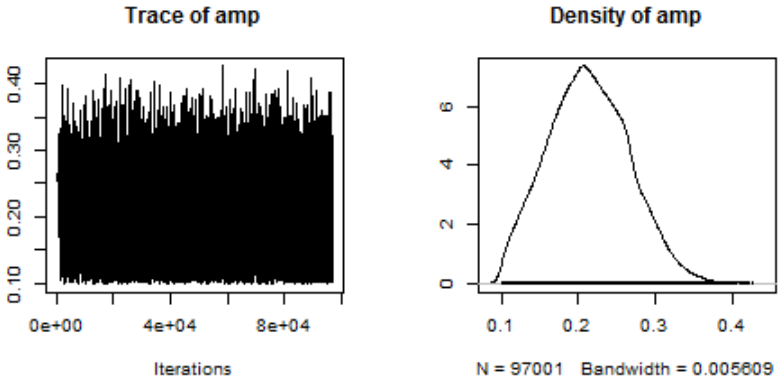

Momauk
Trace of beta
Density of beta
0.00810
0.00816
0.00822
0e+00
4e+04
8e+04
Iterations
0
5000
15000
0.00810
0.00815
0.00820
0.00825
N = 97001 Bandwidth = 1.808e-06


Trace of amp
Density of amp
0.80
0.85
0.90
0.95
0e+00
4e+04
8e+04
Iterations
0
5
10
15
0.75
0.80
0.85
0.90
0.95
N = 97001 Bandwidth = 0.002421

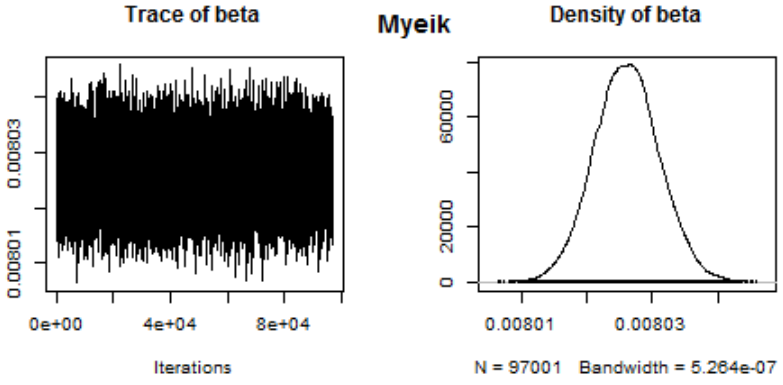

Trace of beta
0.007645
0.007660
0e+00
4e+04
8e+04
Iterations

Mudon

Density of beta
0
50000
150000
0.007645
0.007655
0.007665
N = 97001 Bandwidth = 2.976e-07

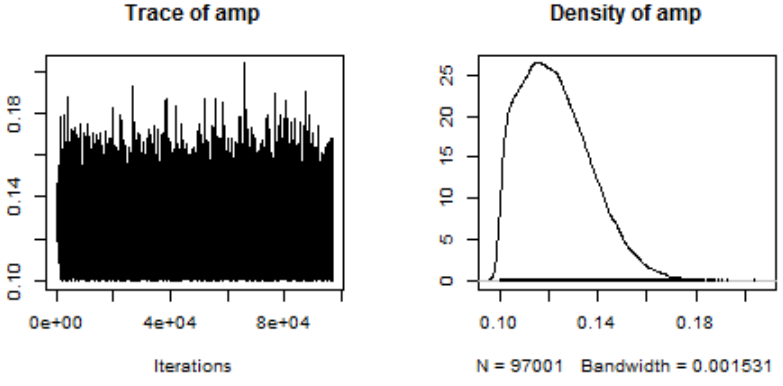

Trace of amp
0.10
0.20
0.30
0.40
0e+00
4e+04
8e+04
Iterations

Density of amp
0
2
4
6
0.1
0.2
0.3
0.4
N = 97001 Bandwidth = 0.005609

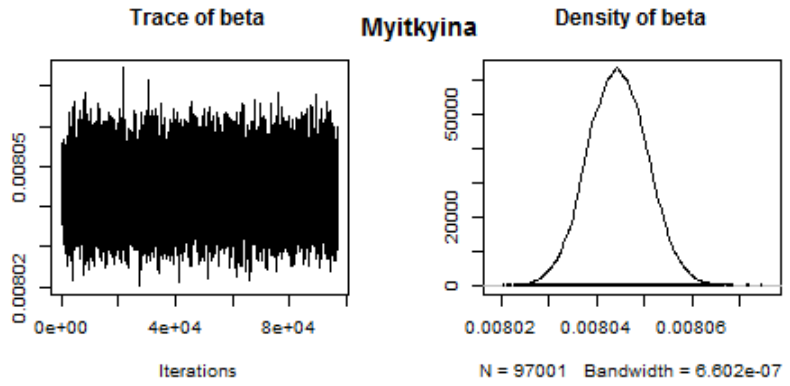

Trace of beta
0.00801
0.00803
0e+00
4e+04
8e+04
Iterations

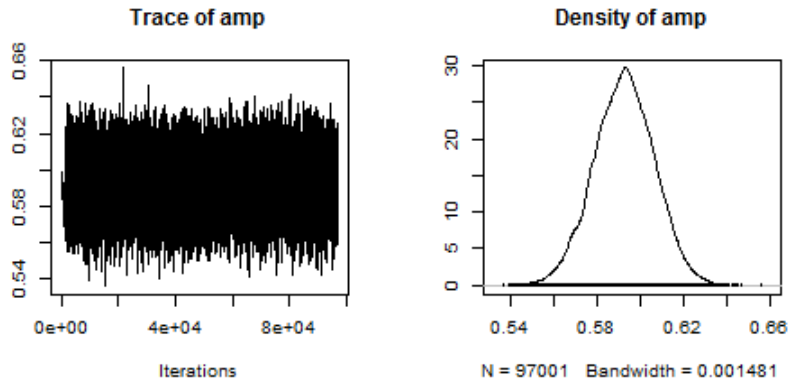
Myeik

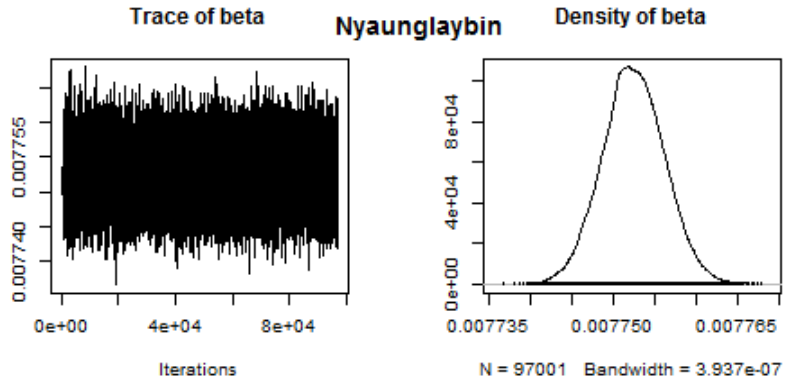
Density of beta
0
20000
60000
0.00801
0.00803
N = 97001 Bandwidth = 5.264e-07

