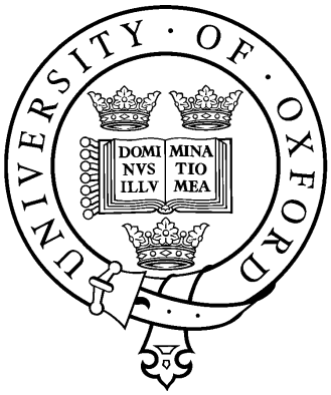
Defining empirical management of acute febrile illness in Myanmar



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Abstract

Fever is a common presenting symptom in primary care in low- and middle-income countries (LMICs). Non-malaria pathogens are now responsible in most cases after a decline of malaria in previously malaria endemic regions of Myanmar. It is important to provide appropriate treatment to those patients after malaria is ruled out by rapid tests or microscopy.

The overall aim of this thesis is to improve management of acute non-malaria febrile illness in Myanmar. Empirical treatment strategies with selected antibiotics were devised and their cost-effectiveness was evaluated using a decision tree modelling approach.

A systematic review on infectious neglected tropical diseases (NTDs) was conducted to collate all reports of NTDs in Myanmar (Chapter 2). The review identified diseases (rickettsial infection and leptospirosis) commonly associated with acute fever and this finding partly informed selection of antibiotics for empirical treatment. A cost-effectiveness analysis of empirical treatment showed empirical treatments being cost-saving and C-reactive protein (CRP) guided empirical treatments being highly cost-effective compared to current practice of care in rural Myanmar (Chapter 3). Alongside this, antibiotic use for acute febrile illness was also explored from the prescriber's perspective by secondary analysis of the data derived from a clinical trial (Chapter 4) and the user's perspective by public engagement activities (Chapter 6). The secondary data analysis found a substantial variation of antibiotic prescription among primary care doctors for acute febrile illness and the variation remained after accounting for patients' clinical presentations and CRP test results. Widespread environmental distribution of *Burkholderia pseudomallei*, the causal organism of melioidosis, which commonly presents as community acquired pneumonia and sepsis, was confirmed by a large nationwide study (Chapter 5).

In conclusion, this thesis uses a multifaceted approach to improve management of acute febrile illness in Myanmar. Findings from this thesis point towards an empirical antibiotic treatment strategy as a potential approach for management of non-malaria febrile illness in rural Myanmar which could be evaluated in field trials.

Statement on impact of COVID-19 pandemic and military coup

During my DPhil study, two major events happened: COVID-19 pandemic and military coup in Myanmar. Both had major impact on my work and thesis. First, the pandemic and its control measures including lockdown and quarantine in 2020 made it impossible to carry out the clinical trial related to acute febrile illness and the field survey on "Antibiotic use and Antimicrobial resistance awareness". In late 2020, the clinical trial was replaced with a modelling project evaluating empirical treatment for management of febrile illness as part of DPhil study. Unfortunately, military coup happened in early 2021, nationwide protests, political unrests and subsequent civil wars forced me to move from Myanmar Oxford Clinical Research Unit in Yangon (Myanmar) to Oxford in late 2021 to complete my DPhil study.

Statement of contributions

My supervisors, Elizabeth Ashley, Frank Smithuis, Ben Cooper and Sir Nicholas White provided methodological and scientific guidance throughout all stage of this work. Additional contributors for each chapter are listed below.

For Chapter two, Elizabeth Ashley and I designed the search strategy for the systematic review and academic librarian Eli Harris conducted the database searches. Htet Naing Lin and Aung Pyae Phyo acted as second reviewers, checking all extracted data.

For Chapter three, my supervisors conceptualised the ideas of empirical treatment for acute fever. Cherry Lim helped check the codes.

For Chapter four, the data was derived from a clinical trial which was designed by Yoel Lubell, Frank Smithuis and Thomas Althaus. Elizabeth Ashley, Alistair McLean and I conceptualised the idea for the secondary analysis. Alistair McLean helped check the codes.

For Chapter five, Frank Smithuis, Elizabeth Ashley, David Dance and Joshua Cohen developed the protocol. Kyaw Soe, Saw Kan Sint and staff from Medical Action Myanmar (MAM) assisted in soil sample collection. Mo Mo Win and her team performed culture and isolation of *Burkholderia pseudomallei*. Alistair McLean advised on the data analysis.

For Chapter six, Phyu Hnin Hlaing led qualitative evaluation of the public engagement activities assisted by Htet Htet Aung.

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I would like to acknowledge and thank to the experts who participated in the elicitation interview.

As a personal note, I would like to thank Mo Yin and Cherry Lim for making me less lonely and enjoyable living in Oxford during my final year of DPhil. Thank you, Sean and Mark for your help with proof reading.

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Finally, special thanks to the Tropical Network Fund (TNF) for funding my DPhil study.

Published works related to this thesis

The following chapters contain work that has been published in peer-reviewed journals. I confirm that I authored and produced the following publications with no more input or advice than would be considered appropriate or acceptable for a thesis. The relevant sections which are re-used from these publications have been referenced at the appropriate parts.

Chapter 4

M. M. M. Swe, E. A. Ashley, T. Althaus, Y. Lubell, F. Smithuis, and A. R. D. McLean. "Inter-Prescriber Variability in the Decision to Prescribe Antibiotics to Febrile Patients Attending Primary Care in Myanmar." *JAC Antimicrob Resist* 3, no. 1 (Mar 2021): dlaa118. https://dx.doi.org/10.1093/jacamr/dlaa118

Chapter 5

M. M. M. Swe, M. M. Win, J. Cohen, A. P. Phyo, H. N. Lin, K. Soe, P. Amorncha, T. T. Wah, K. K. N. Win, C. Ling, D. M. Parker, D. A. B. Dance, E. A. Ashley, and F. Smithuis. "Geographical Distribution of *Burkholderia Pseudomallei* in Soil in Myanmar." PLoS Negl Trop Dis 15, no. 5 (May 2021): e0009372. https://dx.doi.org/10.1371/journal.pntd.0009372

Chapter 6

M. M. M. Swe, P. H. Hlaing, A. P. Phyo, H. H. Aung, F. Smithuis, E. A. Ashley, and P. Y. Cheah. "Evaluation of the Forum Theatre Approach for Public Engagement around Antibiotic Use in Myanmar." PLoS One 15, no. 7 (2020): e0235625. https://dx.doi.org/10.1371/journal.pone.0235625

Submitted work

Chapter 2

M. M. M. Swe, A. P. Phyo, H. N. Lin, B. Cooper, N. J. White, F. Smithuis, E. A. Ashley. “A systematic review on infectious neglected tropical diseases (NTDs) in Myanmar.” PLoS Negl Trop Dis (January 2023).

Abbreviations

ACT	Artemisinin Combination Therapy
AMR	Antimicrobial Resistance
CDC	Centre for Disease Control
CEAC	Cost-Effectiveness Acceptability Curves
CEAF	Cost-Effectiveness Acceptability Frontiers
CRP	C-Reactive Protein
DALYs	Disability Adjusted Life Years
FGD	Focus Group Discussion
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GPS	Global Positioning System
ICER	Incremental Cost-Effectiveness Ratio
IMAI	Integrated Management of Adolescents and Adults Illness
IMCI	Integrated Management of Childhood Illness
INB	Incremental Net Benefit
LMIC	Low- and Middle-Income Countries
LRTI	Lower Respiratory Tract Infection
MAM	Medical Action Myanmar
MOR	Median Odds Ratio
NAP	National Action Plan
NTDs	Neglected Tropical Diseases
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
POC	Point of Care
RDT	Rapid Diagnostic Test
SDG	Sustainable Development Goal
SEE	Structured Expert Elicitation
SHELF	Sheffield Elicitation Framework
STH	Soil Transmitted Helminths
UNICEF	United Nations Children's Fund
URTI	Upper Respiratory Tract Infection
UTI	Urinary Tract Infection
VPC	Variance Partition Coefficient
WHO	World Health Organization
WTP	Willingness to pay

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Chapter 1

Background and literature review

1.1 Introduction

Fever is one of the most common presenting symptoms in patients attending primary care and outpatient facilities in tropical and subtropical countries [1, 2]. Reliable data on the burden of febrile illness in the tropics is quite limited especially for low- and middle-income countries (LMICs). According to the World Health Organization (WHO) report on informal consultation on fever management which gathered all available evidence from previous studies, the incidence of febrile episodes in rural tropical regions is up to ten times per year in children younger than five years of age, and four times per year in older persons. The corresponding figure for urban regions was estimated to be 2.5 and 0.5 times for the two age groups respectively [3].

Febrile illnesses in the tropics are largely caused by infectious diseases of various aetiologies: viruses, bacteria, parasites and fungi. In the past, malaria used to be a leading cause of febrile illness the tropics. Back in 2000, malaria claimed 896,000 lives globally with an estimated 241 million cases. Over the last 20 years, estimated incidence of malaria has declined substantially from 81 cases per 1000 population at risk in 2000 to 56 in 2019 before increasing again to 59 in 2020 due to disruption of services during the COVID-19 pandemic. In term of distribution, about 95% of all global malaria cases occurred in the WHO African region and about 2% in the WHO South-East Asia region [4]. This substantial decline in the global burden of malaria is largely attributed to a substantial investment in malaria programmes and research together with effective vector control, use of insecticide treated mosquito nets,

preventive chemotherapy, availability of malaria rapid tests and effective Artemisinin Combination Therapy (ACT).

The first WHO guideline for the treatment of malaria, published in 2006, recommended empiric, oral, antimalarial therapy for fever without other source in children under five years living in high malaria transmission settings[5]. Since then most febrile patients in malaria endemic regions were presumptively treated with antimalarials until 2010 although the 2006 malaria guideline recommended to confirm malaria (either by microscopy or RDTs) in low to moderate transmission settings [6]. As a result, non-malaria febrile patients were treated unnecessarily with antimalarial drugs, resulting in additional costs and waste of medications without any benefit to them.

With the increasing availability of accurate and affordable malaria rapid tests, the WHO changed its recommendation in 2010 to confirm malaria in all patients suspected of having malaria with rapid tests or microscopy before treatment [3]. This approach has presented health care workers with new challenges in managing febrile patients who are found to be malaria test negative. It has led health workers to use antibiotics as a default treatment for non-malaria febrile illness instead of antimalarials. In 2017, analysis of ten studies, eight in sub-Saharan Africa and two in Afghanistan, demonstrated that introduction of malaria RDTs for fever management reduced antimalarial prescriptions in malaria test negative patients but increased antibiotic prescriptions [7].

There are well developed treatment guidelines for malaria, even for health care workers with limited training at the community level. However, there is a lack of such a guideline for non-malaria febrile illness in order to provide appropriate and effective treatment.

Despite the decline in malaria cases, fever remains a leading cause of seeking care at various levels of health facilities in the tropics. In the South-East Asia region, the burden of infectious diseases together with febrile illness is expected to increase given several factors including the size of its population, pockets of the population living under the poverty line, limited access to health care, poorly planned urbanization and unregulated deforestation [8, 9]. All of these factors are known to be associated with an increased risk of infectious diseases, and most of them can present with acute fever.

1.2 Burden of febrile illness

Defining the burden of febrile illness itself is challenging since fever is a common, non-specific symptom of most infectious diseases. A scoping review on diagnostic tools for acute febrile illness in India emphasized that "fever in the tropics is a nebulous terminology" due to the lack of consensus regarding what symptoms constitute acute febrile illness and what duration distinguishes acute from persistent fever [10]. Fever can be arbitrarily defined as acute for symptoms lasting less than 7 to 14 days, and chronic for symptoms lasting more than 21 days as described in the literature [10-12]. Fever rarely presents in isolation; it is often accompanied by other symptoms; some of which might be specific to a particular organ system. For instance, in an acute febrile patient accompanied by respiratory symptoms, acute respiratory infection is likely to be the culprit. Thus, acute fever can be broadly defined into different febrile syndromes depending on the predominant accompanying symptoms. Well-recognised febrile syndromes include acute respiratory tract infections, fever with gastroenteritis, urinary tract infection and neurological infection [3, 13]. Acute fever without any localizing symptoms is often referred to as undifferentiated febrile illness (AFI) which is a common characteristic of many important infections in the tropics such as malaria,

rickettsioses, leptospirosis, dengue and chikungunya infection [14]. However, a syndromic approach has limitations due to overlapping of symptoms among diseases [15]. For example, cough was present in about 60% of hospitalized children with scrub typhus in northern Thailand and 36% of patients with enteric fever in Nepal [16, 17].

Most febrile patients attending primary care facilities have respiratory symptoms. For instance, more than 50% of febrile episodes in children under five years of age presenting at outpatient clinics in Tanzania were associated with acute respiratory infection and only 5% of those infections were radiologically confirmed pneumonia cases [18]. Other infections, such as meningitis, skin or soft tissue infections, accounted for less than 5% of children's febrile episodes, while gastroenteritis was seen in 10–25% [18]. The remainder had no localizing signs of infection and had urinary tract infections (1–6%) or enteric fevers (2–10%), or bacteraemia (< 2%) [3, 18].

Respiratory tract infection is also common among adults attending primary care. A fever study in Southeast Asia showed that about 80% of adult patients with acute fever attending to primary care clinics had at least one respiratory symptom [19]. Similarly, 80% and 0.6% of adults with non-malaria febrile illnesses were clinically diagnosed as upper respiratory tract infection (URTI) and lower respiratory tract infection (LRTI) in Cambodia [20]. Other diseases that are commonly associated with acute undifferentiated fever included dengue, leptospirosis, rickettsial infection and enteric fever, but their prevalence varies by geographic location [21].

Table 1.1. Estimated global burden of infections and diseases that are commonly associated with febrile illness

Disease/ Infection	Total number of cases	Deaths	DALYs	Reference
URTI	17.2 billion	9464	6 million	GBD 2019 study [22]
LRTI	490 million	2.5 million	97.2 million	GBD 2019 study [22]
Dengue	57 million	36,055	2.4 million	GBD 2019 study [22]
Typhoid and Paratyphoid	13 million	133,366	9.7 million	GBD 2019 study [22]
Leptospirosis	1 million	58,900	-	[23]
Scrub typhus	1 million	-	-	[24]

The Global Burden of Disease (GBD) study estimated that there were 17.2 billion cases of upper respiratory infection globally accounting for 43% of all causes of the GBD in 2019 and contributing to 6 million DALYs [22]. In the same year, there were an estimated 490 million episodes of lower respiratory infection, claiming 2.5 million lives and 97.2 million DALYs worldwide [22]. Dengue infection was estimated at 57 million cases with 36055 deaths and 2.4 million DALYs. The global prevalence of leptospirosis is estimated to be 1.03 million cases and 58,900 deaths, with 48% of cases and 42% of fatalities occurring in adult males 20-49 years old [23]. Scrub typhus, the most important rickettsia infection in terms of disease burden which predominantly occur in the "tsutsugamushi triangle" is estimated to cause 1 million cases posing 1 billion people at risk [24, 25].

1.3 Epidemiology of febrile illness in Southeast Asia

The number of malaria cases in Southeast Asia was estimated to plunge from 22,800,000 in 2000 to 5000,000 in 2020 according to the WHO World Malaria Report [4]. Apart from malaria, other causes of febrile illness in the region have been investigated in several studies but predominantly in the form of single disease

epidemiology studies, for instance, dengue, melioidosis, typhoid, scrub typhus and melioidosis. However, there are few studies that investigated a range of pathogens causing febrile illness in different population, age groups and disease severity.

A study of 439 febrile episodes in 409 pregnant women from 2004 to 2006 along the Thailand-Myanmar border region showed that arthropod-borne (malaria, rickettsial infections and dengue) and other zoonotic diseases (leptospirosis) accounted for almost half of all febrile cases. After excluding malaria, urinary tract infection and respiratory infections, one-third of the remaining cases were caused by leptospirosis or rickettsial infection [26].

Another study that investigated aetiologies of acute undifferentiated febrile illness in 845 patients attending to five rural hospitals in Thailand identified causes of fever in 68% of cases. The most common causes were leptospirosis (37%), scrub typhus (20%) and dengue infection (11%) [27]. A high prevalence of leptospirosis in this study could be partly explained by the fact that three quarters of the study population were agriculture workers.

A large prospective fever study that recruited almost 2000 patients in two provincial hospitals in Laos identified aetiologies in 41% of cases. The top five causes were dengue (8%), scrub typhus (7%), Japanese encephalitis virus (6%), leptospirosis (6%) and bacteraemia (2%) with varying distributions between the two sites [28]. Influenza was tested in a subset of population over a specific period of time and found to be positive in 32% among those tested.