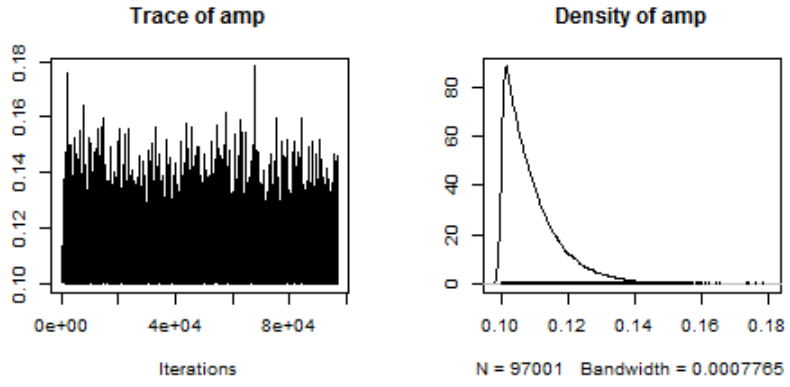

Trace of amp
0.10
0.14
0.18
0e+00
4e+04
8e+04
Iterations

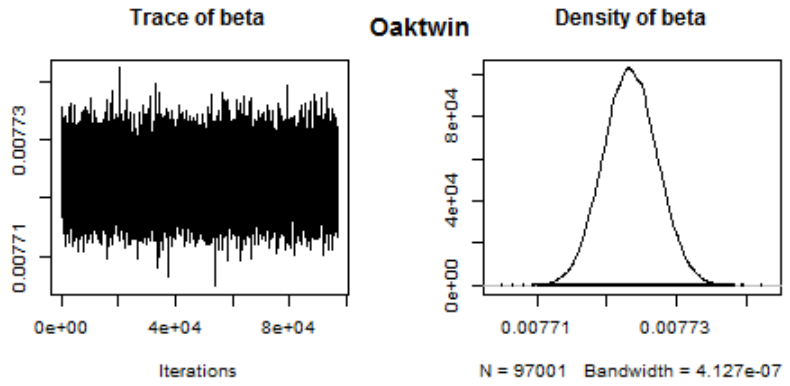
Density of amp
0
5
10
15
20
25
0.10
0.14
0.18
N = 97001 Bandwidth = 0.001531

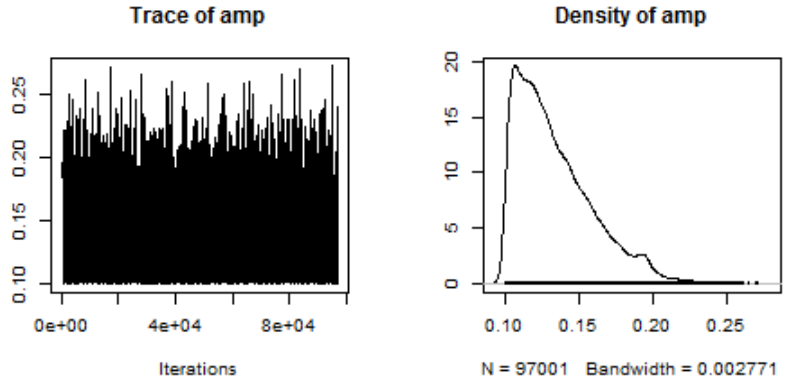

Trace of beta
Myitkyina
Density of beta
0.00805
0.00802
0e+00
4e+04
8e+04
Iterations
50000
20000
0
0.00802
0.00804
0.00806
N = 97001 Bandwidth = 6.602e-07

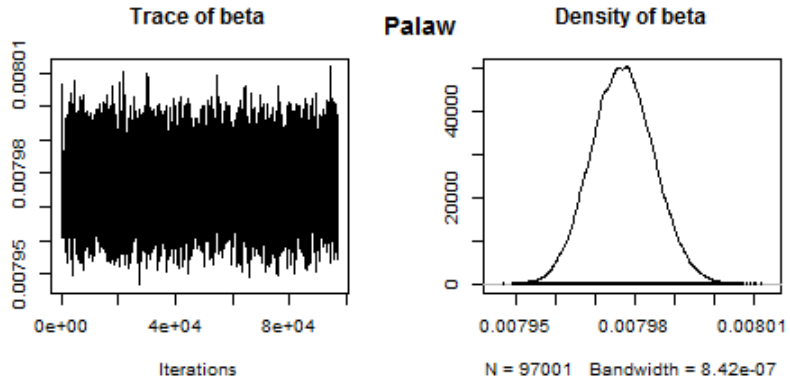

Trace of amp
Density of amp
0.66
0.62
0.58
0.54
0e+00
4e+04
8e+04
Iterations
30
20
10
5
0
0.54
0.58
0.62
0.66
N = 97001 Bandwidth = 0.001481

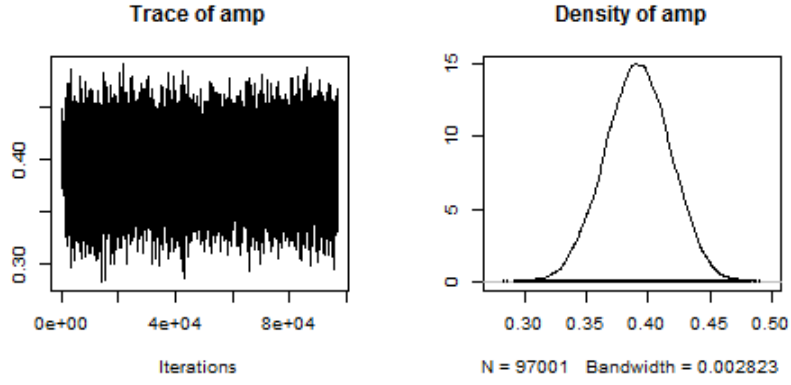

Trace of beta
Nyaunglaybin
Density of beta
0.007755
0.007740
0e+00
4e+04
8e+04
Iterations
8e+04
4e+04
0e+00
0.007735
0.007750
0.007765
N = 97001 Bandwidth = 3.937e-07

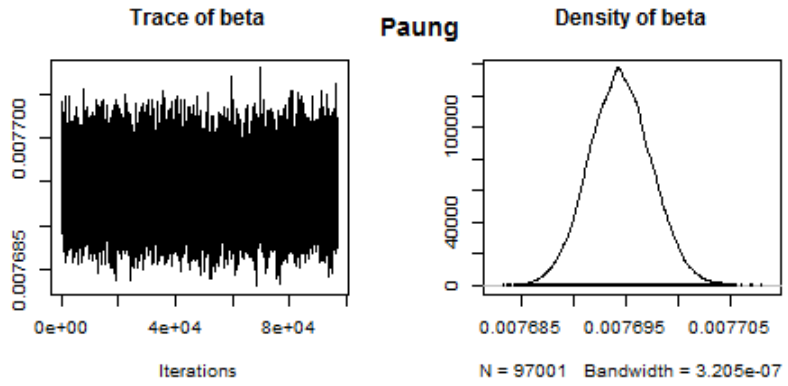

Trace of amp
Density of amp
0.18
0.16
0.14
0.12
0.10
0e+00
4e+04
8e+04
Iterations
80
60
40
20
0
0.10
0.12
0.14
0.16
0.18
N = 97001 Bandwidth = 0.0007765

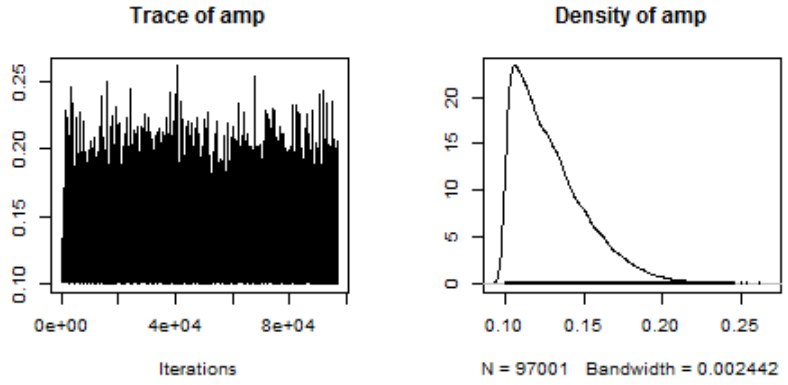

Trace of beta
Oaktwin
Density of beta
0.00771
0.00773
0e+00
4e+04
8e+04
Iterations
0e+00
4e+04
8e+04
N = 97001 Bandwidth = 4.127e-07

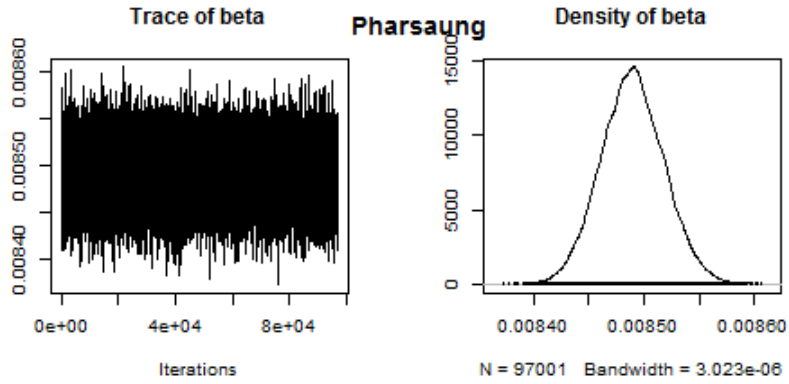

Trace of amp
Density of amp
0.10
0.15
0.20
0.25
0e+00
4e+04
8e+04
Iterations
0
5
10
15
20
0.10
0.15
0.20
0.25
N = 97001 Bandwidth = 0.002771

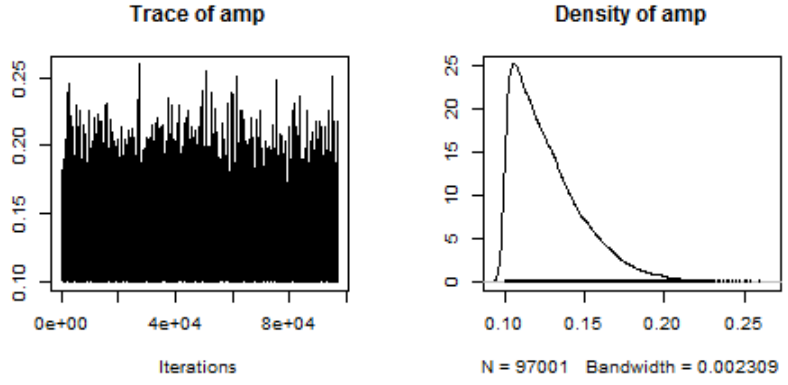

Trace of beta
Palaw
Density of beta
0.00795
0.00798
0.00801
0e+00
4e+04
8e+04
Iterations
0
20000
40000
0.00795
0.00798
0.00801
N = 97001 Bandwidth = 8.42e-07

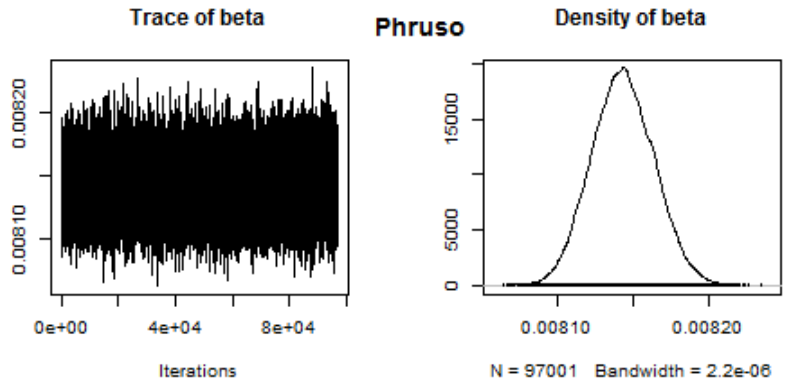

Trace of amp
Density of amp
0.30
0.40
0e+00
4e+04
8e+04
Iterations
0
5
10
15
0.30
0.35
0.40
0.45
0.50
N = 97001 Bandwidth = 0.002823


Paung
Trace of beta
Density of beta
0.007685
0.007700
0e+00
4e+04
8e+04
Iterations
0
40000
100000
0.007685
0.007695
0.007705
N = 97001 Bandwidth = 3.205e-07


Trace of amp
Density of amp
0.10
0.15
0.20
0.25
0e+00
4e+04
8e+04
Iterations
0
5
10
15
20
0.10
0.15
0.20
0.25
N = 97001 Bandwidth = 0.002442

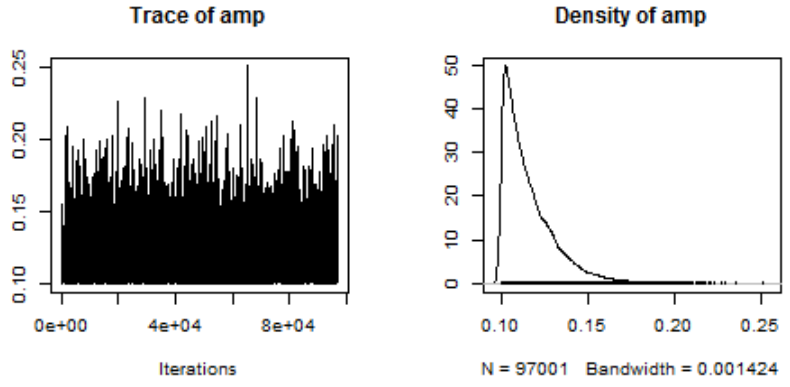

Pharsaung
Trace of beta
Density of beta
0.00840
0.00850
0.00860
0e+00
4e+04
8e+04
Iterations
0
5000
10000
15000
0.00840
0.00850
0.00860
N = 97001 Bandwidth = 3.023e-06


Trace of amp
Density of amp
0.10
0.15
0.20
0.25
0e+00
4e+04
8e+04
Iterations
0
5
10
15
20
25
0.10
0.15
0.20
0.25
N = 97001 Bandwidth = 0.002309

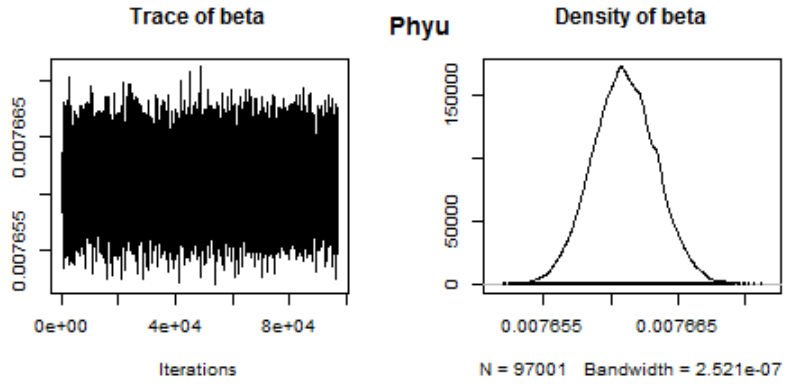

Trace of beta
0.00820
0.00810
0e+00
4e+04
8e+04
Iterations

Phruso

Density of beta
15000
5000
0
0.00810
0.00820
N = 97001 Bandwidth = 2.2e-06

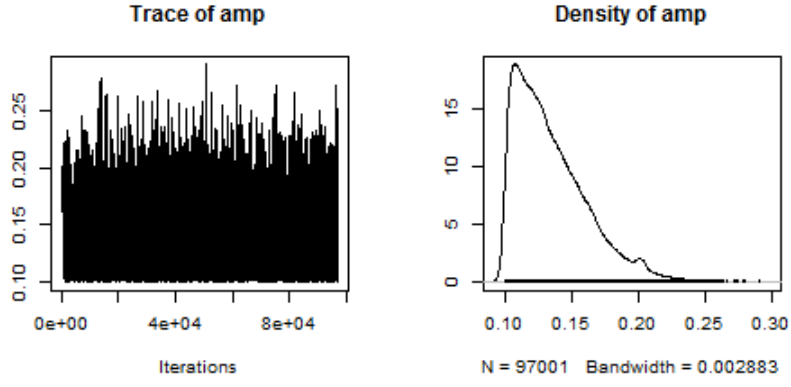

Trace of amp
0.25
0.20
0.15
0.10
0e+00
4e+04
8e+04
Iterations

Density of amp
50
40
30
20
10
0
0.10
0.15
0.20
0.25
N = 97001 Bandwidth = 0.001424