A large study that included 9997 acute febrile patients attending nine health care clinics in rural Cambodia identified aetiologies in 38% of patients. Influenza was the most

common pathogen followed by dengue, malaria, leptospirosis and blood-borne pathogens which include *Salmonella* Typhi [29].

A similar distribution of aetiologies has been reported in systematic review articles. A recent systematic review on aetiologies of acute undifferentiated febrile illness, which included 15 studies from Southeast Asia region, found that viral aetiologies were more common than bacterial aetiologies (33% compared to 21%). Dengue and influenza each accounted for 11% of cases whereas leptospirosis, rickettsial diseases, typhoid and malaria were identified in 12%, 4 %, 3% and 2% of cases respectively [21].

Another systematic review on aetiologies of non-malaria febrile illness (NMFI) in South and Southeast Asia showed that bacterial and viral aetiologies were reported in 51.2% and 35.1% of 2310 included articles respectively, whereas parasitic and fungal aetiologies were reported in 5.5% and 2.2% respectively. It is worth noting that this review did not report prevalence, but rather aetiologies in the included articles. The frequently reported bacterial aetiologies were *Salmonella* Typhi, *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae* while dengue virus, chikungunya virus, Japanese encephalitis virus were commonly reported viral pathogens among included studies [30].

A scoping review of 30 studies on the epidemiology of febrile illness in Asia reported that the most frequent aetiology was dengue (reported in 50% of the included studies), followed by leptospirosis (27%), scrub typhus (23%) and *Salmonella* serovar Typhi (20%) [12]. Another review article that mapped non-malaria febrile illnesses aetiology in the Mekong region of Southeast Asia, which included 146 studies, showed that the most frequently reported pathogen was dengue virus (n = 70), followed by *Orientia tsutsugamushi* and *Rickettsia* species (scrub typhus/murine typhus/spotted fever group

n = 58), *Leptospira* spp. (n = 35), *Salmonella* enterica serovar Typhi and Paratyphi (enteric fever n = 24), *Burkholderia pseudomallei* (melioidosis n = 14), and Japanese encephalitis virus (n = 18) [31].

Although there are heterogeneities regarding study design, study population and diagnostic methods, findings from the above studies and review papers highlight that respiratory infections are common in febrile patients both in children and adults; malaria cases have declined substantially; there is a predominance of viral over bacterial infections; and most bacterial infections, such as leptospirosis, rickettsioses and typhoid are treatable with empirical antibiotics.

1.4 Guidelines and tools for management of fever

1.4.1 World Health Organization (WHO) guidelines

WHO has published guidelines and tools for the management of common illnesses including febrile illness for different age groups at different levels of healthcare (Figure 1.1).

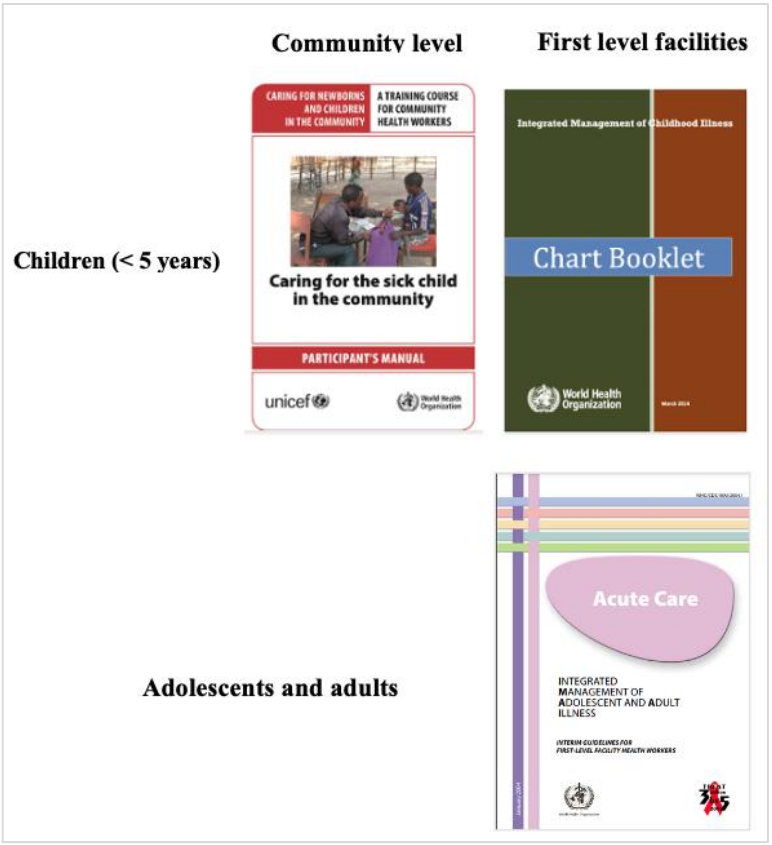


Figure 1.1. WHO guidelines for the management of common illnesses for different age groups at primary health care level and below

The Integrated Management of Childhood Illness (IMCI) guideline is designed for children under five years of age. It was conceived in the mid-1990s by WHO and UNICEF to train and improve skills of health care providers at first level care facilities and district hospitals in resource limited settings, aiming to improve access and quality of care for newborns and children [32]. IMCI is based on algorithms and flow charts

that enable health care providers to use a systematic approach when assessing children for danger signs that require urgent referral to hospital and categorizing illnesses according to their severity for malaria, fever, pneumonia, diarrhoea, measles, otitis media, and malnutrition. Levels of severity are colour coded, with pink for severe cases to be urgently referred after initial treatment, yellow for moderate illnesses to be treated at facilities, and green for mild illnesses that require supportive care at home with return precautions [5, 33].

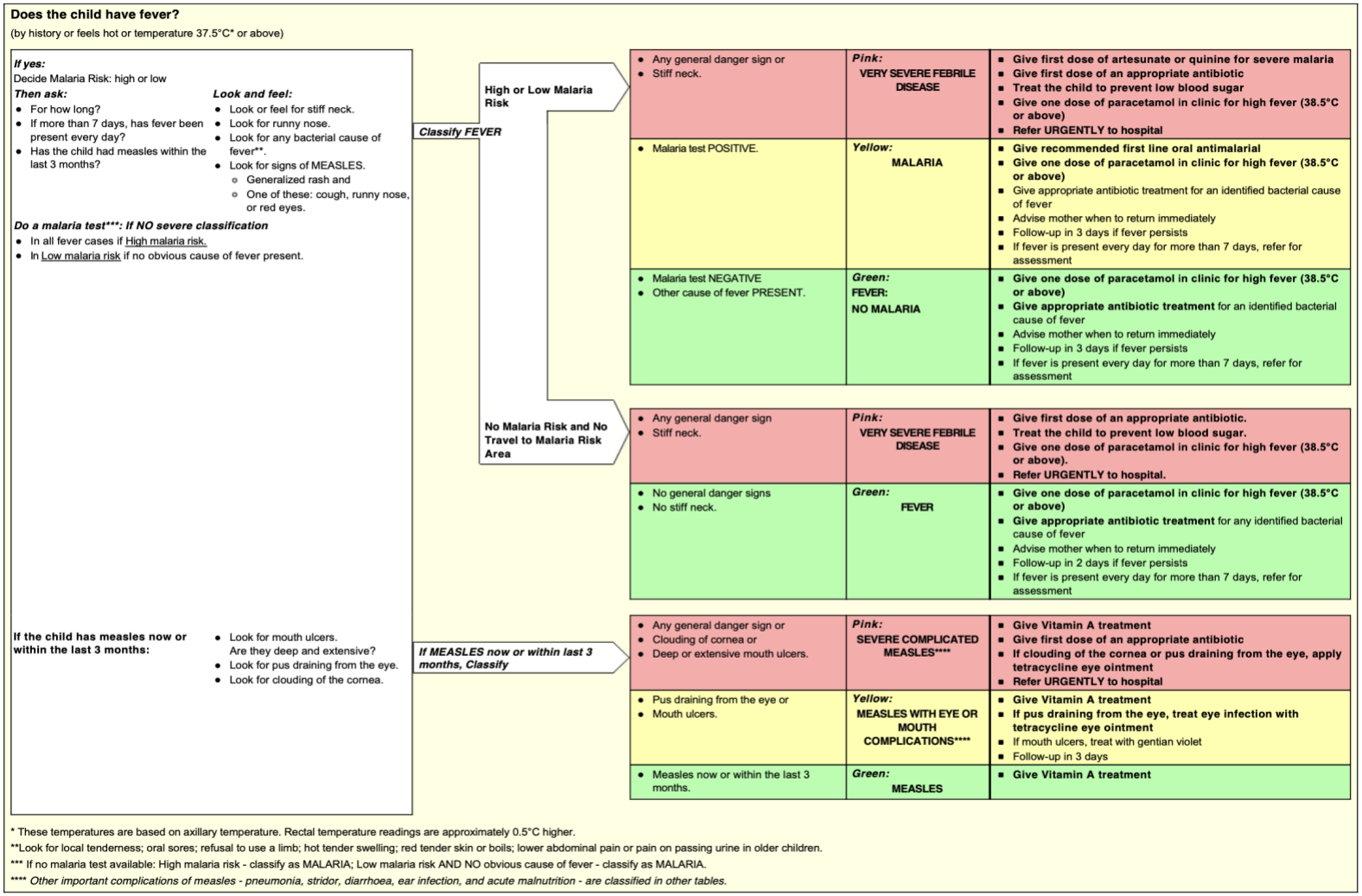


Figure 1.2. IMCI management algorithm for acute fever with colour coded classification for severity (Source: IMCI distance learning course 2014)

Upon evaluating the danger signs, severe febrile illnesses such as severe malaria, severe dengue, meningitis, and sepsis are identified and referred urgently. All non-severe febrile children with high or low risk of malaria are tested with malaria RDTs and treated depending on the test's result. For children with negative malaria test and those with no risk of malaria, health care workers are advised to give antibiotics if there is any sign or symptom of identifiable bacterial infections. Localised infections such as pneumonia cases are treated with amoxicillin [3].

The impact of IMCI has been evaluated in several studies in different geographic regions. A reduction in childhood mortality has been reported in two studies. A cluster randomized control trial in India reported 14% and 15% reduction in neonatal and infant mortality in the intervention compared to the control clusters [34]. One year after IMCI implementation in Egypt, a retrospective analysis found a two-fold reduction (3.3% vs 6.3%) in under-five mortality [35]. In addition, IMCI has been demonstrated to improve quality of care, including more thorough evaluations and better counselling for caretakers [36, 37].

It has limitations, however, when it comes to identifying children who could benefit from antibiotic treatment. When compared to physician diagnosis and decision making, a study in Bangladesh found a sensitivity of 78 % and specificity of 47 % for identifying children with probable bacterial infections [38]. Furthermore, the guideline relies heavily on the clinical judgement of health care workers without providing any further guidance on how to identify possible bacterial infections, especially for febrile children with a negative malaria test and those with no localising signs. As a result, there is a risk of misuse of antibiotics which is a major driver for emergence of antibiotic resistant

bacteria. Additionally, a thorough clinical assessment takes time to gather relevant history and important physical signs.

Despite training on the IMCI guideline, adherence rates for assessment and physical examination among health workers remained low in resource limited countries [39]. There is wide variation in adherence with different parts of the algorithm, and sometimes severe febrile cases had not receiving IMCI recommended treatment and not all severely ill children being referred [40-42]. The poor adherence of health care workers to guidelines in resource limited settings is a complex process to which several factors contribute: low motivation, not being convinced in IMCI as a valuable approach, guideline complexity, being physically or cognitively overloaded with other jobs and dissatisfaction with the salary [43, 44]. Integrated Community Case Management (iCCM) is a simplified version of IMCI, and it involves identifying and referring children with danger signs and treating malaria, pneumonia and diarrhoea at home with appropriate medication [3].

Another WHO sponsored guideline is Integrated Management of Adolescents and Adults Illness (IMAI) for first level facilities and district hospitals. Although there are differences between adults and children in terms of disease aetiologies and burden, adolescents and adults have been given less priority partly due to their lower mortality risk compared to children [3]. Some infections like HIV and tuberculosis are more common in adults, and opportunistic infections can also present as febrile illness [45]. Furthermore, occupational exposure, especially in rural areas, puts them at increased risk for certain diseases such as melioidosis, leptospirosis and rickettsial infections.

The guideline for management of febrile illness in IMAI is based on the current WHO treatment guideline for malaria [45]. IMAI for first level health facilities recommends

to test for malaria (either RDT or microscopy) in febrile patients with high- and low-risk of malaria, give antimalarials to those with a positive malaria test, and antibiotics to those with signs of severe illness or apparent bacterial infections [46]. Severe illness or persistent fever cases (> 7 days) with no apparent diagnosis are referred for further investigation and treatment.

It has been shown that WHO recommendations are rarely adopted and used in low-resource areas. There are a number of reasons for this, including poor dissemination, limited training and monitoring, and insufficient human and other resources [45].

Given the fact that there are gaps in these guidelines, limitations of clinical judgement in identifying bacterial infections (especially in patients with undifferentiated symptoms) and scarce diagnostic facilities in remote areas, it is hard to identify febrile patients who could benefit from antibiotics in primary care facilities. This can lead to inappropriate use of antibiotics which include prescribing antibiotics for patients with non-bacterial infection and failure to prescribe antibiotics to patients with probable bacterial infection [47, 48].

Inappropriate use of antibiotics has been shown in a number of studies. A study that examined appropriateness of antibiotics prescription for over 5000 episodes of childhood illnesses (pneumonia, malaria and diarrhoea) managed with IMCI guideline in Papua New Guinea found that 11% of the children did not receive antibiotics when they should have and 29% received antibiotics when they should not have [49]. A Cochrane review, which included eight controlled trials from African countries, Afghanistan, and Myanmar, showed that the use of malaria RDTs by community health workers and drug store vendors for management of fever was found to increase antibiotics prescription in patients with negative malaria RDTs [50].

1.4.2 Potential of point of care diagnostic tests to improve the management of febrile illness

Use of point-of-care diagnostic tests is an appealing option to improve the management of non-malaria febrile illnesses. This approach can assist health care workers in deciding whether to prescribe antibiotics and selecting appropriate antibiotics for particular types of bacterial infection such as scrub typhus. Although pathogen specific rapid tests are increasingly available, there are several factors that hinder their use in routine practice.

First, most pathogen specific rapid tests do not have enough accuracy except a few such as influenza, respiratory syncytial virus and dengue infection [51, 52]. Rapid tests to detect common bacterial infections associated with febrile illness are not sensitive enough to deploy in routine practice. For example, a study that investigated aetiologies of fever in the tropics found a poor performance of antibody-based rapid tests for typhoid and leptospirosis. In that study, the sensitivities of three rapid tests for *Salmonella* Typhi ranged from 29 to 67% and sensitivities of two rapid tests for leptospirosis were only 9% and 16% [53]. In addition, rapid tests to diagnose some bacterial infection need to be adapted to the local context. For instance, rapid tests that detect antibodies, e.g., for diagnosis of scrub typhus, might require their positivity thresholds to be adjusted depending on background antibody titres in the population to optimize their diagnostic accuracy [54].

An alternative to pathogen specific rapid tests is testing of biomarkers of host inflammation. Although inflammation can be induced by both infectious and non-infectious diseases, some biomarkers have demonstrated the capability of discriminating infections that need antibiotics, as opposed to those that only need symptomatic treatment [55, 56]. C-reactive protein and procalcitonin are two host

biomarkers that have been widely studied for the management of febrile illness in primary care [56-59]. It has been shown that CRP is more effective than procalcitonin in distinguishing bacterial from viral infections in well-characterised samples collected from febrile patients in three Southeast Asian countries; the area under the receiver operating characteristic (*AUROC*) for CRP was 0.83 compared with 0.74 for procalcitonin [60]. A rapid test for CRP that is accurate and inexpensive is already available on the market [61, 62].

When rapid tests with acceptable accuracy are available, they can be used independently, sequentially, or in combination to reach the definite diagnosis of acute fever. However, information regarding their impact and cost-effectiveness of multiple tests are largely unknown, and there is few evidence on how to optimize their use especially in the context of seasonal and spatial heterogeneity regarding aetiologies of acute fever in the tropics [63]. Furthermore, training of health care workers to perform and interpret multiple tests could be challenging, especially in resource-limited remote areas of LMICs.