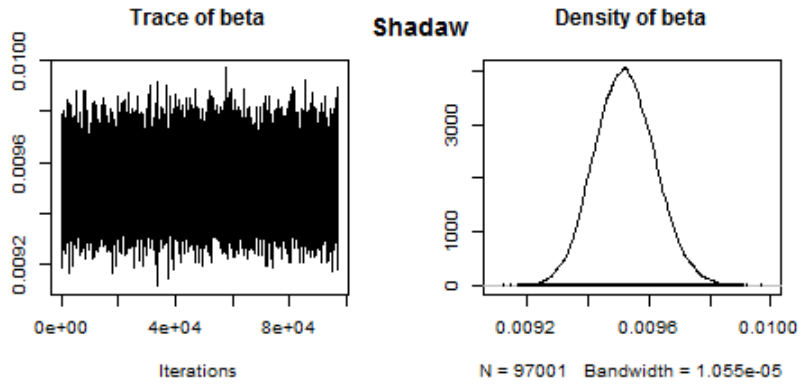

Trace of beta
0.007665
0.007655
0e+00
4e+04
8e+04
Iterations

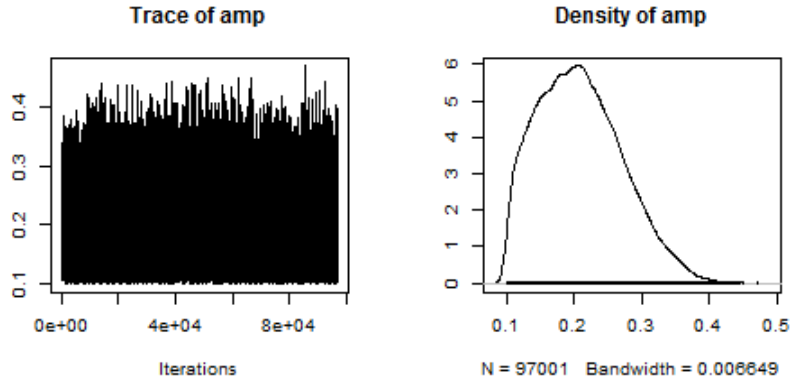
Phyu

Density of beta
150000
50000
0
0.007655
0.007665
N = 97001 Bandwidth = 2.521e-07

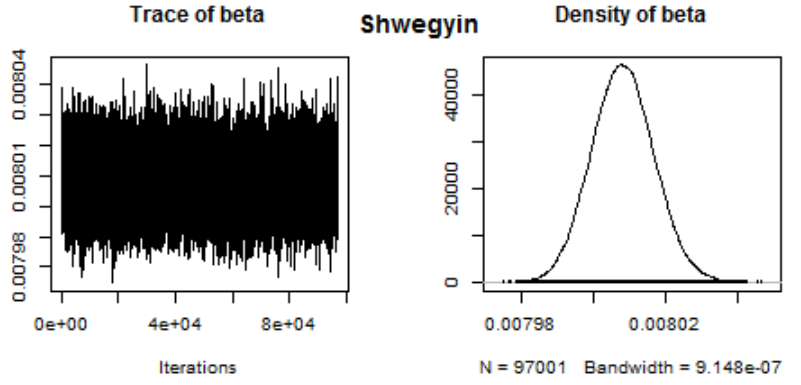

Trace of amp
0.25
0.20
0.15
0.10
0e+00
4e+04
8e+04
Iterations

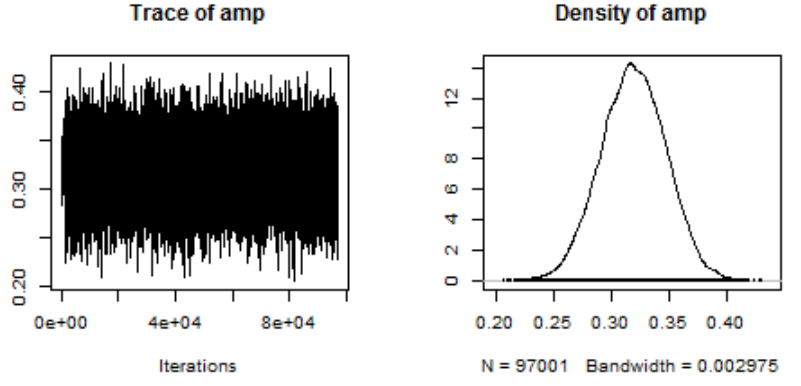
Density of amp
15
10
5
0
0.10
0.15
0.20
0.25
0.30
N = 97001 Bandwidth = 0.002883