1.5 Antimicrobials for the management of fever

Bacterial infection used to be a major cause of morbidity and mortality worldwide before the discovery of antibiotics. Since the discovery of penicillin in 1928 followed by mass production in the mid-1950s, antibiotics have saved millions of lives by successfully treating many bacterial infections, enabling modern medical procedures such as organ transplants and cancer chemotherapy [64]. In parallel, misuse of antibiotics has led to a rapid rise in antimicrobial resistance (AMR) and there is a concern about going back to the pre-antibiotic era [65]. The link between overuse of antibiotics and the emergence of antibiotic-resistant bacteria has been well documented

[66]. Although antibiotic resistance can occur naturally, overuse of antibiotics is accelerating the process.

The majority of febrile patients were presumably treated with antimalarials in malaria endemic regions until at least 2010. After the decline of malaria incidence and introduction of the "confirm and treat" malaria treatment strategy, antibiotics have become a default treatment of choice in place of antimalarials for non-malaria febrile patients [67, 68]. Between 2000 and 2018, global antibiotic use in humans increased by 46% with differences among countries; while consumption rates remained steady in HICs, there was a 76% increase in consumption in LMICs [69]. Most of these antibiotic prescriptions are regarded as unnecessary. WHO's situational analysis in twelve countries in Asia between 2011 to 2015 reported a high rate of antibiotic prescription across public sector primary care facilities. The prescription rate for patients with upper respiratory infections ranged from 34% in Bhutan to 87% in Myanmar and 94% in India; more than half of the countries had not developed or implemented national AMR strategy at the time of assessment [47].

Additionally, the practice of non-prescription antimicrobial use is common in LMICs, and half of the antibiotics used are purchased over the counter [70, 71]. A multi-country public awareness survey conducted in 2015 by WHO demonstrated that people were aware of antibiotic resistance, but they did not fully comprehend its causes; 43% of respondents said that they would buy the same antibiotics, or request those from a doctor, if they are sick and antibiotics helped them get better when they had the same symptoms before [72]. This kind of perception could result in inappropriate use of antibiotics, which in turn contributes to the emergence of antibiotic-resistant bacteria.

In addition, 44% of respondents in that survey thought that antibiotic resistance only affects people who regularly take antibiotics.

The prevalence of self-medication with antibiotics is high in Southeast Asia with an overall rate of 43%, ranging from 7.3% to 85.6%; common cold, sore throat, fever, gastrointestinal tract diseases, and respiratory diseases were the most common reasons [73]. Community pharmacies are the main source of non-prescription antibiotic use in Asia [74]. A recent public awareness survey about antibiotic use and antibiotic resistance in Myanmar found that almost 60% of respondents purchased antibiotics without a prescription and only half of respondents were aware of antibiotics resistance [75]. Ease of access and over the counter availability of antibiotics due to a poor regulatory framework could accelerate the emergence of antibiotic resistant bacteria.

Despite this, there are pockets of the population in LMICs who have difficulty in accessing essential antibiotics to prevent mortality from treatable infection such as pneumonia. A modelling study estimated that universal provision of antibiotics to under five years children could avert 445 000 deaths out of an estimated total of 590 000 deaths from pneumonia across 101 countries which equated to 75% reduction in the deaths from pneumonia [76]. Therefore, a priority should be to have a balance between sustainable access and sustainable effectiveness of antibiotics. The provision of proper diagnostic services and quality universal health care, as well as the financing of these services must be coordinated jointly in order to achieve this goal, as well as the restraint of inappropriate use of antimicrobials [77].

Non-medically trained health workers such as community health workers and malaria volunteers have been allowed to give antimalarials. Well supported community-based health workers are the key operatives in controlling malaria in resource limited settings

of endemic countries [78]. Under strict protocols, they might be able to prescribe a limited number of antibiotics to treat other common illnesses. However, whether they should be allowed to prescribe antibiotics in Myanmar is still under debate while other neighbouring countries are letting community health workers to prescribe antibiotics after appropriate training [79, 80].

1.6 Myanmar at a glance

1.6.1 Geography and sociodemographic characteristics

Myanmar is located in the Southeast Asia region and has a total area of 678,500 square kilometres [81]. Its borders are shared with China in the north and east, Lao P.D.R and Thailand in the east, and India and Bangladesh in the west. The country can be categorized into five physiographic regions: the northern mountains, western ranges, eastern plateau, central basin and lowlands, and coastal plains. It has a monsoon climate with three distinct seasons: rainy (May to October), winter (November to February) and summer (March to April) [81].



Figure 1.3 Myanmar border with neighbouring countries

There are 14 administrative regions (Ayeyawady, Bago, Magway, Mandalay, Sagaing, Tanintharyi and Yangon) and states (Chin, Kachin, Kayar, Kayin, Mon, Shan and Rakhine), and one union territory (Naypyitaw). They are further sub-divided into 70 districts and 330 townships, 84 sub-townships, 398 towns, 3063 wards, 13,618 village tracts and 64,134 villages [82]. In 2019, the population was estimated to be 51.1 million, with 70 % residing in rural areas. The life expectancy at birth was 69.4 years for both genders [83].

The agricultural sector dominates the country's economy contributing to 32% of GDP and employing more than 60% of the labour force [84]. The country GDP per capita was 1187 USD in 2019, the lowest in the region. The poverty rate in Myanmar was 24.8% suggesting one in four people were considered poor according to the Myanmar Living Conditions Survey in 2017. The poverty rate was 6.7 times higher in rural areas

than in urban areas [85]. As of 2021, Myanmar was classified as a lower-middle income country by the World Bank [86]. Due to the combined effect of the military takeover in early 2021, the COVID-19 pandemic and internal conflict, the World Bank estimated that about 40% of the population were living below the national poverty line in 2022 [87].



Figure 1.4. Myanmar with 14 states and regions

1.6.2 Healthcare system

Healthcare expenditure in Myanmar has been consistently low for many years. Between 2001 and 2011, only 2 - 2.4% of the country GDP was used for health expenditure, the lowest among countries in the WHO Southeast Asia and Western Pacific regions [88].

Health services are provided by a mix of private and public providers but there is a significant difference between urban and rural areas in terms of access to public and private hospitals. Access to healthcare and utilization are relatively low in rural areas, where most of the poor reside. There are public rural health centres in rural areas, but they provide a limited range of healthcare services [88].

With very low government healthcare expenditure, healthcare was largely financed by out-of-pocket payments accounting for 76% of all total healthcare expenditure in 2019 [89]. In addition, there is a shortage of health care professionals with a skilled health professional density of 15 per 10,000 people [88]. This figure is far below than WHO recommended benchmark of 23 per 10,000 population. In terms of health service utilization, only 58% and 57% of children under five with acute respiratory infection and acute fever seek care from health facilities; 62% of children with diarrhoea received oral rehydration therapy [90, 91].

1.6.3 Burden of infectious diseases

Myanmar is facing a high burden of communicable diseases. The under-five mortality rate was 44 per 1000 live births and infant mortality rate was 35 per 1000 live births in 2020 [90]. The top three causes of mortality in under-five children were neonatal disorder, lower respiratory infections and diarrhoeal diseases [92]. There was a low rate of complete immunization coverage among 12–23-month-old children in Myanmar, with 68% in urban areas and 51% in rural areas, according to Myanmar Demographic and Health Survey (2015-2016) [91]. Respiratory infections are common among primary care clinics and GBD study estimated that there were 129 million cases of upper respiratory infections claiming 46,000 DALYs in 2019 in both genders of all ages in Myanmar [22]. In the same year, the burden of lower respiratory tract infection was

estimated to be 1,490,000 episodes in males of all ages contributing to 11700 deaths and 1,360,000 episodes in females of all ages contributing to 9720 deaths [93].

In terms of specific diseases, TB, HIV-AIDS, and malaria are the leading causes of death and illness. The morbidity and mortality of malaria declined by 81% and 93% between 2005 and 2014 [94]. A nationwide survey in 2018 estimated that the prevalence of bacteriologically confirmed adult pulmonary tuberculosis cases to be 486 per 100,000 with a higher prevalence among males, older age groups and remote villages [95]. A high burden of tuberculosis is likely to be contributed to by uncontrolled urbanization with overcrowding in urban slum areas, poverty and limited accessibility to health facilities in rural regions.

Myanmar also has one of the highest HIV prevalence rates among the adult population in Asia having a prevalence of 0.8% in the reproductive age group between 15-49 years [96]. However, only one fifth of reproductive age men and women (18 - 59 years) had comprehensive knowledge of HIV according to the nationwide Myanmar Demographic and Health Survey (2015-16) [97].

A surveillance study in Yangon estimated the annual incidence of typhoid at 391 per 100,000 and paratyphoid at 107 per 100,000 [98]. Vector borne viral diseases such as dengue and Japanese encephalitis are also contributing to high morbidity and mortality. Myanmar was listed as a country with a high burden of dengue infection in Asia Pacific region having multiple outbreaks in the past decade. Between 2011 and 2015, there were about 90,000 hospitalized dengue cases claiming 393 lives; 97% of cases were in children [99]. This statistic only represents hospitalized cases; hence the true burden of dengue is likely to be much higher.

Aside from these specific diseases, estimates on other communicable diseases in Myanmar are scarce contributed by consistently low budget spending on healthcare, restriction on academic freedom and poor laboratory infrastructure. However, based on the high burden of common infectious diseases and findings from neighbouring countries, it is very likely that morbidity and mortality of melioidosis, leptospirosis, rickettsioses and other neglected tropical diseases could be high in Myanmar. Moreover, due to a dysfunctional health system and political unrest following the military takeover of power, the burden of HIV, malaria and tuberculosis are likely to increase again.

1.7 Thesis structure

The main focus of this DPhil thesis is on improving the management of acute febrile illness in Myanmar, including understanding which pathogens are most important in different regions, patient and prescriber drivers of antibiotic use and possible approaches to improve management in remote areas. Specific objectives are to 1) gather information on neglected tropical infectious diseases in Myanmar, 2) evaluate the cost-effectiveness of different empirical treatment strategies for non-malaria febrile illness in rural Myanmar, 3) assess and quantify variation of antibiotic prescription for acute fever among primary care doctors, 4) investigate geographic distribution of *Burkholderia pseudomallei* (the causal organism of melioidosis) in environmental soils across the country, 5) evaluate a public engagement project to raise awareness about "fever and antibiotic use".

Specific objective 1 (Chapter 2): To gather information on neglected tropical infectious diseases in Myanmar

I conducted a systematic review on neglected tropical infectious diseases (NTDs) in Myanmar. The database search was carried out in four international databases and one national database (which stores locally published papers and grey literature). The purpose of this chapter was to collate all published and grey literature on NTDs in Myanmar. Details on the selection of articles, characteristics of included articles, distribution of reported aetiologies by age groups, and geographic location of reported NTDs are presented.

Specific objective 2 (Chapter 3): To evaluate the cost-effectiveness of different empirical antibiotic treatment strategies for non-malaria febrile illness in rural Myanmar

This chapter describes a mathematical modelling study of the impact of different empirical treatment strategies on mortality of non-malaria febrile illness in rural Myanmar. A cost-effectiveness analysis was performed using a decision tree modelling approach. I have used various data sources: a large village health workers database from a medical aid organisation in Myanmar for the distribution of febrile syndromes, survey data on the current practice of care, efficacy data of antibiotics from the literature. For uncertain or unavailable data, an expert elicitation exercise was performed.

Specific objective 3 (Chapter 4): To assess and quantify variation of antibiotic prescription for acute fever among primary care doctors

This chapter focuses on antibiotic prescription for management of acute febrile illness in primary care in Myanmar. It is a secondary analysis of data derived from a clinical trial investigating the impact of point of care C-reactive protein (CRP) testing on management of acute febrile illness. The variation of antibiotic prescription among primary care doctors, despite the implementation of a treatment guideline, was assessed

and quantified. Then, influence of patient characteristics on the prescription variation was explored.

Specific objective 4 (Chapter 5): To investigate the geographic distribution of *Burkholderia pseudomallei* in the environmental soil across the country

This chapter investigates the distribution of *Burkholderia pseudomallei*, the causal organism of melioidosis, in the environmental soil in all states and regions of Myanmar. This disease commonly presents as fever with pneumonia, sepsis, and abscess and is an important infectious disease with a high mortality in the Southeast Asian region. Although melioidosis was first described in Myanmar in 1911, the disease disappeared from sight for several decades except for occasional reports in recent years.

Specific objective 5 (Chapter 6): Implementation and evaluation of a public engagement project on "fever and antibiotic use"

This chapter describes implementation and evaluation of a public engagement project on the topic of "fever and antibiotics use" using forum theatre performance. The engagement activities were carried out in a peri-urban area of Yangon (former capital city). Qualitative evaluation was carried out by focus groups discussion and the findings are presented.

Conclusion (Chapter 7): Discussion, implications and future research direction

I summarise the main findings from the preceding chapters and discussed how these findings could impact on policy change and practices. The results are also interpreted in the context of limitations and future directions of work are discussed with relation to management of acute febrile illness.

Chapter 2

A systematic review on infectious neglected tropical diseases (NTDs) in Myanmar

2.1 Abstract

Background

Neglected tropical diseases (NTDs) affect most impoverished communities in developing countries like Myanmar in Southeast Asia. NTDs have been understudied and underreported in Myanmar.

Methods

We conducted a systematic review of published and grey literature (1900 - 2021) on neglected tropical infectious diseases (NTDs) in Myanmar. We searched four international databases: PubMed, EMBASE, Ovid Global Health, and Web of Science Core Collection and one national database: Myanmar Central Biomedical Library (including locally published papers and grey literature). The selection criteria included articles with all types of study designs conducted in humans, that reported NTDs, recognised by WHO, US CDC, and listed in PLoS NTDs, of current or past infections. We also included melioidosis and rickettsioses which we consider meeting the definition of an NTD.

Results

A total of 5573 records were retrieved and screened, of which, 651 (12%) met the selection criteria and were included in this review. Of the included articles, 428 (65%) were published after 2000 and 360 (55%) were from two regions (Yangon and Mandalay) of Myanmar. Of the included articles, 205 (31%) reported bacterial NTDs, 205 (31%) reported viral NTDs, 147 (23%) reported helminth NTDs, 28 (4%) reported

protozoal NTDs and 37 (6%) reported more than one type of aetiology. Based on reported frequency in descending order, bacterial NTDs were leprosy, *Escherichia coli* enteritis, salmonellosis, cholera, shigellosis, melioidosis, leptospirosis and rickettsioses; viral NTDs were dengue, chikungunya and Japanese encephalitis virus (JEV) infection; protozoal NTDs, amoebiasis, giardiasis and leishmaniasis, and helminth NTDs were ascariasis, trichuriasis, hookworm disease, filariasis and strongyloidiasis.

Conclusion

This review summarises the reported NTDs in Myanmar over 100 years. The findings suggest that most NTDS are likely to be under reported, especially from most regions of the country not close to academic centres. Research capacity building together with strengthening of laboratory systems would lead to better understanding of the true burden of NTDs in Myanmar.

2.2 Introduction

Neglected tropical diseases (NTDs) are a group of preventable and treatable diseases prevailing in tropical countries and unduly affecting the poorest rural communities. The World Health Organization (WHO) lists 20 diseases as NTDs, of which 19 are communicable diseases and the other is snake bite. NTDs cause serious health problems including long term complications and sometimes disfigurement of affected individuals as well as social and economic burdens. The burden of NTDs is tremendous, causing an estimated 200,000 deaths and 19 million disability adjusted life years (DALYs) annually [100]. In addition, 20% of the world population, approximately 1.5 billion people, are at risk of NTDs. The Global Burden of Disease (GBD) study estimated that there were 2.3 billion cases of WHO-prioritized NTDs in 2013 with the highest incidence in Southeast Asian countries [101]. As NTDs are associated with more disabling and disfigurement than deaths, their collective DALYs burden was comparable to diarrhoeal diseases, HIV/AIDS, tuberculosis and malaria [102]. Despite the devastating burden NTDs impose on global health, research on these diseases has been underfunded compared with HIV/ AIDS, tuberculosis, and malaria [103].

Myanmar (formerly Burma) is one of the least developed countries in Southeast Asia and has a population of 51 million people, of whom 70% live in rural areas [104, 105]. Since 1962, Myanmar has been governed by a military regime, with a brief period of civilian rule between 2011 and the coup d'état in early 2021. For several decades, health care expenditure has been consistently low at 0.2 to 0.3% of gross domestic product (GDP) prior to 2011 and increased to 4-6% between 2014 and 2019 [106, 107]. This chronic underinvestment in the health sector result in poor health care infrastructure, a limited health care workforce, inefficient disease control activities and a high burden of communicable diseases in Myanmar. Infectious diseases still pose a huge burden,

and parasitic diseases and specific infections cause the most deaths according to 2012 hospital statistics [108]. The global burden of disease(GBD) 2013 study indicates that Myanmar is one of the top ten countries with the highest NTD incidence or absolute prevalence [101]. Having a military coup in 2021 combined with civil war and a collapsed health system will only lead to an increase in diseases of this kind.