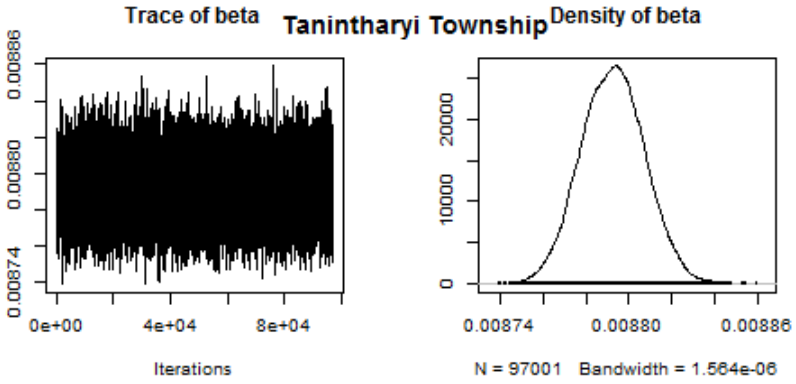


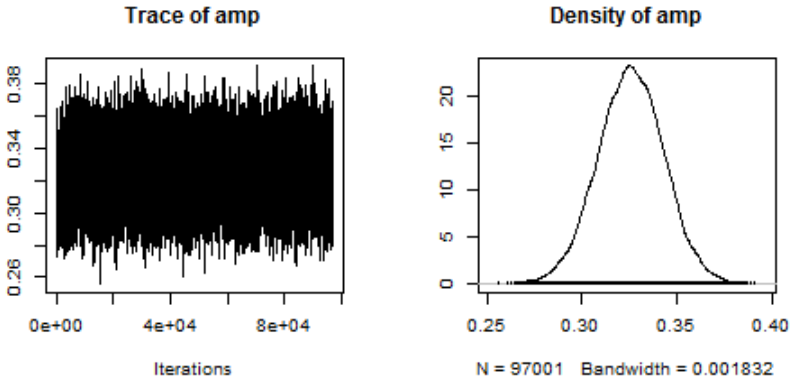
Shadaw

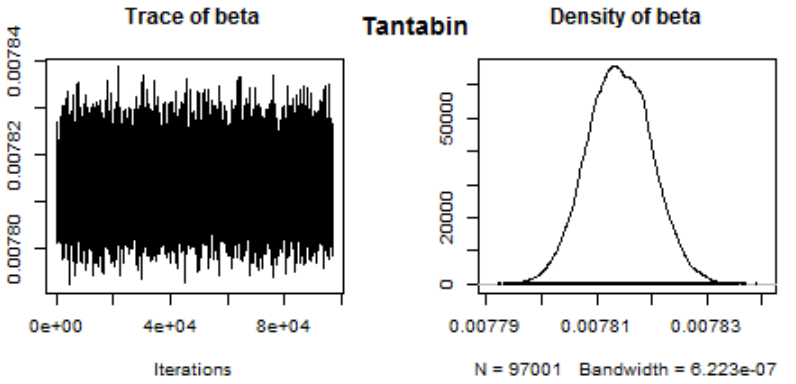


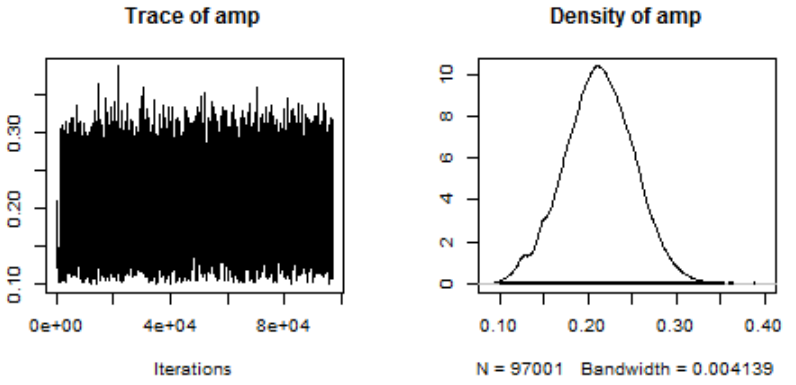


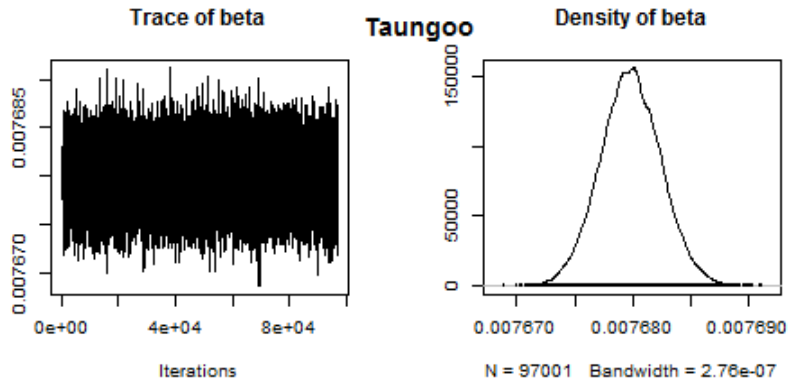
Shwegyin

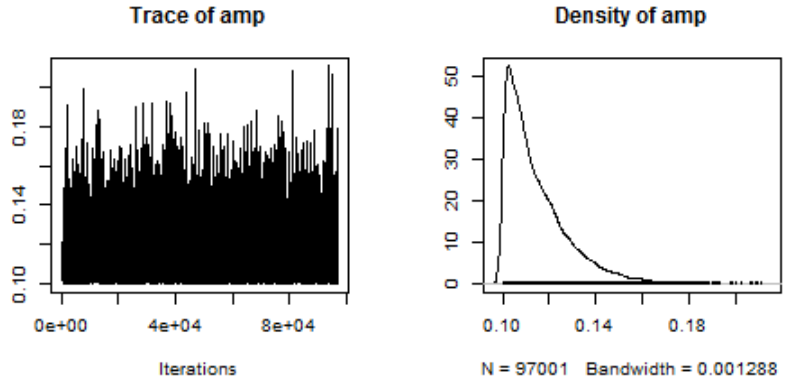

Trace of beta
Tanintharyi Township
Density of beta
0.00874
0.00880
0.00886
0e+00
4e+04
8e+04
Iterations
0
10000
20000
0.00874
0.00880
0.00886
N = 97001 Bandwidth = 1.564e-06

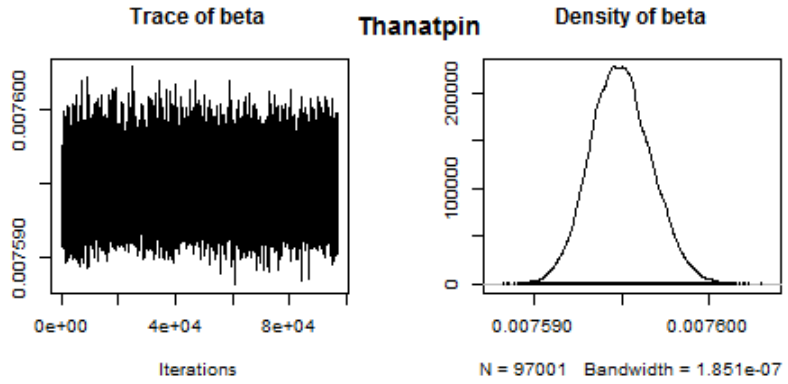

Trace of amp
Density of amp
0.26
0.30
0.34
0.38
0e+00
4e+04
8e+04
Iterations
0
5
10
15
20
0.25
0.30
0.35
0.40
N = 97001 Bandwidth = 0.001832

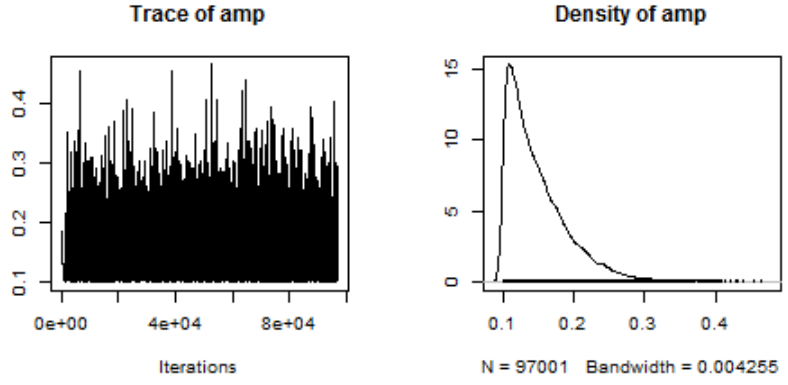

Trace of beta
Tantabin
Density of beta
0.00780
0.00782
0.00784
0e+00
4e+04
8e+04
Iterations
0
20000
50000
0.00779
0.00781
0.00783
N = 97001 Bandwidth = 6.223e-07

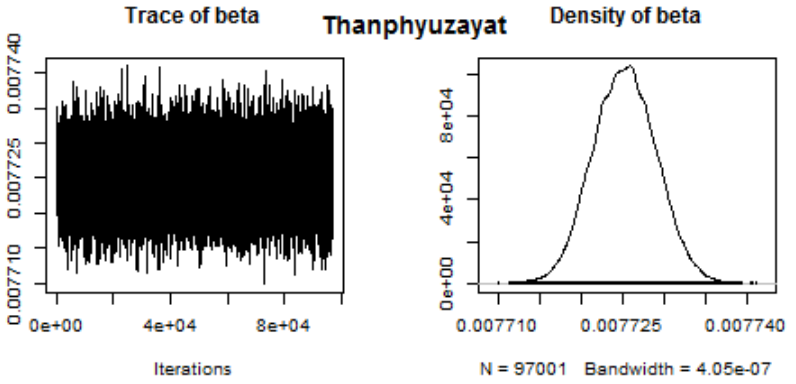

Trace of amp
Density of amp
0.10
0.20
0.30
0e+00
4e+04
8e+04
Iterations
0
2
4
6
8
10
0.10
0.20
0.30
0.40
N = 97001 Bandwidth = 0.004139

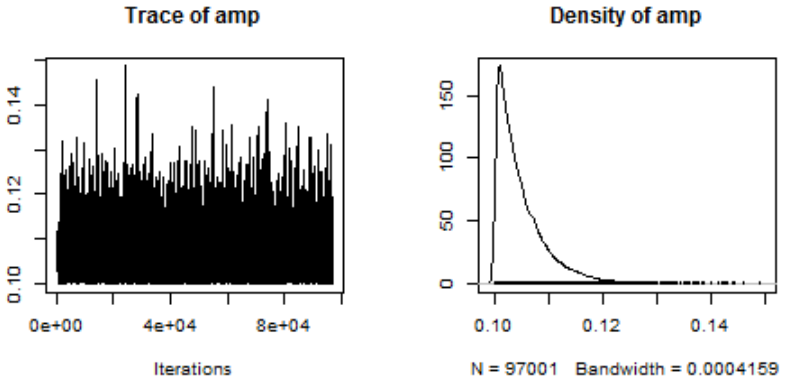

Taungoo
Trace of beta
Density of beta
0.007685
0.007670
0e+00
4e+04
8e+04
Iterations
150000
50000
0
0.007670
0.007680
0.007690
N = 97001 Bandwidth = 2.76e-07

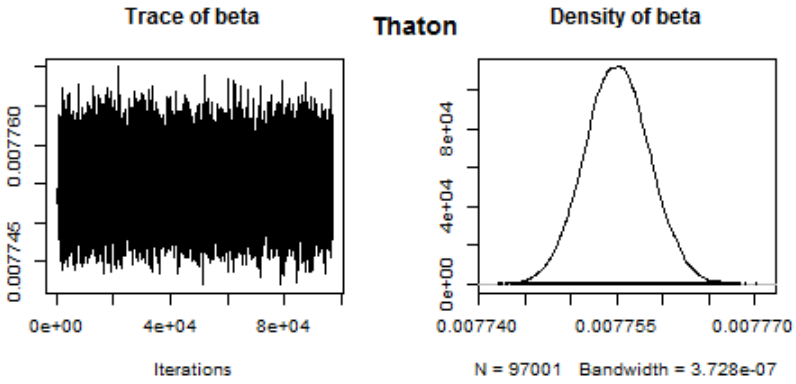

Trace of amp
Density of amp
0.18
0.14
0.10
0e+00
4e+04
8e+04
Iterations
50
40
30
20
10
0
0.10
0.14
0.18
N = 97001 Bandwidth = 0.001288