With the imposition of economic sanctions combined with neglect and corruption under the military regime, the country's health care system ranked second worst in the world in 2000 with a slight improvement during the 10-year period of civilian government between 2011 and 2020. In addition, academic research also declined dramatically, because of severe restriction of professional freedoms [109]. Moreover, most of the studies conducted by medical universities and research institutions inside Myanmar were published in local journals, which made them inaccessible to international scholars. Due to this reason, Myanmar-related studies are typically absent from systematic reviews via international databases [21, 110, 111]. Furthermore, due to a lack of investment in healthcare infrastructure for many decades, Myanmar's laboratory capacity, including the number of microbiologists, is extremely low.

During World War II, the western alliance troops reported the presence of scrub typhus and other rickettsial diseases in northern Myanmar, but reports of such diseases have largely disappeared since then [112, 113]. However, a recent serological study in Myanmar indicates a widespread distribution of scrub typhus and other rickettsial diseases [114]. Similarly, melioidosis was also first described in Myanmar in 1912 but went unreported for several decades [115]. Since then, few cases have been reported except for a recent report of cases from a surveillance study [116]. A recent nationwide study also confirmed that *Burkholderia pseudomallei*, which causes melioidosis, has

been isolated in soil in several regions of Myanmar [117]. The points above indicate that most of the diseases of regional interest and NTDs in Myanmar are underrecognized or understudied.

Considering these circumstances, a review of these diseases in Myanmar is necessary to gain a better understanding. The purpose of this review is to document all the reported NTDs and diseases of regional interest in Myanmar in the past 100 years, considering both peer-reviewed research and the grey literature.

2.3 Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [118] and the protocol for this review is registered in the international prospective register of systematic reviews (PROSPERO Registration ID: CRD42018092627).

2.3.1 Diseases (Pathogens) selected for the review

We selected NTDs recognized by the WHO, US CDC, and PLOS Neglected Tropical Diseases (Appendix Table 1) to include in this review. We also included rickettsial diseases and melioidosis, as diseases of regional interest because they are common in Southeast Asia. However, as other commentators have noted, they are so neglected they are not even recognized as NTDs by the WHO [119].

2.3.2 Literature search strategy

The database search was carried out in four international databases (PubMed, EMBASE, Ovid Global Health, and Web of Science Core Collection) and one national database (Myanmar Central Biomedical Library) containing grey literature (locally

published papers, conference presentations, and dissertations). The last database search was done on 22 June 2021. We used MeSH headings and free text terms without restricting the study design or time period (Appendix Table 2).

2.3.3 Study selection and full text review

Initial screening of results from the database search was carried out by two reviewers (MMMS and HNL) who independently reviewed all titles and abstracts. Any discrepancies raised from the screening were resolved by a third reviewer (APP). After screening, we looked at full-text (for published studies) and abstracts (for conference presentations) to assess eligibility against pre-specified selection criteria (Table 2.1). For excluded articles the reason for exclusion was recorded. Details of the study selection process are presented in the PRISMA flow diagram (Figure 2.1).

Table 2.1 Inclusion and exclusion criteria

Inclusion criteria		**Exclusion criteria**
1. Observational studies		1. Editorials/ narrative review
2. Intervention studies		2. Qualitative studies
3. Outbreak reports and investigations		3. Environmental surveys and non-human studies
4. Case reports and series		4. Snake bite studies

2.3.4 Data extraction

Data from included articles were extracted into a spreadsheet. Extracted variables included the following: year of publication, first author's name, study period, age group of participants, location of the study, study design, study setting, type of samples, number and name of reported pathogens, methods of diagnosis, number of individuals tested (if reported), number of individuals who tested positive (or) proportion of individuals who tested positive (if reported) for the reported pathogens and title of the study.

Included articles

We categorised included articles into (1) case reports and case series, (2) outbreak investigation, (3) serosurvey or prevalence study, (4) surveillance study, (5) observation study (6) intervention study and (7) others.

Study population and geographical location

We divided the study population into two groups: children (under 12 years) and adults (12 years and above). In term of geographic location, articles were grouped into states and regions of Myanmar rather than the exact location.

Reported Diseases and/ or Pathogens

We categorised reported pathogens and/or diseases into five main groups: viral, bacterial, protozoal, helminths, and fungal NTDs.

Analysis and assessment of risks of bias

The included articles varied substantially in terms of study design, population, setting, sample types, diagnostic methods, and information about those being tested. Consequently, the incidence and prevalence of the reported pathogens could not be estimated through meta-analysis. Further, we were not able to assess bias using currently available tools [120, 121]. As a result, we devised an assessment tool that emphasizes the ascertainment of diagnosis in the included articles, as we considered it the largest potential source of bias. We categorised risk of bias into “high” or “low” risk depending on whether included articles used standard laboratory methods, recommended by either United States CDC, WHO or literature, to diagnose reported diseases or pathogens (Appendix Table 3).

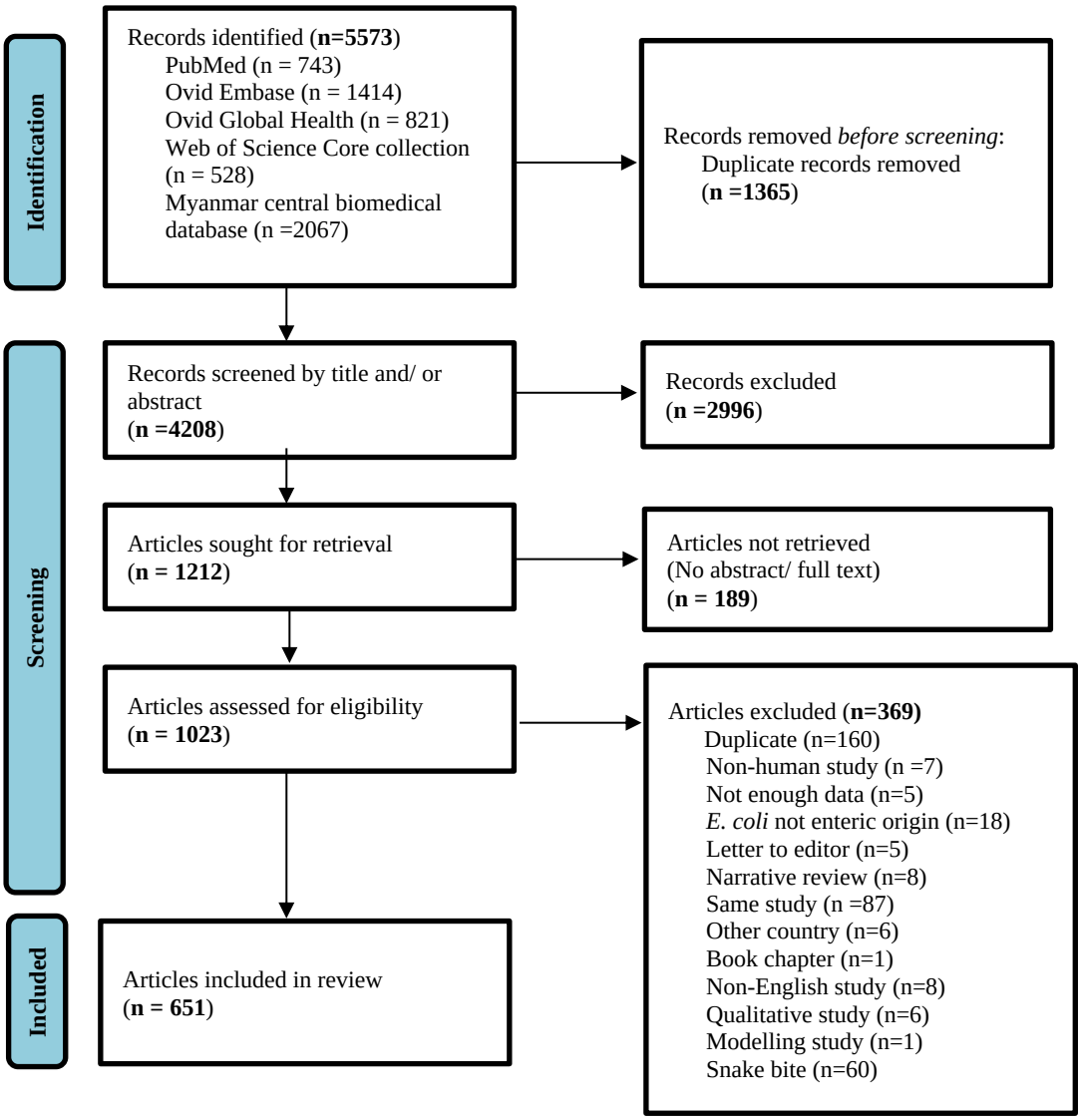


Figure 2.1 PRISMA flow diagram showing process of articles selection

2.4 Results

A total of 5573 articles were identified through the database search. Of these, 651 articles were included in this review (Figure 2.1). Among them, the earliest was published in 1906 and 65% (428) of them were published after 2000. In terms of the source, 39% (253) of included articles were published in international peer-reviewed journals, 27% (178) were conference papers, 18% (115) were locally published and 12% (75) were theses and dissertations.

Regarding study design, almost half (48%, 314) were observational studies followed by 18% (117) serosurveys or prevalence studies, 12% (81) case reports or case series, whereas intervention studies accounted for 7% (48) (Figure 2.2).

2.4.1 Study population and study settings

In terms of study population, children were the focus of 34% (219) of the included articles and adults were the focus of 31% (204); 15% (96) of articles covered both age groups, and 20% (132) did not specify the age of their subjects (Figure 2.2). In terms of study setting, 54% (354) were hospital-based studies and 21% (139) were population and community-based studies. The remaining were clinic-based (4%), or laboratory-based (4%); 10% (67) did not specify the type of setting.

2.4.2 Type of samples

There were a variety of samples collected and analysed in the included articles. The most frequently analysed samples were blood and serum which featured in 244 studies (37%), followed by stool specimens in 166 articles (25%). Cerebrospinal fluid was tested in 6 (1%) articles and 38 (6%) articles analysed more than one type of specimen, while 109 (17%) articles did not specify sample type. The remaining 87 (13%) articles analysed pus, skin smears, wound swabs, and other tissue samples.

2.4.3 Diagnostic methods

Different diagnostic methods were used in the articles included. They are classified into serology (including immunoassay), culture, molecular, multiple diagnostic methods, others, and not mentioned. Serology was used in 143 (22%) articles, followed by culture in 92 (14%), microscopy in 46 (7%), molecular methods in 37 (6%) while 186 (29%)

articles used more than one type of diagnostic method, and 128 (20%) of articles did not mention the diagnostic method.

2.4.4 Geographic location

The majority of articles included were concentrated in two regions of Myanmar: Yangon (45%) and Mandalay (10%). In 47 (7%) articles, the studies were conducted near the Thailand-Myanmar border, while in 13% the location was not specified. A total of 21 (3%) articles were conducted outside Myanmar in travellers returning from Myanmar or in immigrants to other countries from Myanmar (Figure 2.6, Figure 2.7 and Appendix Table 4).

2.4.5 Reporting aetiology

Among the 651 included articles, 230 (35%) reported bacterial aetiology, 205 (31%) reported viral aetiology, 147 (23%) reported helminths and 28 (4%) reported protozoal aetiology whereas 37 (6%) reported more than one type of aetiology. In terms of number of reported diseases or pathogens per article, 505 (78%) considered single diseases or pathogens, 132 (20%) reported two to five, while the remaining 14 (2%) reported six to seven diseases or pathogens (Figure 2.3).

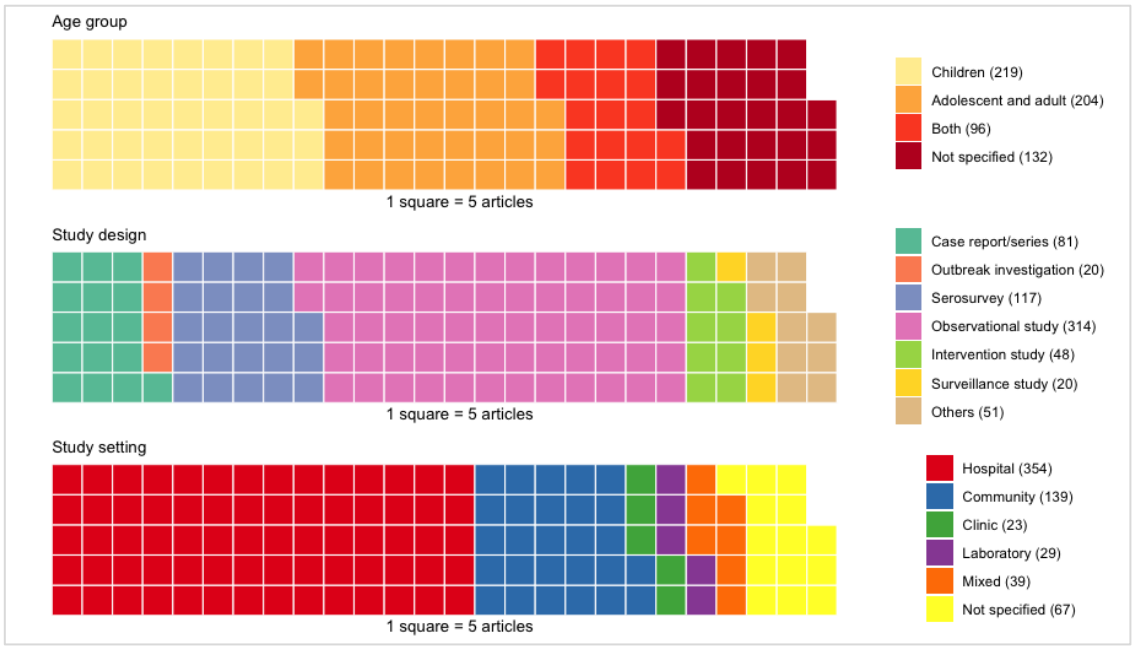


Figure 2.2. Waffle plots showing distribution of participant age, study design and study setting of included articles

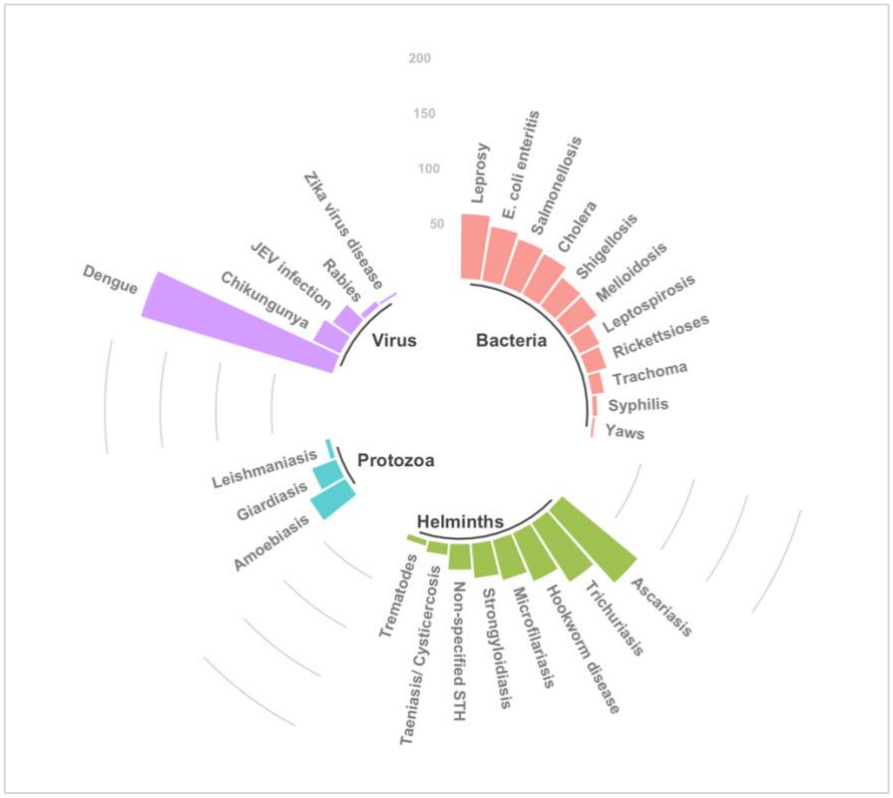


Figure 2.3. Circular bar plot showing distribution of articles reporting NTDs by aetiology. Four articles that reported deep fungal infection (mycoses) are not shown in the figure for clarity. STH (soil transmitted helminth infections)

Bacterial NTDs

Out of 651 articles, at least one bacterial NTD was reported in 310 articles. Among the reported bacterial diseases, enteric bacteria (*Escherichia coli, Vibrio cholerae, Salmonella* and *Shigella spp.*) were the most common and reported in 166 articles. NTDs caused by enteric bacteria were reported more frequently in 79 articles reporting findings in children. In contrast, diseases like leprosy, melioidosis, rickettsioses and leptospirosis were reported in 61 articles in the adult population (Figure 2.4, Figure 2.5 and Appendix Table 5).