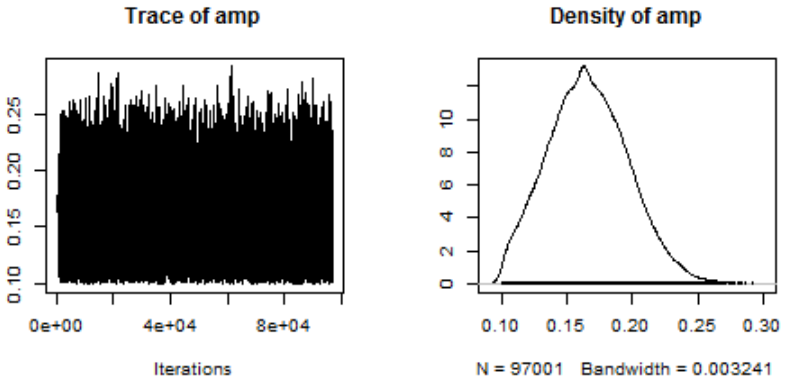

Thanatpin
Trace of beta
Density of beta
0.007600
0.007590
0e+00
4e+04
8e+04
Iterations
200000
100000
0
0.007590
0.007600
N = 97001 Bandwidth = 1.851e-07

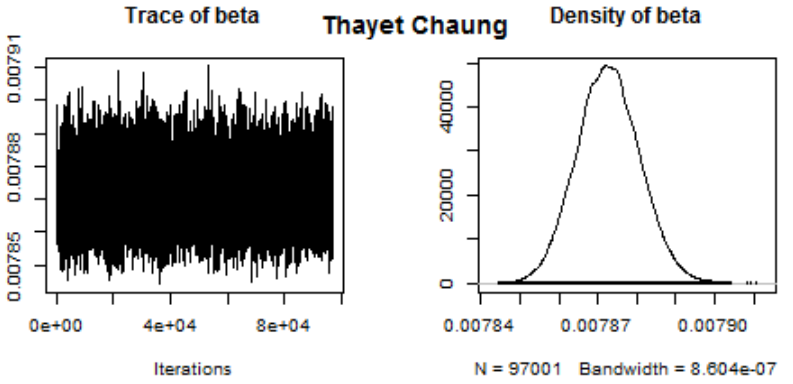

Trace of amp
Density of amp
0.4
0.3
0.2
0.1
0e+00
4e+04
8e+04
Iterations
15
10
5
0
0.1
0.2
0.3
0.4
N = 97001 Bandwidth = 0.004255

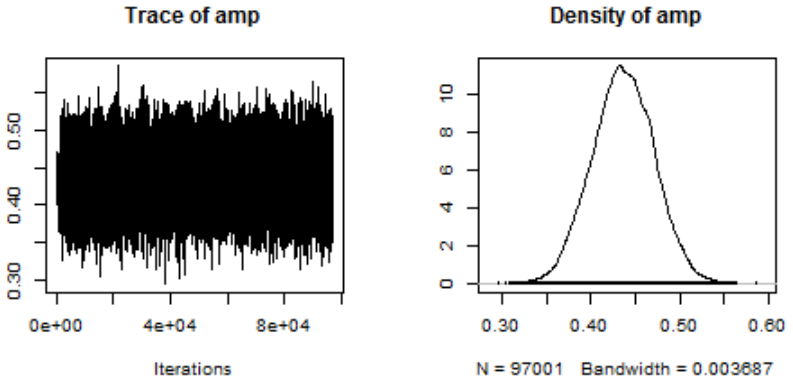

Thanphyuzayat
Trace of beta
Density of beta
0.007710
0.007725
0.007740
0e+00
4e+04
8e+04
Iterations
N = 97001 Bandwidth = 4.05e-07

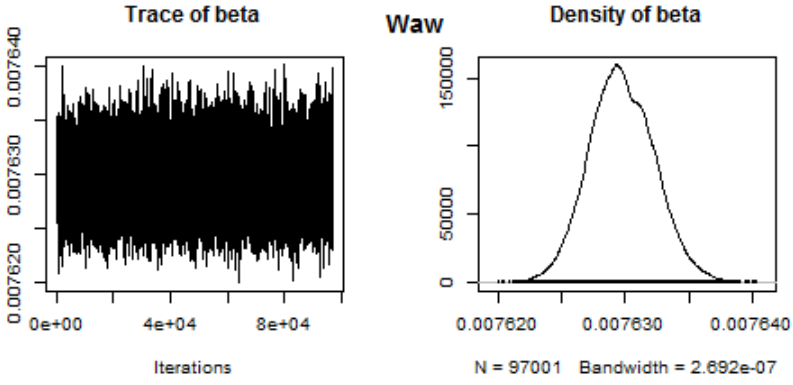

Trace of amp
Density of amp
0.10
0.12
0.14
0
50
100
150
0e+00
4e+04
8e+04
Iterations
N = 97001 Bandwidth = 0.0004159

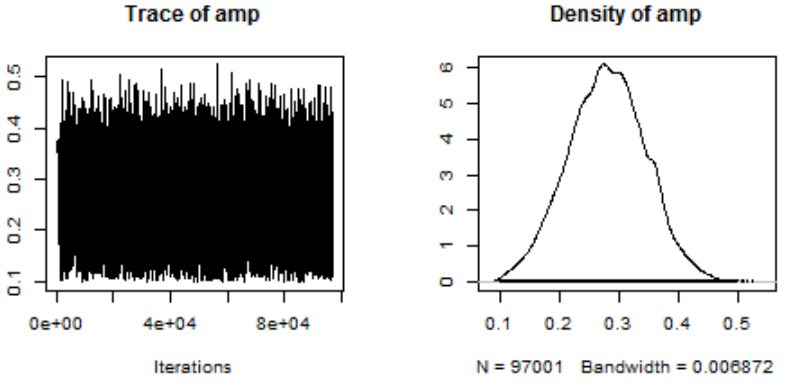

Thaton
Trace of beta
Density of beta
0.007745
0.007760
0e+00
4e+04
8e+04
0.007740
0.007755
0.007770
Iterations
N = 97001 Bandwidth = 3.728e-07

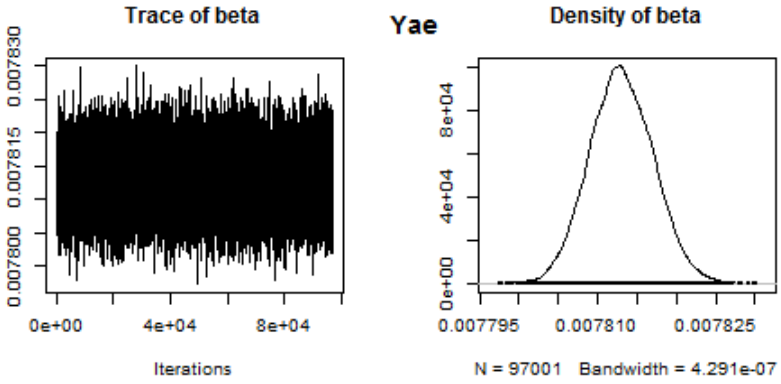

Trace of amp
Density of amp
0.10
0.15
0.20
0.25
0
2
4
6
8
10
0e+00
4e+04
8e+04
0.10
0.15
0.20
0.25
0.30
Iterations
N = 97001 Bandwidth = 0.003241


Trace of beta
Thayet Chaung
Density of beta
0.00791
0.00788
0.00785
0e+00
4e+04
8e+04
Iterations
40000
20000
0
0.00784
0.00787
0.00790
N = 97001 Bandwidth = 8.604e-07


Trace of amp
Density of amp
0.50
0.40
0.30
0e+00
4e+04
8e+04
Iterations
10
8
6
4
2
0
0.30
0.40
0.50
0.60
N = 97001 Bandwidth = 0.003687