Viral NTDs

Out of 651 included articles, 234 reported at least one viral NTD. Arboviral diseases (dengue, Chikungunya, JEV infection and Zika virus disease) were reported in 229 out of 234 articles. The top reported viral pathogen was dengue, which was reported in 180 articles, of which 106 were in children and 35 were in adults (Figure 2.4, Figure 2.5 and Appendix Table 5). Of the 180 articles that reported dengue infection, seven used clinical diagnosis (WHO dengue classification). Chikungunya and JEV infection were reported in 27 and 20 articles respectively. Rabies virus was reported in only five and Zika virus in two articles.

Protozoal NTDs

Three protozoal NTDs were reported in 64 articles included in this review. Amoebiasis was the top reported protozoal NTD, and it was reported in 37 articles followed by Giardiasis in 23 articles. Both were commonly reported in children. Leishmaniasis was reported in four articles (Figure 2.4, Figure 2.5 and Appendix Table 5).

Helminthiasis

Helminth NTDs were reported in 304 articles. Ascariasis was the most reported helminthiasis, and it was reported in 88 articles, followed by Trichuriasis and Hookworm infection in 63 and 47 articles. These top three helminth infections were reported more frequently in children compared with adults (97 compared with 41 articles). However, Strongyloidiasis was reported more in adults than children (19 compared with 6 articles). Microfilariasis was reported in 37 articles, 21 of which considered only adults while 13 considered all age groups. Taeniasis, including cysticercosis and trematode infection, was reported in 10 and five articles respectively (Figure 2.4, Figure 2.5 and Appendix Table 5).

Fungal NTDs

Deep fungal infection (mycetoma) was reported in four articles (Figure 2.4 and Appendix Table 5).

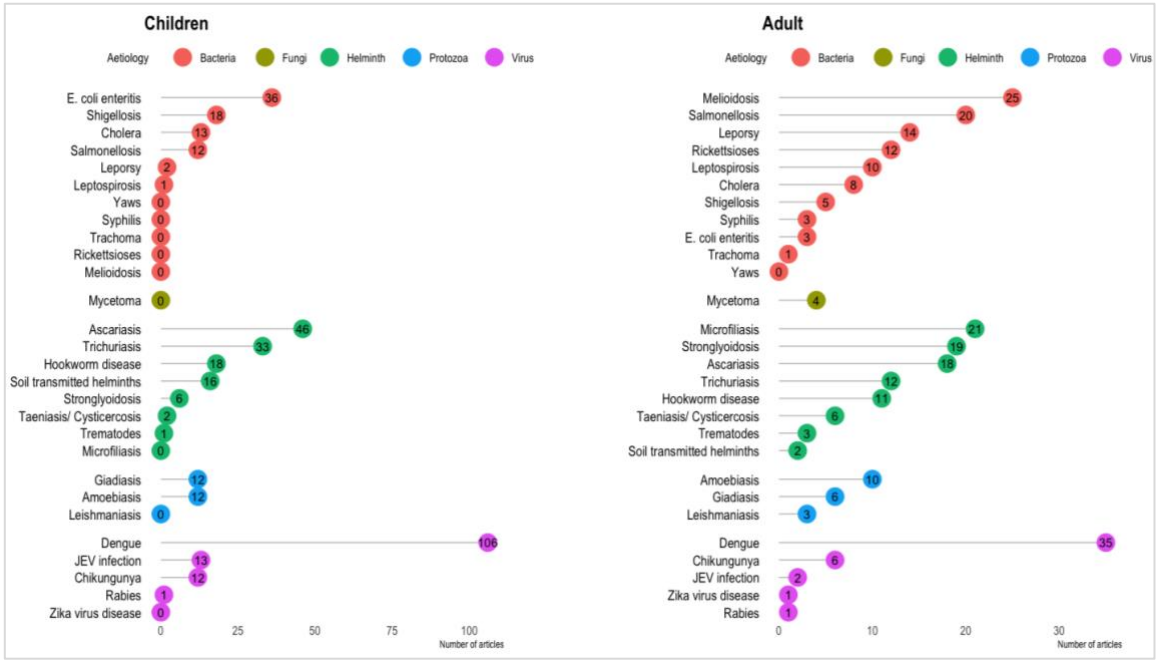


Figure 2.4 Lollipop plots showing number of articles reporting NTDs stratified by aetiology in children and adults

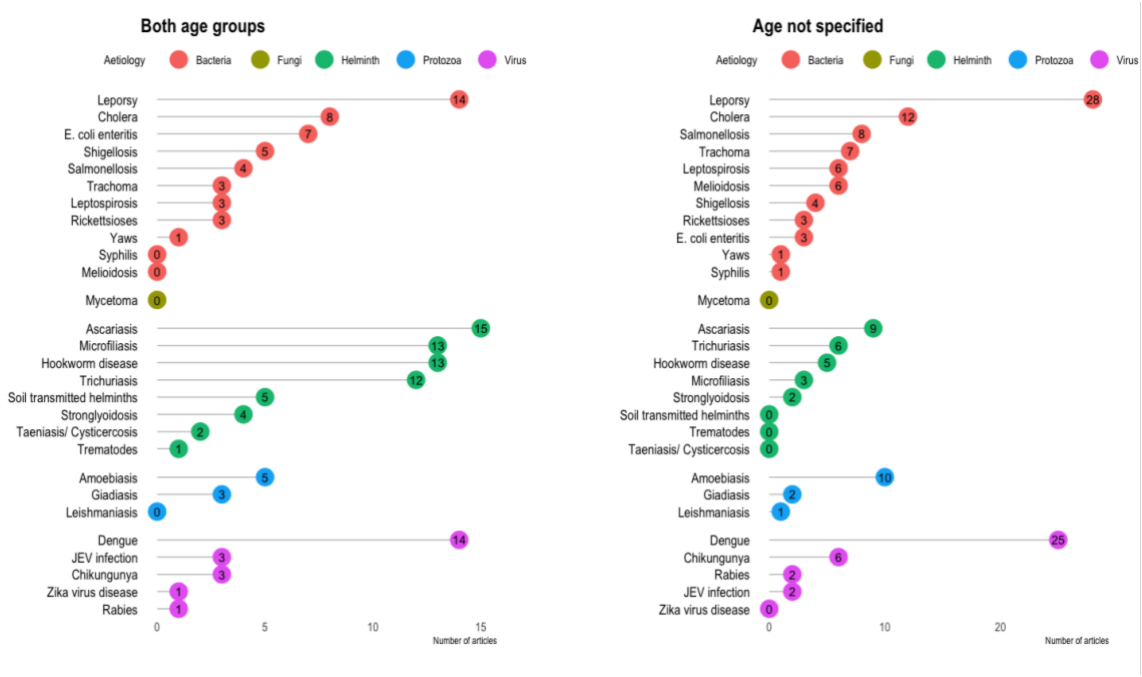


Figure 2.5 Lollipop plots showing number of articles reporting NTDs stratified by aetiology in both age group and non-specified age group

NTDs reported among returned travellers and Myanmar migrants

Among included articles, 11 reported NTDs in returned travellers, 20 in Myanmar migrants/ refugees in other countries and eight in ex-prisoners-of-war in Myanmar. Strongyloidiasis was reported in all eight articles in ex-prisoners-of-war. Melioidosis and rickettsial diseases were reported in 7 out of 11 articles in returned travellers; the remaining four articles reported chikungunya, salmonellosis, hookworm infection and mycetoma.

Risk of bias assessment

Of the 651 included articles, the risk of bias in terms of methods used to ascertain diagnosis was considered to be high in 99 (15%), low in 445 (68%) and could not be ascertained in 107 (16%) articles. Most of the articles considered to be of high risk did

not report details of diagnostic methods other than vague term such as “serological test” or they did not mention whether the test was done in paired sera.

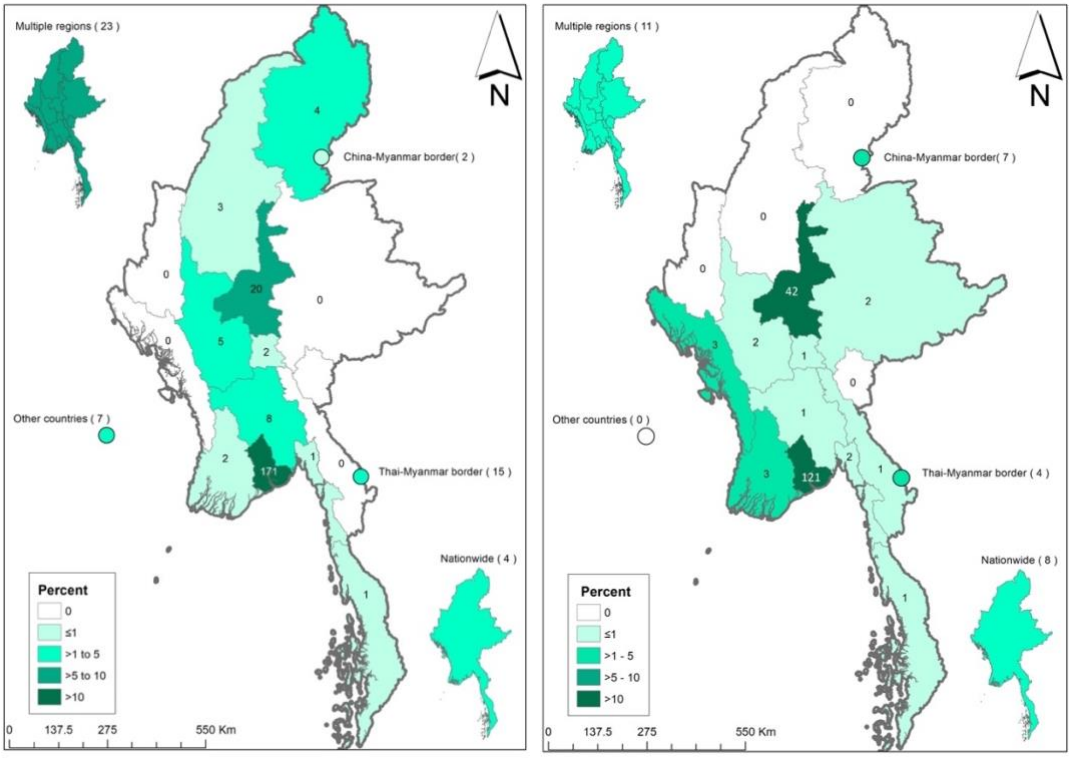


Figure 2.6. Maps showing distribution of included articles: bacterial NTDs (left) and viral NTDs (right). The number inside each region represents frequency of articles and the colour represents percentage of total articles of corresponding aetiology.

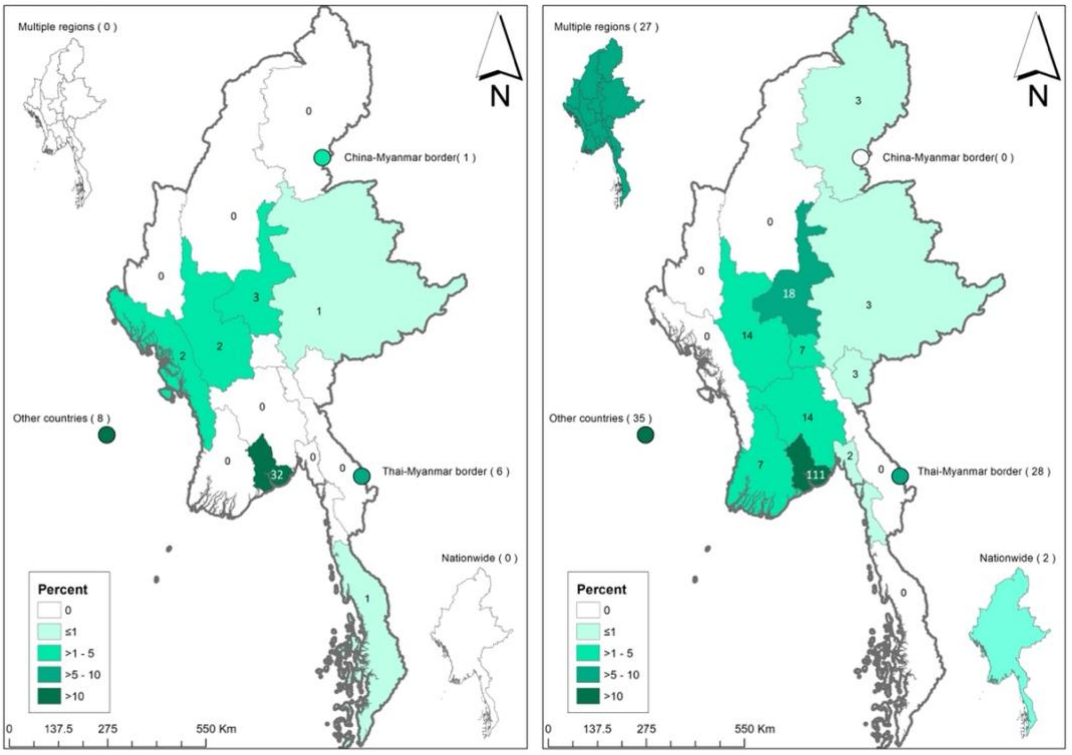


Figure 2.7. Maps showing distribution of included articles: protozoal NTDs (left) and helminthiasis (right). The number inside each region represents frequency of articles and the colour represents percentage of total articles of corresponding aetiology.

2.5 Discussion

The purpose of this review was to collate all available information on neglected tropical infectious diseases described in Myanmar in the past 100 years until 2021 for the first time. We conducted a literature search of four international databases and one local database for locally published articles. We screened 5573 records and included 651 articles in this review.

We presented several relevant findings regarding NTDs in this review. In terms of aetiology, bacterial NTDs were the most reported, followed by helminthiasis and viral NTDs. NTDs caused by protozoa were reported least frequently. Among bacterial NTDs, enteric diseases that were most reported included *Escherichia coli* enteritis, cholera, salmonellosis, and shigellosis. These enteric pathogens are mainly transmitted

through the faecal oral route, and they are associated with poor hygiene, contaminated drinking water and low socio-economic conditions. A higher prevalence of these enteric NTDs suggests a lack of social development including inaccessibility to clean and safe water in Myanmar. This is supported by recent studies on quality of drinking water in rural and urban regions of Myanmar. A household drinking water survey carried out in a peri-urban region of Myanmar found that 94% of the drinking water samples were contaminated with faecal coliforms and nearly 25% of households did not use any water purification methods for drinking water [122]. Another survey carried out in a rural delta region showed that faecal coliform contamination was detected in all drinking water sources investigated [123]. The studies above suggest the majority of the population in both urban and rural Myanmar do not have access to safe drinking water. Improving such access to safe drinking water, alongside improvements to sanitation and hygiene (WASH) are needed to reduce the burden of these diseases. Ensuring availability of clean water and sanitation to everyone is one of the 17 sustainable development goals adopted by the United Nations Member States in 2015. However, because of the recent coup in Myanmar in early 2021, the situation is likely to deteriorate.

We included melioidosis and rickettsial diseases in this review as they are diseases of regional interest and largely neglected. Several Southeast Asian countries, including Myanmar's neighbour Thailand, frequently report them and their prevalence in the region is high. For example, Thailand and Laos had severely under-reported melioidosis cases before the disease was actively investigated [124, 125]. Melioidosis is now the second most common cause of community-acquired bacteraemia in northeast Thailand, after *E. coli*, and the number of melioidosis-related deaths is higher than for common

infections like malaria, dengue, measles, and leptospirosis [126]. Although melioidosis was first described in Yangon (Myanmar) in 1911, it largely disappeared from sight for several decades except for a few sporadic reported cases in recent years [115]. A modelling study estimated that the disease burden was still high in Myanmar with an estimated cases of more than 6000 and 3000 deaths annually [127]. In this review, melioidosis was reported in 31 articles most of which considered only adults, including four reports in returned travellers. Being an agricultural country and with a widespread presence of the bacteria causing melioidosis (*Burkholderia pseudomallei*) in the environmental soil confirmed by a large nationwide soil study, it is likely that melioidosis is under-recognized. A possible explanation could be due to lack of awareness among clinicians as well as lack of familiarity of laboratory staff in isolating the pathogen [117]. In addition, the problem could be compounded by weak laboratory infrastructure together with a shortage of microbiologists.