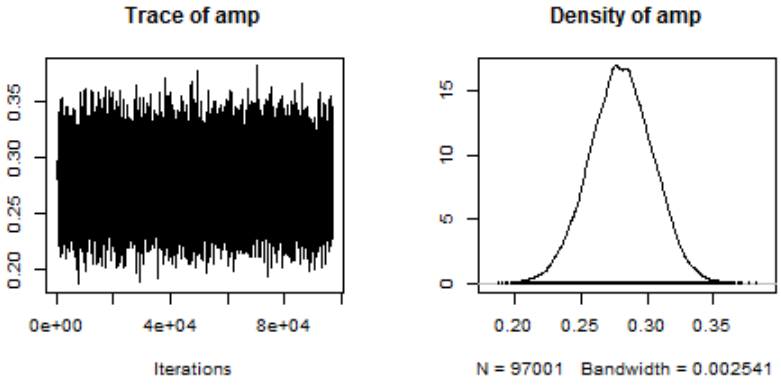

Trace of beta
Waw
Density of beta
0.007640
0.007630
0.007620
0e+00
4e+04
8e+04
Iterations
150000
50000
0
0.007620
0.007630
0.007640
N = 97001 Bandwidth = 2.692e-07


Trace of amp
Density of amp
0.5
0.4
0.3
0.2
0.1
0e+00
4e+04
8e+04
Iterations
6
5
4
3
2
1
0
0.1
0.2
0.3
0.4
0.5
N = 97001 Bandwidth = 0.006872


Trace of beta
0.007800
0.007815
0.007830
0e+00
4e+04
8e+04
Iterations

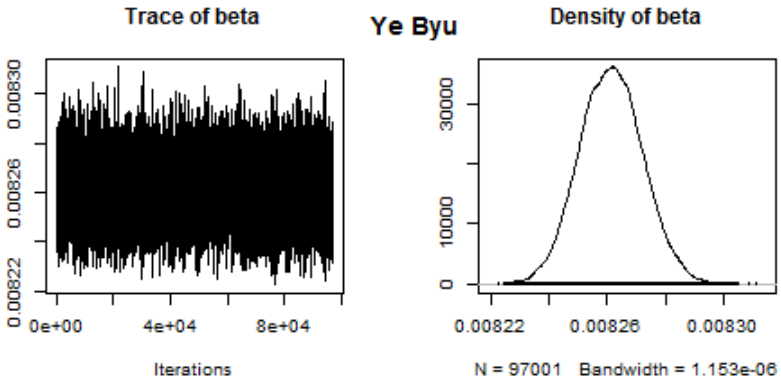
Yae

Density of beta
0e+00
4e+04
8e+04
0.007795
0.007810
0.007825
N = 97001 Bandwidth = 4.291e-07


Trace of amp
0.20
0.25
0.30
0.35
0e+00
4e+04
8e+04
Iterations

Density of amp
0
5
10
15
0.20
0.25
0.30
0.35
N = 97001 Bandwidth = 0.002541

Ye Byu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0e+00
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Iterations

Density of beta
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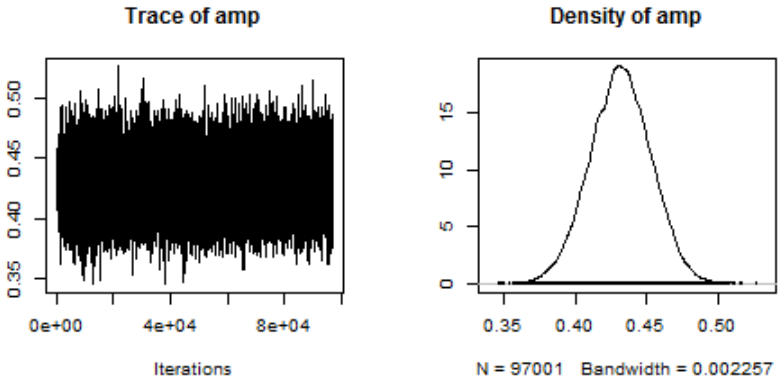
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0.50
0e+00
4e+04
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Iterations

Density of amp
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0.40
0.45
0.50
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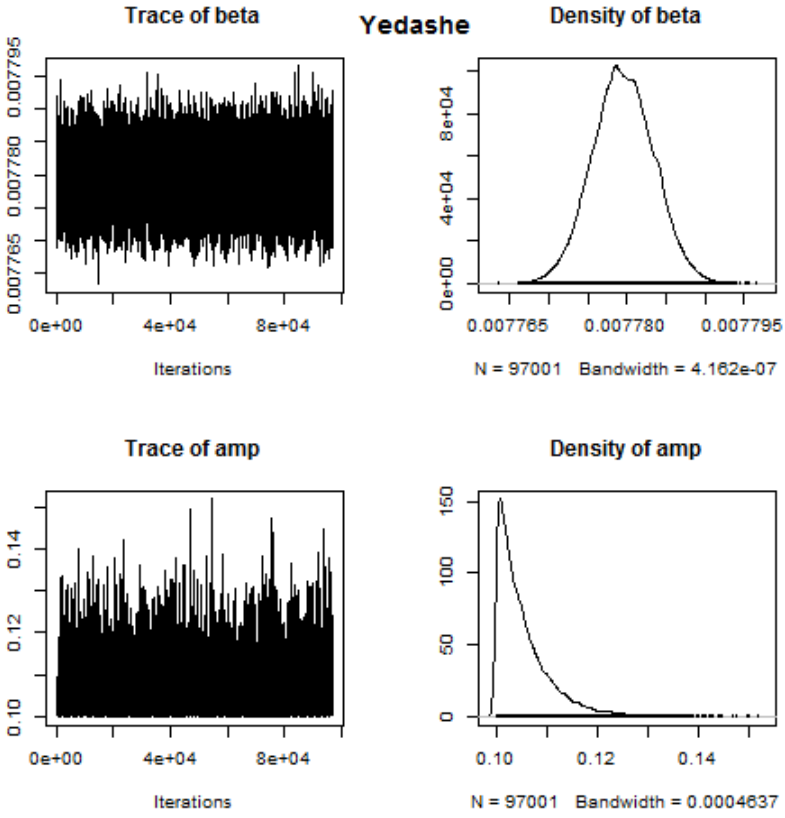
Yedashe
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0.007780
0.007795
0e+00
4e+04
8e+04
Iterations
Density of beta
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4e+04
8e+04
0.007765
0.007780
0.007795
N = 97001 Bandwidth = 4.162e-07
Trace of amp
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0.12
0.14
0e+00
4e+04
8e+04
Iterations
Density of amp
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100
150
0.10
0.12
0.14
N = 97001 Bandwidth = 0.0004637

A.2 Geographic resource allocation algorithm evaluation

In order to check the algorithm is functioning as expected and to assess computational efficiency, a comparative analysis was conducted on randomly generated allocation problems. The resource allocation algorithm was compared against of comprehensive "brute-force" simulation of all possible combinations, selecting the allocation option with maximum impact that falls within budget. Cost and effect properties of each intervention-patch option was generated at random from uniform distributions ranging between US$ 100 – 1000 for cost and 1 to 10 DALYS averted for effect. Three intervention options were defined and evaluated allocation separately for allocation problems of 2, 3, 4, 5, 6, 7 and 8 patches (N). The budget was set at US$ 600 multiplied by the number of patches.

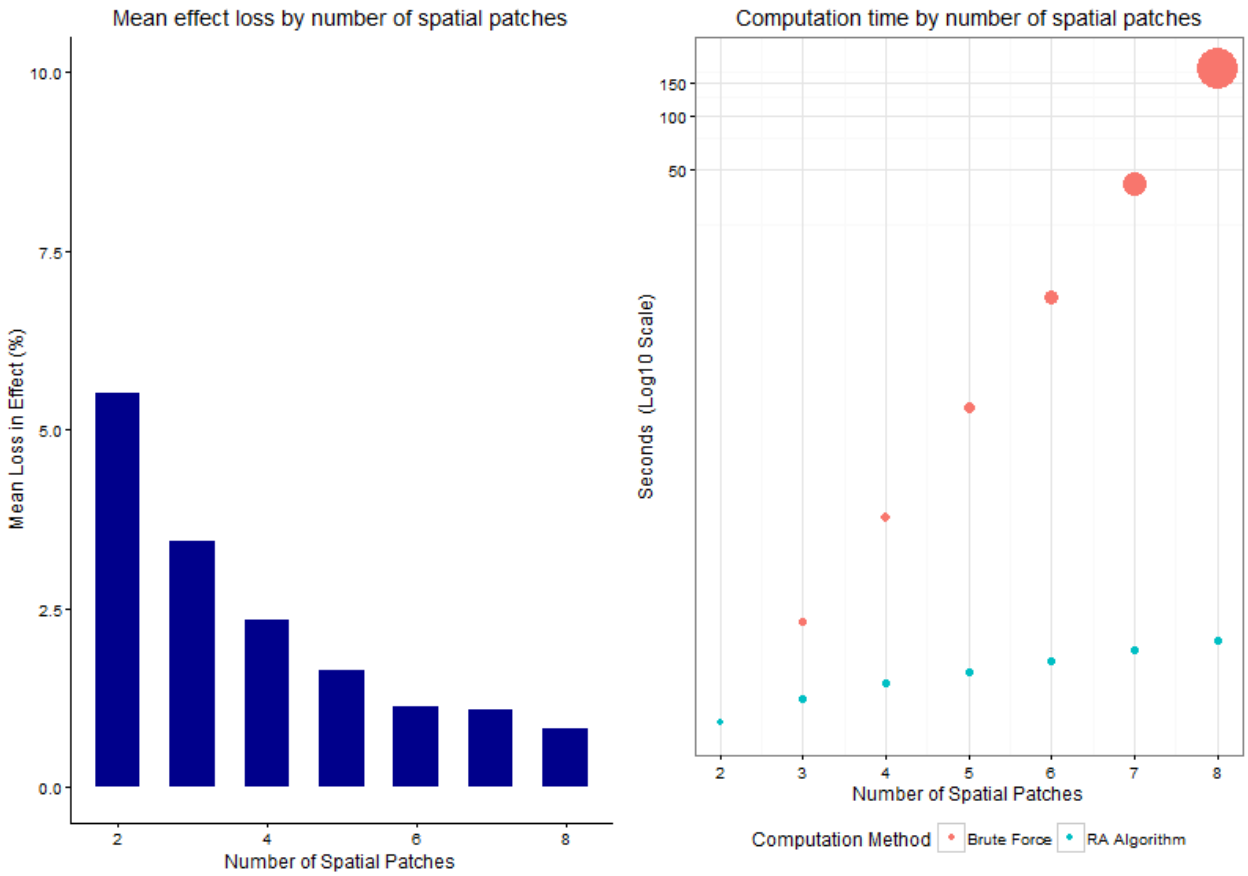
Table S1: Summary of resource allocation algorithm evaluation

N	Budget (US$)	Optimal Impact (DALYs averted)	Lost Impact (%)	Combinations	Brute-force Computation (seconds)	Algorithm Computation (seconds)
2	1200	14.45	5.52	16	0.04	0.04
3	1800	22.31	3.44	64	0.16	0.06
4	2400	30.37	2.35	256	0.58	0.07
5	3000	38.10	1.63	1024	2.40	0.08
6	3600	46.31	1.14	4096	9.82	0.09
7	4200	53.72	1.08	16384	41.45	0.11
8	4800	61.95	0.82	65536	179.68	0.12

Each simulation consists of a set of interventions with randomly generated cost and effect properties being assigned an allocation solution by i) brute-force simulation and ii) the resource allocation algorithm. The simulation result is the difference between the brute-force approach (optimal allocation) and the resource allocation algorithm. For each patch number 500 simulations were run with resampled costs and effects for each simulation.

There is a small expected loss in effect of an algorithm derived solution compared with the true optimal solution that decreases exponentially with increasing number of patches (5.52% loss with 2 patches falling to 0.82% loss with 8 patches) (Table S1, Figure S1). The relative computation time is also striking in this evaluation for an 8 patch allocation problem brute-force computation took an average of 179.68 seconds for a single simulation while the resource allocation algorithm took just 0.12 seconds. Moreover the computational demands also rise exponentially with number of patches for brute-force computation but do not for the algorithm.

Figure S1: Comparison of "brute-force" and algorithm based allocation solutions



A.3 Software Platforms for Economic Evaluation

During the course of this DPhil I have used three different platforms for economic evaluations: Excel, TreeAge and R. Below are some notes on some of the advantages and disadvantages of each for the purpose of economic evaluation. Overall I find Excel to be best for costing and R for outcome modelling.

Excel is easy to use and most people are likely to have experience with the programme prior to using it for economic evaluation. It is part of the standard Microsoft Office suite and is therefore very widely available, though not free. Excel is widely used for budgeting, accounting and other financial management tasks and is therefore an easy environment to work with cost data. It is also relatively straightforward to develop decision trees and Markov models in the grid-based interface. To undertake more advanced analysis, some knowledge of visual basic is needed. For example, to develop macros that iterate Monte Carlo sampling for probabilistic sensitivity analysis. There is in built in functionality to create figures from results which is user friendly though at times restrictive.

TreeAge is specifically designed for healthcare economic evaluation. There is more of a learning curve to use the software than Excel but the graphical interface for constructing decision models makes it easier to visualise decision tree models and the ability to assign uncertainty ranges and sampling distributions to parameters make univariate, multivariate and probabilistic sensitivity analysis easier than Excel. However, TreeAge is not flexible. If you want to do anything that does not fall within standard economic evaluation methods

you quickly run into problems. While the ability to output model diagrams and various figures including cost effectiveness plane, tornado diagram, cost effectiveness acceptability curves and so on, the graphics outputs are not particularly refined.

R is a free, open source, statistical software platform that is growing rapidly in popularity. R itself is a statistical programming language but many users access it through the user friendly RStudio interface. Since R is essentially a programming language there is a steeper learning curve for most users, particularly those without experience of other programming languages. However, once the basics have been mastered, the extensive online support generated by the active community of R users and developers makes troubleshooting easy. The main advantage with R is the vast functionality, that continues to grow as developed generate new packages. The fact that R is free is also a big advantage when working with colleagues or offering workshops in low income countries. As a health economist, I use R not only for the core tasks of economic evaluation but, among other things: to reduce simulation time using parallel computing, to produce maps presenting model results and to create interactive user interfaces for model. Depending on the context, R may be less convenient for handling cost data than excel. But for the majority of tasks including data manipulation, analysis, modelling and graphical presentation of results, R is far superior.

Below are a few further notes on selected R packages.

deSolve, rootSolve and simecol

Solver for differential equations and working environment for dynamic models. Developed by Thomas Petzoldt, Karline Soetaert and others.

The simecol package is particularly useful as it converts the dynamic model, along with other component parts such as its parameters and initial conditions, into a single "S4" object. This makes further post-simulation analysis such as cost effectiveness analysis neater, particularly when using a large number of different model scenario.

dplyr, tidyr, ggplot2 and other packages in the "Hadleyverse"

A range of packages that facilitate data manipulation and graphical presentation. Developed by Hadley Wickham and others.

dplyr and tidyr make data manipulation much easier than the base R methods. The innovation that underpins the array of functions in these packages is the "piping" operator %>%, which allows code to be written as a series of sequential actions undertaken on a data frame.

ggplot2 introduces an approach to developing elegant data graphics using layers of "geoms" to build complex graphs. The package is reportedly now used by the Financial Times: http://blog.revolutionanalytics.com/2016/09/financial-times-quantitative-journalism.html

maptools, ggmap, rgeos, [leaflet] and other mapping packages

Numerous packages and other software can be harnessed by R to produce maps. Developed by various authors.

Dedicated GIS software such as ARCGIS or QGIS are superior for producing high quality, detailed maps. However for presenting simulation results as geographic heatmaps R is sufficient and being able to generate these graphics in the same platform used for the analysis is a significant advantage.

Shiny

Allows the development of interactive user interfaces. Developed by RStudio.

Shiny is an increasingly popular R package that facilitates the development of interactive interfaces, allowing users to explore data or to run bespoke simulations on simple models. A degree of further investment in learning to adapt existing R code into the reactive Shiny framework is required but it is reasonably straight forward and the tutorials available from RStudio are very good.

FitR

Fitting infectious disease transmission models. Developed by Sebastian Funk and others.

FitR is a suite of functions for fitting transmission models to data, including using Markov Chain Monte Carlo (MCMC) methods. This removes the need for moving to another platform such as WinBUGS for MCMC fitting. At the time of writing FitR is not available on the Comprehensive R Archive Network (CRAN), where most packages are can be obtained.