Scrub typhus, one of the important rickettsioses, occurs mainly in the "tsutsugamushi triangle" area which ranges from northern Japan and Eastern Russia in the north to northern Australia in the south and Pakistan in the west, causing nearly a million cases each year among an estimated 1 billion people at risk [24, 128]. Although Myanmar is located inside the “tsutsugamushi triangle”, rickettsial diseases have not been reported frequently. However, scrub typhus and murine typhus are widespread in Thailand and a leading cause of febrile illness along the Thailand-Myanmar border [129, 130]. In this review, rickettsial diseases were reported in 18 articles, of which 4 were in returned travellers. A recent seroprevalence survey has confirmed widespread distribution of rickettsial diseases in several regions of Myanmar [114]. Given the above

circumstances, it is highly likely that rickettsioses are being neglected, under-diagnosed and under-recognized in Myanmar.

In our review, we identified 234 included articles that reported at least one viral NTD; dengue was the most reported, followed by chikungunya, Japanese encephalitis virus infection, rabies and zika virus disease. These viral NTDs, except rabies, are vector-borne diseases and transmitted through the bite of mosquitoes. These diseases were reported more in children than adults. We identified reporting of Zika virus infection in only two articles published in 2018 and 2020. It is notable that outbreaks of these mosquito-borne diseases are associated with urbanization and overcrowding, and success of control measures also depends on community cooperation. Surprisingly, we identified only five articles that reported rabies in this review although the number of reported deaths due to rabies was higher than malaria in Myanmar in 2015 [131]. This finding suggests that rabies is prevalent in Myanmar, but it is likely to be understudied. We found a range of viral and bacterial NTDs that are known to be associated with febrile illness reported in the included articles. Among them, arthropod-borne viral infections were most frequently reported, particularly dengue infection. Among bacterial NTDs associated with febrile illness, salmonellosis was the most reported disease and found in 44 articles. This was followed by melioidosis, rickettsioses and leptospirosis reported in 31, 18 and 20 articles respectively. As reported by neighbouring countries in the region, these diseases might be common aetiologies associated with acute febrile illness in Myanmar, with implications for empirical treatment strategies. For instance, rickettsioses and leptospirosis were reported as common causes of acute febrile illness in Thailand-Myanmar border region and Thailand [129, 132].

We identified only three protozoal NTDs: amoebiasis, giardiasis and leishmaniasis in this review. The first two are enteric pathogens transmitted through contaminated water and food. As there is no vaccine for prevention, the primary preventive measure for these diseases is provision of safe water and good hygiene. All four articles that reported leishmaniasis were published after 2004: two in Rakhine state (on the western coast of Myanmar bordering with Bangladesh) and two among Myanmar migrants in Thailand and Malaysia. This suggests *Leishmania* is prevalent among certain populations in Myanmar but simply not being diagnosed and studied. In endemic regions, leishmaniasis has been reported as an important opportunistic infection in people living with HIV [133]. Myanmar has an HIV prevalence of 0.8% , and is thus regarded as having a generalized epidemic of HIV [134]. Given that there was no reports of leishmaniasis before 2004, it would be of interest to explore disease prevalence in the HIV infected population.

Helminth NTDs were reported in about a quarter of the included articles. Ascariasis and Trichuriasis are the most reported helminth infections, followed by hookworm infection and filariasis. Soil transmitted helminth (STH) infections are well known to be associated with poor sanitation which is common in impoverished rural populations. Besides eating contaminated vegetables and drinking contaminated water, they can also be transmitted through soil contaminated by eggs from human faeces in places with poor sanitation. WHO recommends administration of annual preventive chemotherapy to target populations which includes pre-school and school-age children as well as reproductive-age women in endemic countries. Myanmar is listed as an STH-endemic country, and preventive chemotherapy has been implemented with high coverage over the last five years [135]. Diagnosis is simple and inexpensive as STH infections are

usually diagnosed by microscopic examination of stool. This may explain why a large number of articles related to STH are found in this review.

In terms of location of studies in the included articles, there is uneven geographic spread across the 15 regions of Myanmar with more than 50% located in two regions: Yangon and Mandalay. This is likely to reflect the interest of researchers and proximity to research institutions. This claim would be supported by these regions having a higher density of research institutions. The findings may also have been influenced by publication bias because accidental findings of cases are more likely to be reported and researched in some regions but not thoroughly investigated elsewhere.

Some NTDs that have been eliminated from neighbouring countries are still prevalent in Myanmar. For instance, Thailand has achieved elimination of lymphatic filariasis as a public health problem since 2017 [136]. However, a number of regions in Myanmar still suffer from persistent transmission of filariasis even after repeated rounds of mass drug administration since the launch of elimination campaign in 2000 [137]. Furthermore, there was a long delay in eliminating other NTDs like trachoma and leprosy , eliminated in 2020 and 2003 respectively, compared to neighbouring countries [138, 139].

This review has several limitations. One of them is heterogeneity of the included articles regarding study designs and diagnostic methods, making them impossible to combine in a meta-analysis. In addition, we were not able to estimate the prevalence or incidence of NTDs given limited information on the denominator and numerator of the study population in the included articles. Moreover, most of the reported NTDs are concentrated in a few regions, making it impossible to interpret them as a true reflection of the distribution across the country. The points above should be taken into account

when interpreting the findings. In terms of our risk of bias assessment on ascertainment of diagnosis, 15% of articles were considered to be high risk and 68% to be low risk. Most articles reporting enteric bacterial NTDs, and helminthiasis are in the low-risk category since these NTDs are diagnosed by microscopy and culture of stool instead of sophisticated diagnostic methods.

Our review also has several strengths. One of these is inclusion of grey literature that is often excluded from systematic reviews. This provides a more comprehensive overview of existing knowledge on neglected tropical diseases in Myanmar. In addition, we described some diseases such as melioidosis and rickettsioses that have disappeared for several decades, but which have been sporadically reported in recent years. These diseases, together with leptospirosis, should be considered as common causes of non-malaria febrile illness and sepsis in Myanmar. With the exception of melioidosis, which requires a prolonged course of specific antibiotics, they can be treated with simple antibiotics such as azithromycin or doxycycline. These findings indicate the necessity to raise awareness of these diseases among clinicians and researchers as well as highlighting the need to gain a better understanding of these diseases in different regions of Myanmar.

Last but not least, the findings in this review could be largely shaped by the political situation of Myanmar over several decades. In the past 60 years, there was only a brief period of civilian led government between 2010 and 2021. The military takeover of power in early 2021 and continued low health care budget will likely worsen the fragile health system and increase the burden of NTDs in Myanmar. In an unstable political climate with a collapsing health system, diseases that have been eliminated in recent years may return.

2.6 Conclusion

In conclusion, this systematic review provides an overview of the neglected tropical diseases that had been reported in Myanmar since 1900. It can serve as baseline information to inform the future research direction on NTDs in Myanmar. In addition, the review confirms that certain diseases that are common in Southeast Asia region like melioidosis and rickettsial diseases are also prevalent in Myanmar, but they are likely be underreported and unrecognized.

Chapter 3
Evaluation of empirical antibiotic treatment for non-malaria febrile illness in rural Myanmar: A decision tree analysis

3.1 Abstract

Background

Malaria is on the decline and acute febrile illness is now mostly caused by pathogens rather than Plasmodium in Myanmar. Empirical antibiotic therapy for remote areas should be chosen based on the likely pathogens, cost-effectiveness, and impact of antibiotics on emergence of antibiotic resistant bacteria.

Method

We developed a decision tree model to evaluate the cost-effectiveness of two oral empirical prescription strategies compared to the current practice of care: antibiotic treatment and C-Reactive Protein guided antibiotic treatment. We considered two age groups: children (1-12 years) and adolescents and adults (over 12 years), and four empirical antibiotic regimens: amoxicillin, azithromycin, combination Tx (amoxicillin plus azithromycin) and doxycycline (for over 12 years). We performed deterministic and probabilistic sensitivity analysis. We carried out expert elicitation as part of quantifying the uncertainty of parameters.

Findings

Empirical treatment with the proposed antibiotics was found to be cost saving in both age groups compared with current practice. Amoxicillin and azithromycin treatments were found to save 6.5 US$ and 7 US$ per DALY averted respectively in children whereas doxycycline, amoxicillin, azithromycin treatment saved 19.8 US$, 16.2 US$ and 15.2 US$ per DALY averted in adolescents and adults compared with current practice. CRP guided empirical antibiotic treatment was found to be highly cost-

effective in both age groups. In children, all CRP guided empirical antibiotics costed less than 10 US$ per DALY averted and CRP guided azithromycin was the most cost-effective treatment with 4.4 US$ per DALY averted. In adolescents and adults, CRP guided doxycycline was the most cost-effective with 4.3 US$ per DALY averted.

Conclusion

Empirical antibiotic treatments with and without CRP testing is likely to be cost-effective for management of non-malaria febrile illness in rural Myanmar.

3.2 Introduction

Acute fever is one of the most common presenting symptoms among patients attending primary care facilities in the tropics. There are a number of pathogens that can cause acute febrile illness, either alone or in co-infection. Malaria used to be a common cause but is no longer a leading cause of febrile illness in most regions of Asia. In the WHO South-East Asia region, malaria deaths decreased by 75% between 2000 and 2020, mostly due to improved access to diagnosis, treatment, and insecticide-treated nets [4]. In 2021, there were over 4.8 million malaria tests performed in the Greater Mekong region, and only 1.3% of those tests were positive [140].

Although the majority of febrile illnesses are self-limiting in nature, a fraction of them is caused by serious but treatable infections such as malaria, rickettsial infections, leptospirosis, and enteric fever. Additionally, fever studies in Southeast Asia showed that up to a third of febrile patients with a bacterial infection went unrecognized [28, 63]; some with pathogens associated with a high mortality without appropriate treatment [141, 142]. At the same time, a substantial proportion of patients without bacterial infections are getting antibiotics without any benefit to them, which promotes the emergence of antibiotic-resistant bacteria [143, 144].

Management of non-malaria febrile cases using WHO guidelines and clinical algorithms has shown moderate and inconsistent performance [37, 145]. These guidelines rely heavily on health workers' clinical judgement on causes of fever without further guidance. Furthermore, they do not cover causes of acute fever apart from apparent and obvious ones such as pneumonia and diarrhoea [3]. In recent years, various electronic clinical decision algorithms with modification of existing guidelines and integration of rapid tests have been developed and evaluated in resource-limited settings [146]. Most of them are aimed at under five children and they have shown

potential for improvement of the management of febrile illness and rational use of antimicrobials [146-148].

The burden of malaria in Myanmar has declined substantially, and in 2021 only 3.9% of malaria rapid diagnostic tests (RDTs) were positive and more than 80% of cases were in high-burden malaria hotspots [140]. This finding implies that non-malaria pathogens are often responsible for acute febrile illness in Myanmar. Literature on aetiologies of non-malaria febrile illness in the country is sparse except for a few studies of individual diseases or pathogens related to febrile illness. These studies have reported that treatable bacterial infections are common after apparent causes of fever have been ruled out. A study conducted along the Thailand-Myanmar border found that rickettsial infections and leptospirosis were responsible for one-third of febrile cases after excluding malaria, pyelonephritis and acute respiratory infections [26]. The prevalence of enteric fever among febrile patients ranged from 2.5% in children to 4.5% in adolescents and adults in urban Myanmar [149, 150].

In rural Myanmar, health services are primarily provided through basic health staff (BHS) in rural health centres [88]. Apart from malaria rapid tests, other diagnostic tools for management of febrile illness are not available at this level of care. Consequently, large numbers of febrile patients without malaria are getting treated with antibiotics. For instance, the antibiotic prescription rate in patients with upper respiratory tract infection (URTI) ranged from 80 to 100% in rural health centres as reported by the WHO situational analysis in 2014 [151]. Even when biomarkers are available to be used to identify bacterial infections in febrile patients, they cannot inform selection of antimicrobials. In those cases, health care workers have to decide what antimicrobials should be used to cover pathogens that are common in the region.

Although pathogen-specific rapid tests are already available for certain pathogens such as Group A *Streptococcus*, *Salmonella* Typhi, dengue, RSV and influenza, a number of reasons are hindering their use: not enough data to inform selection of most clinically relevant RDT, lack of evidence on impact and cost-effectiveness information to support their use, low sensitivity of the tests and insufficient evidence regarding quality of many RDTs [152]. While waiting for new point of care tests to be developed, febrile patients should be treated with appropriate antibiotics that cover common pathogens causing febrile illness supported by previous fever studies. The ideal empirical regimen should be active against the common treatable pathogens, as narrow spectrum as possible, well-tolerated, short-course, and safe for administration in children and pregnant women.

Improving the management of fever at the peripheral level will also promote appropriate treatment and referral and thus reduce the occurrence of severe disease and death. Fever diagnostic and management algorithms could be modified as more information becomes available such as incorporation of biomarkers or other diagnostic tests. Therefore, treatment options could be proposed now, and scenarios could be simulated for different antimicrobial agents, combinations or interventions. Standardisation of empirical therapy means patients are more likely to receive an appropriate targeted treatment for their infection, delivered at the correct dose. If empirical regimens are shown to have potential to be cost-effective and useful by modelling, this could inform further fieldwork to evaluate the empirical regimens for management of non-malaria fever.

3.3 Objectives

The main objective was to evaluate the cost-effectiveness of different empirical antibiotic treatments for non-malaria febrile illness in rural Myanmar. Other objectives were:

1. To design empirical antibiotic regimens for non-malaria febrile illness
2. To evaluate the impact of different empirical antibiotic regimens on mortality and morbidity compared with the current practice of care
3. To model the impact of empirical regimens in terms of reduction in unnecessary antibiotic prescription

3.4 Methods

3.4.1 Study design

This was a cost-effectiveness analysis of empirical treatment for non-malaria febrile illnesses attending primary care facilities in rural Myanmar. The analysis was framed in the evidence-based decision context of the PICO framework [153]; the population was non-severe cases of febrile illness in patients over one year of age with a negative malaria test; the intervention was empirical treatment (two scenarios were considered: empirical antibiotic treatment and CRP guided empirical antibiotic treatment); the comparator was the "current practice of care"; the outcomes were mortality and disability adjusted life years (DALYs).

A 28-day time horizon was adopted given the acute nature of febrile illnesses assuming that time was sufficient to capture the outcomes and costs related to treatment (care) of acute febrile illness. Also, we assumed that outcomes and costs were independent of the treatment scenarios after 28-days. The context of primary care level facilities was chosen because about 70% of the Myanmar population are residing in rural areas where

health services are primarily provided through a network of rural health centres, sub-centres (in village tracts and villages) and community health workers (in remote villages). A societal perspective (opportunity cost due to illness and AMR cost contributed by empirical treatment) was adopted in this analysis. A decision tree model was developed using silver decision tree software (a free and open-source software, https://silverdecisions.pl/) [154] and the analysis was run in R version 4.1.2.

3.4.1.1 Empirical treatment (Intervention)

The intervention was oral empirical treatment with different antibiotics which included 1) amoxicillin, 2) azithromycin, 3) combination treatment (amoxicillin and azithromycin), and 4) doxycycline (for over 12 years of age).

Amoxicillin and doxycycline are listed in the "**Access**" group, and azithromycin is listed in the "**Watch**" group of the World Health Organization (WHO) AWaRe (Access, Watch, Reserve) classification of antibiotics; all three antibiotics are included in the WHO 2021 Essential Medicines List [155].

Rationale for the choice of antibiotics

1) Amoxicillin

Amoxicillin is an aminopenicillin from the beta lactam class of antibiotics. It is active against a range of Gram-positive and Gram-negative organisms and spirochaetes [156]. Resistance has emerged globally to varying degrees in some important pathogens (e.g., *Escherichia coli*, *Salmonella* spp., *Haemophilus influenzae* and *Streptococcus pneumoniae*). Amoxicillin has been selected principally for its activity against the pneumococcus and *Leptospira* spp. but will also treat other beta- haemolytic

Streptococci that may present as an acute febrile illness e.g., *Streptococcus pyogenes*. The prevalence of in vitro penicillin resistance in pneumococci in Asia has been shown to vary across the region [157]. However, a recent systematic review and meta-analysis showed a 7.5 to 11.5% reduction in circulating pneumococci resistant to first-line antibiotic treatments for pneumonia after implementation of pneumococcal conjugate vaccine (PCVs) [158].

2) Azithromycin

Azithromycin is a macrolide antibiotic that accumulates intracellularly and has a longer half-life (approximately 68 hours) and broader spectrum of activity than other antibiotics from the same class [159]. It is active against most Gram-positive bacteria and some Gram-negative bacteria including multidrug resistant *Salmonella enterica* serovars Typhi and Paratyphi, and *Haemophilus influenzae,* as well as intracellular pathogens responsible for atypical pneumonia (*Mycoplasma* spp., *Chlamydophila* pneumoniae, *Legionella* spp.). It has been used to treat scrub typhus successfully as an alternative to doxycycline, is active against *Leptospira* spp. and *Bartonella* spp. and possesses moderate antimalarial activity [160-163]. Macrolide resistance in Streptococci is increasing.

3) Combination treatment with amoxicillin and azithromycin

When amoxicillin and azithromycin are combined, their antimicrobial activity is expected to be broader than when they are used alone. Azithromycin, for instance, could be beneficial for treatment of pneumonia caused by atypical pathogens, amoxicillin-resistant enteric fever, and some rickettsial infections. The positive benefits of beta

lactam and macrolide combination treatment for moderate-severity community acquired pneumonia has been demonstrated in a number of studies [164-166]. However, the benefit of combined amoxicillin and azithromycin treatment has not been investigated for undifferentiated non-malaria febrile illness.

4) Doxycycline

Doxycycline is a synthetic derivative of tetracycline and inhibits bacterial protein synthesis by binding with the 30S ribosomal subunit [167]. It has broad therapeutic spectrum and activity against a wide range of organisms. It is readily available, cheap and has excellent bioavailability after oral administration with few serious adverse events (SAE) [168]. Doxycycline has been used to treat a range of infections including malaria (prevention and as a partner drug for treatment), sexually transmitted infections (STI, i.e., pelvic inflammatory disease, chlamydia, syphilis), rickettsial illnesses (leading causes of treatable undifferentiated febrile illness in Asia), acute sinusitis, community acquired pneumonia, Lyme disease, skin infections and acne [169]. Antimicrobial activities of the empirical antibiotics are shown in Table 3.1.

Table 3.1 Antimicrobial activity of amoxicillin, azithromycin and doxycycline against common causes of non-malaria febrile illness in Southeast Asia region

Syndrome and disease/ pathogen	Amoxicillin	Azithromycin	Doxycycline
Acute lower respiratory tract infection			
- *Streptococcus pneumoniae*	++	+	-
- *Haemophilus influenzae*	+	+	+
- *Mycoplasma pneumoniae*	-	++	++
- *Chlamydophila pneumoniae*	-	++	++
- *Legionella pneumophila*	-	++	-
- *Bordetella pertussis*	-	++	-
- *Staphylococcus aureus*[1]	-	+	-
Undifferentiated fever			
- Rickettsial disease (scrub typhus, murine typhus)	-	++	++
- Leptospirosis	++	++	++
- Enteric fever (*Salmonella enterica* serovar Typhi)	+	++	-
Dysentery			
- Shigellosis	+	++	+
- *Entamoeba histolytica*	-	-	-
Urinary tract infection			
- *Escherichia coli*	+	+	+

[1] More commonly a cause of post-viral pneumonia rather than primary respiratory infection

Keys:

- *no or variable activity; not recommended*
+ *activity dependent on local resistance patterns*
++ *active/treatment of choice*

Dosage and duration of empirical treatment

Dosage and duration are selected to treat common causes of non-malaria febrile illnesses: uncomplicated acute lower respiratory tract infections, rickettsial disease, leptospirosis, and enteric fever. The WHO revised guidelines for management of childhood pneumonia recommends oral amoxicillin 40mg/kg/dose twice daily for three days for fast breathing pneumonia and five days for chest indrawing pneumonia [170]. Spirochaetes are highly sensitive to penicillin and usually a seven-day course is recommended. A single dose of azithromycin is an alternative treatment. Different dosing regimens of azithromycin have been used to treat rickettsial infections ranging

from a single dose to five days, both with apparent success [162, 171]. Azithromycin has been introduced to treat enteric fever after the emergence of quinolone-resistant *S. enterica* serovar Typhi in Vietnam and extensively drug-resistant strains in Pakistan [172, 173]. Azithromycin doses of 10 to 20 mg/kg/day have been used, typically for at least five days [174-176]. Doxycycline is the drug of choice to treat rickettsial disease and a typical dose of 200 mg/day with different durations (a single dose to 7 days have been investigated); they are shown to be effective at treating scrub typhus [171, 177, 178]. Table 3.2 shows the dose and duration of antibiotics considered for empirical treatment.

Table 3.2 Dosage and duration of empirical treatment

Antibiotics	Dosage	Duration
Children (1 – 12 years)		
Amoxicillin	80-90 mg/kg/day in 2 divided doses	5 days
Azithromycin	20 mg/kg once daily	3 days
Combination Tx (Amoxicillin + Azithromycin)	same as above	3 days
Adolescents and adults (> 12 years)		
Amoxicillin	1 gm 8 hourly	5 days
Azithromycin	1 gm once daily	3 days
Combination Tx (Amoxicillin + Azithromycin)	same as above	3 days
Doxycycline	200 mg for 1st dose, then 100 mg 12 hourly	5 days

Prescription strategies of empirical treatment

In brief, all non-malaria febrile patients were categorised into six febrile syndromes: upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI), undifferentiated fever, fever with dysentery, fever with watery diarrhoea and fever with

suspected urinary tract infection (UTI). All of them receive empirical antibiotics in "Empirical treatment" strategy except those with URTI and watery diarrhoea (for the latter, oral rehydration salt and zinc tablets to be provided as per the WHO guidelines). In the "CRP guided empirical treatment" strategy, a CRP rapid test will be performed in patients with URTI, LRTI and undifferentiated fever to decide the prescription of empirical antibiotics. A CRP threshold of > 10 mg/l was considered as an indication for empirical antibiotic prescription (Table 3.3).

A Cochrane review in 2022, which included 12 trials, found that the use of point of care CRP testing was associated with a reduction in antibiotic prescription at initial consultation as well as within 28 days without affecting recovery in patients with acute respiratory infection [179]. The accuracy of CRP has been evaluated in serum samples collected from febrile patients in three prospective studies in Cambodia, Laos and Thailand [28, 180]. The study demonstrated that a CRP threshold of 10 mg/L had a 95% sensitivity of detecting bacterial infections with a specificity of 49% [60]. A 10 mg/L threshold was selected to guide antibiotic prescription given the remoteness of the rural setting in Myanmar. Details of the prescription strategies are outlined in Table 3.3.

Table 3.3 Prescription strategies of empirical antibiotic treatment

Febrile syndromes	Empirical treatment (Antibiotics - Yes/ No)	CRP guided empirical treatment (Antibiotics - Yes/ No)
URTI*	No	Yes (if CRP > 10 mg/L)
LRTI*	Yes	Yes (if CRP > 10 mg/L)
Undifferentiated fever*	Yes	Yes (if CRP > 10 mg/ L)
Fever with dysentery	Yes	Yes
Fever with diarrhoea	Oral rehydration salt + zinc tablets	Oral rehydration salt + zinc tablets
Fever with suspected UTI	Yes	Yes
* CRP test will be performed to decide prescription of empirical antibiotics for "CRP guided empirical treatment" scenario		

3.4.2 Decision tree model

The decision tree is the simplest form of the decision model, and it provides a visual illustration of the possible pathways for each intervention or scenario [181]. They are usually displayed from left to right starting with a decision node (square nodes) and ending with terminal nodes (triangle nodes). A decision node indicates a decision point between alternative options. A chance node (circular node) represents a point where there is a probability that two or more mutually exclusive events will occur; they are illustrated as branches (pathways) coming out of the chance node.

Each pathway has a probability associated with it, which represents the likelihood of the occurrence of a particular event. Alternatively, it is the proportion of an apparently homogeneous cohort of patients who will experience an event. From left to right, the first probabilities in the tree represent the probabilities of an event. A subsequent probability is conditional, which means that it is based on whether an earlier event occurred. Multiplying the probabilities along each pathway provides the joint probability of the corresponding pathway. Each pathway has its own costs associated

with events along the pathway. The expected costs of each pathway are calculated by weighting the pathway cost by the joint probability of each pathway.

3.4.2.1 Model structure

The decision trees were developed separately for the two age groups: children (1- 12 years), and adolescents and adults (> 12 years) given differences in the distribution of febrile syndromes with underlying aetiologies, risk of mortality, and life years gained when premature death was averted. For both age groups, severe cases, as identified by the presence of general danger signs or severe signs and symptoms, will be referred to nearest hospitals for further treatment and they were not included in this analysis. Thus, the scope of this analysis focuses on non-severe cases of non-malaria febrile patients attending primary care facilities in rural Myanmar. Figure 3.1 shows the decision trees for children, adolescents and adults, each starting with non-malaria febrile cases. There are three treatment scenarios for non-severe cases: 1) current practice of care, 2) empirical antibiotic treatment, and 3) CRP guided empirical antibiotic treatment. There are three empirical antibiotics for children and four empirical antibiotics for adolescents and adults.

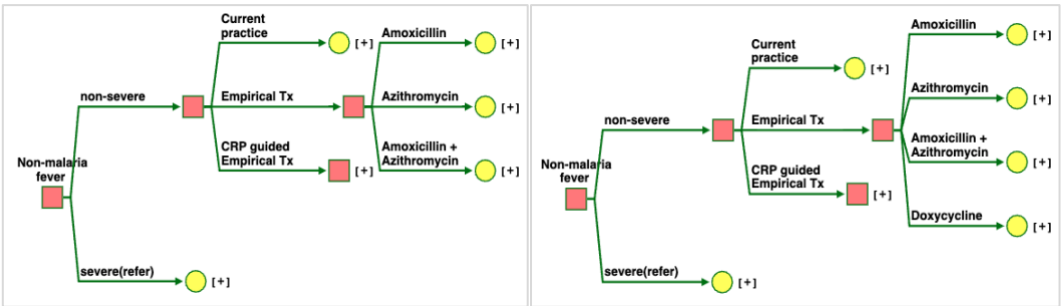


Figure 3.1 Decision trees for children (left) and adolescents and adults (right)

3.4.2.2 Decision trees for scenarios

Patients with URTI and LRTI could have either viral or bacterial aetiologies with corresponding mortalities. Patients with undifferentiated febrile illness could have one of the five aetiologies: viral, leptospirosis, rickettsioses, bacteraemia and other (other causes); each having a corresponding mortality. We did not consider different aetiologies for febrile patients with dysentery, watery diarrhoea and suspected UTI because antibiotic prescribing is less ambiguous in those cases. In the "current practice of care" scenario (Figure 3.2), a proportion of patients could get antibiotic prescriptions. Those with bacterial infections will benefit from antibiotic treatment while those with viral infections will not. Patients with dysentery and suspected UTI with antibiotics will also benefit from it. In case of fever with diarrhoea, a proportion of patients will get oral rehydration therapy. A detailed illustration of decision pathways under "current practice of care" is shown in Figure 3.2.

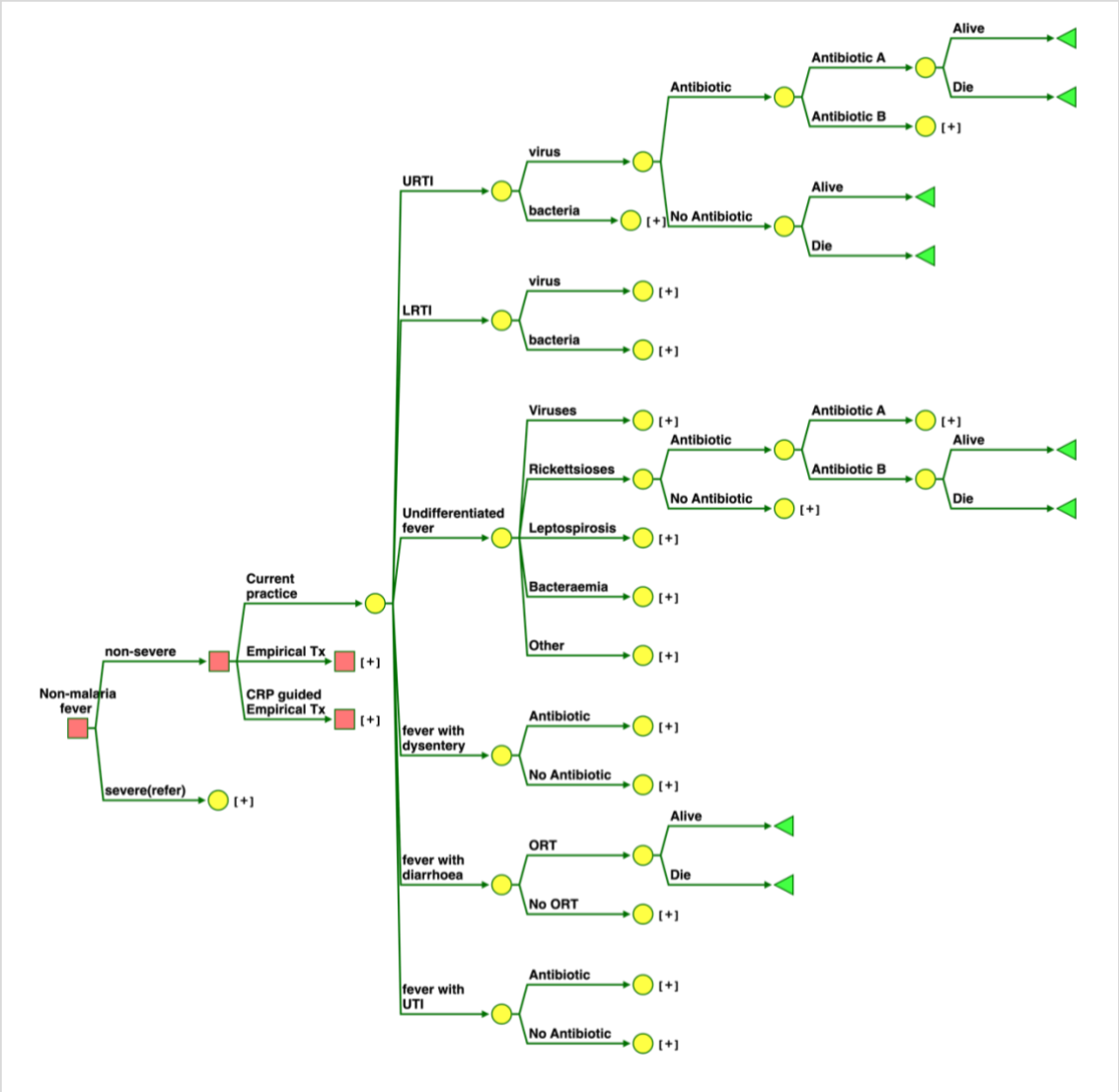


Figure 3.2 Decision pathways under current practice of care (ORT- oral rehydration therapy)

In the "empirical treatment" scenario , there are three antibiotic regimens. For each regimen, prescription will be made according to the prescription strategy stated in Table 3.3. Detailed pathways under the "empirical treatment" scenario for children are shown in Figure 3.3.

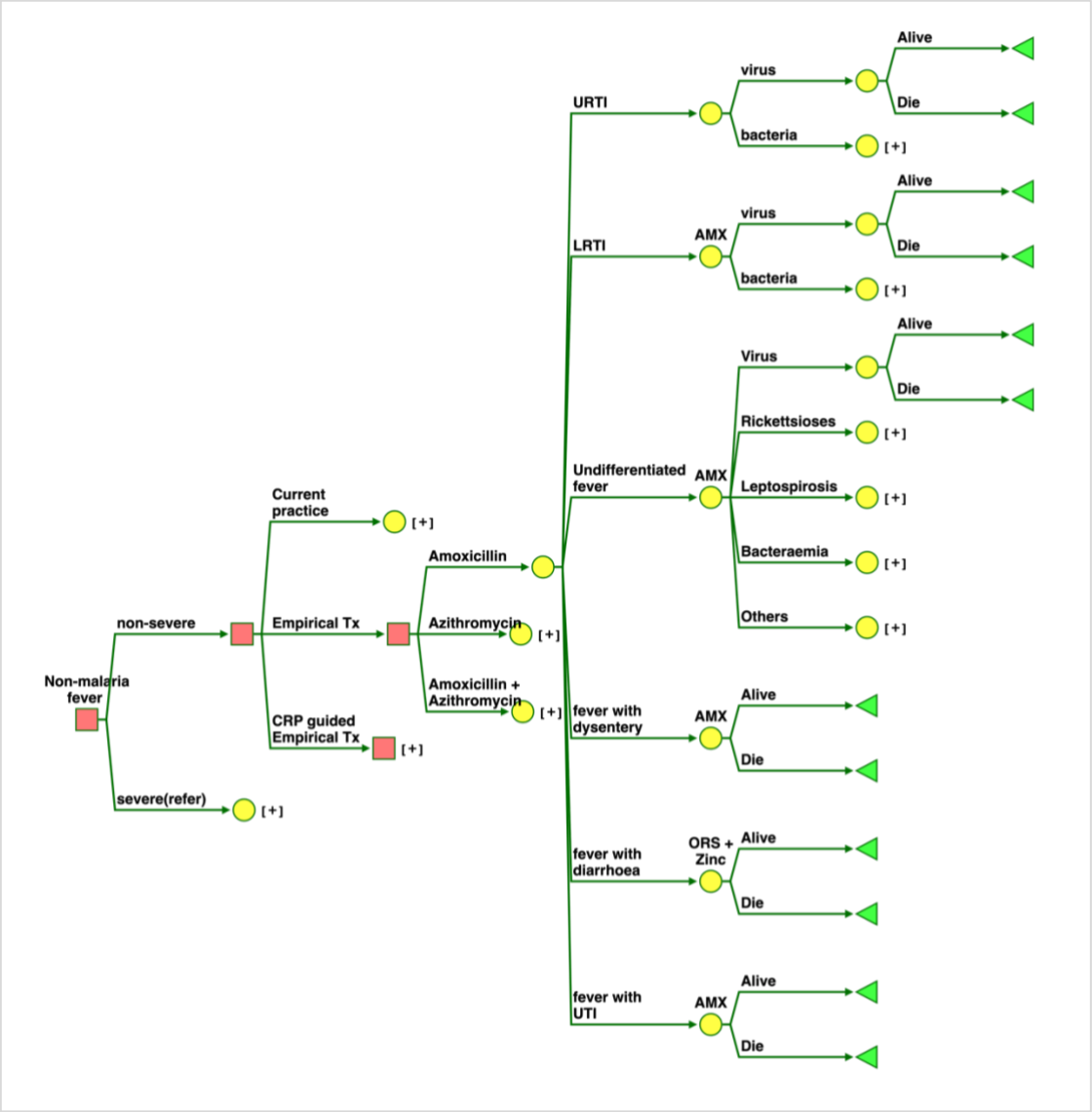


Figure 3.3 Decision pathways under the "empirical treatment" scenario for children

In the “CRP guided empirical treatment” scenario, a point of care CRP test will be performed in patients with URTI, LRTI and undifferentiated fever; those with CRP higher than the threshold value will get empirical antibiotics. Detailed pathways under the “CRP guided empirical treatment” scenario for children are shown in Figure 3.4.

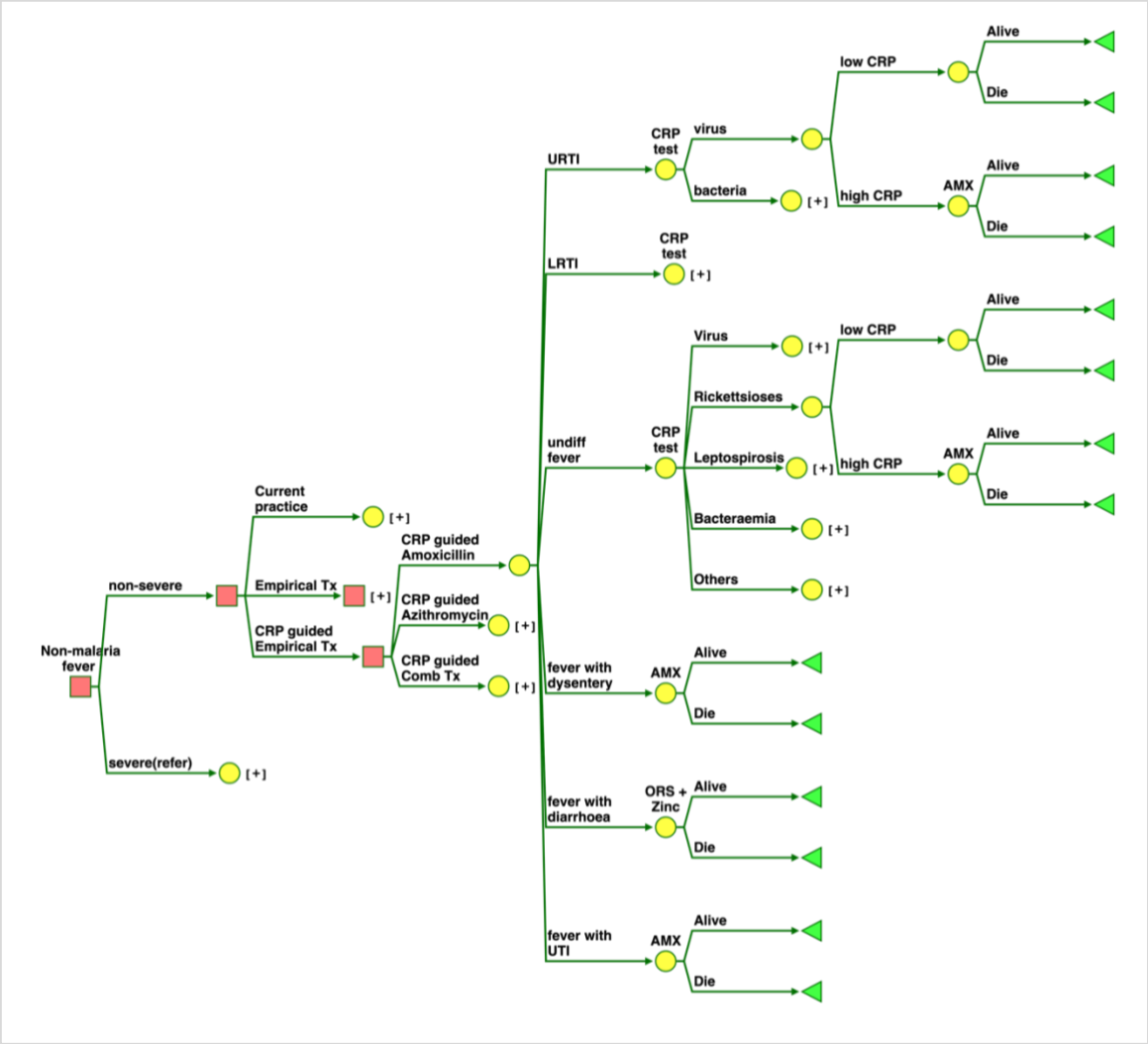


Figure 3.4 Decision pathways under "CRP guided empirical treatment" scenario for children. AMX = Amoxicillin.

3.4.3 Model parameters and sources

The base case values of the model parameters were derived from the prevalence (proportion) from the collected data or literature or assumed (when values could not be derived from available data or the literature).

For univariate sensitivity analysis, lower and upper bounds of the parameters were set as follows. For parameters that were derived from collected data, the ranges were set at the 95% binomial confidence intervals of the corresponding data. For parameters

derived from the literature, the range was set at +/- 10% of the base case value, while for the assumed parameters the range was set at +/- 30% of the base case value or based on plausibility and expert opinion.

For probabilistic sensitivity analysis, all chance nodes with two branches (binary), beta distributions were assigned to the probability parameters. The prior chosen corresponds to the posterior that would be obtained from beta-binomial conjugacy using a vague (non-informative) prior of beta($\alpha = 1, \beta = 1$). If the data are available in the form of x events out of n trials, the corresponding posterior would be beta ($\alpha + x,\ \beta + n - x$). If the data are only available as the point estimate (from the literature or assumed parameter), alpha (α) and beta (β) values of the binomial distribution were derived from the point estimate (μ) and standard error (s) using the following formula [181].

$$\alpha = \mu\left[\frac{\mu(1-\mu)}{s^2} - 1\right]$$

$$\beta = \alpha.\frac{(1-\mu)}{\mu}$$

For chance nodes with more than two branches, Dirichlet distributions were used, which is conjugate with the multinomial distribution. The beta ($\beta_1,\ \beta_2,\ \beta_3, \ldots., \beta_n$) values of Dirichlet distributions were derived from counts of events ($x_{1,}x_2, \ldots, x_n$) of interest of the total samples. Using the vague prior, the corresponding posterior would be Dirichlet(1+$x_1, 1 + x_2, \ldots, 1 + x_n$).

We assigned gamma distributions to all cost parameters due to the skewed nature of the cost bounded by 0. The shape (k) and scale (θ) parameters for gamma distribution were calculated as below.

$$k = c^2, \qquad \theta = c^2\mu$$

where c denotes the coefficient of variation (standard error) and μ denotes the mean cost.

3.4.3.1 Population

The population for the model cohort was taken from the 2019 Myanmar inter-censal survey [83]. At that time there were a total of 51 million people (51,144,607) in Myanmar and 71.2% were residing in rural areas; 21% of them were children (< 12 years) and 77% were adolescents and adults (> 12 years) (Table 3.4).

Annual incidences of febrile illness were estimated from the prevalence of fever (14 days preceding the survey) for children (Myanmar Demographic and Health Survey, MDHS) and adolescents and adults (A survey on treatment-seeking behaviour among persons with acute undifferentiated fever in the endemic regions of Myanmar) [91, 182]. The prevalence data was converted into annual incidence using the equation as below:

$$\lambda \approx \frac{-ln\,(1-P(w))}{w+D}$$

Where λ is the annual incidence, $P(w)$ is the period prevalence of the given period w and D is the average duration of febrile illness (we assumed 5 days for average duration of fever).

Table 3.4 Population parameters

Description	Number	Prevalence of fever[1]	Incidence of fever[2]
Total population	51,144,607	-	-
Rural population ○ 1 - 12 years ○ > 12 years	36,414,960 7,654,425 28,054,085	 0.063 0.027	 1.25 0.53
[1] Prevalence of fever in the past 14 days [2] Incidence per person per annum			

3.4.3.2 Distribution of febrile syndromes

Parameters for the distribution of different febrile syndromes for both age groups were derived from the village health worker consultation database (2017-2018) from Medical Action Myanmar, an international non-governmental organization (INGO) which provides malaria and basic health care services in remote areas of Myanmar through a network of more than 2000 community health workers (https://mam.org.mm/healthcare-and-research/research). Parameters for the distribution of febrile syndromes are shown in Table 3.5.

Table 3.5 Parameters for the distribution of different febrile syndromes in non-severe cases of non-malaria febrile illness in rural Myanmar

Parameter	Base case value	Range for sensitivity analysis[1]		Probability distribution	Reference
		Low value	High value		
Proportion of febrile children with					
URTI (n=54225)	0.754	0.751	0.758	Dirichlet (54226,14817, 1596,15,1196,22)	The MAM data contained 71,866 non-severe cases of febrile children.
LRTI (n=14816)	0.206	0.203	0.209		
Undifferentiated fever (n=1595)	0.022	0.021	0.023		
Dysentery (n=14)	0.0002	0.0001	0.0003		
Watery diarrhoea (n=1195)	0.017	0.016	0.018		
UTI (n=21)	0.0003	0.0002	0.0004		
Proportion of febrile adolescents and adults with					
URTI (n=140917)	0.769	0.767	0.771	Dirichlet (140918,36693, 3011,38,2393,186)	The MAM data contained 183,233 non-severe cases of febrile adolescents and adults.
LRTI (n=36692)	0.20	0.198	0.202		
Undifferentiated fever (n=3010)	0.016	0.015	0.017		
Dysentery (n=37)	0.0002	0.014	0.0003		
Watery diarrhoea (n=2392)	0.013	0.012	0.014		
UTI (n=185)	0.0001	0.0009	0.0011		

[1] The ranges are 95% binomial confidence intervals of the corresponding febrile syndromes.

3.4.3.3 Aetiologies of febrile syndromes

Due to lack of empirical data related to aetiologies of acute febrile illness in rural Myanmar, the parameters were referenced from studies carried out in Thailand-Myanmar border regions and countries in the Southeast Asia (SEA) region. Detailed parameters on distribution of aetiologies are shown in Appendix Table 1.

3.4.3.4 Parameters for untreated mortalities

Data for untreated mortalities of different aetiologies associated with acute febrile illness is sparse or unavailable due to ethical reasons as well as provision of empirical antibiotics in most cases with suspected bacterial infection. Parameters were referenced from systematic review articles where available. Otherwise, assumed parameters were based on expert opinion and plausibility. Parameters on probabilities of untreated mortalities are shown in Appendix Table 2 for children and Appendix Table 3 for adolescents and adults.

3.4.3.5 Parameters for current practice of care

The current practice of care data was informed by a survey which interviewed basic health care workers (HCW) in four regions of Myanmar. The survey was conducted in February and March 2022. A total of 33 health workers were interviewed about their practice regarding treatment of acute fever in children and adults. Of the 33 health workers, 22 (67%) and 9 (27%) said they gave antibiotics to febrile children with respiratory symptoms and undifferentiated symptoms, respectively. For adolescents and adults, 22 (67%) and 14 (42%) responded that they gave antibiotics to patients with respiratory infection and to those with undifferentiated fever. Parameters for antibiotic prescription rate and type of antibiotics (beta-lactam, azithromycin, ciprofloxacin and chloramphenicol) are listed in Appendix Table 4.

3.4.3.6 Parameters for efficacy of antibiotics

Efficacy data were derived from the treatment success rates from trials in the literature. The efficacy was treated as a reduction in the risk of untreated mortality. For instance, 90% treatment success implied a 90% reduction in the risk of mortality when treated.

Efficacy parameters for children are shown in Appendix Table 5 (empirical antibiotics) and Appendix Table 6 (antibiotics used in current practice). Efficacy parameters for adolescents and adults are shown in Appendix Table 7 (empirical antibiotics) and Appendix Table 8 (antibiotics used in current practice).

3.4.3.7 Parameters for calculation of Disability Adjusted Life Years (DALYs)

DALY is a measure of health burden (reduction in life expectancy and diminished quality of life). It is calculated by the sum of YLL (years of life lost due to premature mortality) and YLD (years lost due to disability). Parameters for calculation of DALYs are listed in Appendix Table 9.

3.4.3.8 Cost parameters

Cost parameters were converted to 2022 US$ and a 5% discounting rate was used given the LMIC setting as suggested by the literature [183]. The currency exchange rate used in this analysis was from the UN operational rates of exchange as of 1 November 2022 (1 US$ = 2100 MMK) https://treasury.un.org/operationalrates/OperationalRates.php. The cost for a single consultation was estimated using cost data from a study that described the cost analysis of malaria community health workers (CHWs) in Myanmar [184]. The cost parameters for antibiotics were estimated based on the price available on the UNICEF supply catalogue (2022) https://supply.unicef.org/. The economic cost of AMR contributed by a single course of antibiotics was based on findings from a modelling study in the Thailand setting [185]. It was adjusted for Myanmar using purchasing power parity (PPP) rate from 2021 [186]. Details on cost parameters are shown in Appendix Table 10.

3.5 Analysis

3.5.1 Deterministic analysis

Using the decision tree model, the expected cost and outcomes for each strategy were estimated. The outcomes were predicted number of deaths, disability adjusted life years (DALYs), and overtreated cases. The incremental cost-effectiveness ratio (ICER) was expressed as incremental cost per the number of DALYs averted in 10,000 febrile patients, calculated by dividing the incremental cost by the absolute incremental number of DALYs averted in 10,000 febrile patients.

$$ICER = \frac{Incremental\ cost}{Incremental\ effectiveness} = \frac{C_1 - C_0}{E_1 - E_0}$$

C_1 = cost of the intervention
C_0 = cost of the reference
E_1 = DALY averted (intervention)
E_0 = DALY averted (reference)

3.5.2 Quantifying uncertainty by sensitivity analysis

Given the uncertainty of various parameters, univariate and probabilistic sensitivity analyses were performed.

3.5.2.1 Univariate sensitivity analysis

The univariate analysis was undertaken by varying one parameter at a time through a range while all other parameters remained constant at base case values. The first aim of the univariate analysis was to select parameters that influenced the model outcome the most for expert elicitation. For this purpose, the number of deaths averted was used as the outcome when comparing empirical treatment to current practice. Ten parameters (five from each age group) excluding prescription parameters for current practice were

selected for expert elicitation interview to quantify uncertainty. We believe that uncertainty of prescription parameters could be improved by further data collection rather than the expert elicitation. The parameters that had the greatest influence on the outcomes are shown as Tornado diagrams in Appendix Figure 1 for children and Appendix Figure 2 for adolescents and adults. The second aim was to assess the impact of each parameter on the outcome (ICER) of the model.

3.5.3 Expert elicitation

3.5.3.1 Context

Typically, evidence used to establish cost-effectiveness in health care decision making is uncertain, especially when the input parameters are derived from multiple different sources or sparse. It is important to characterise uncertainty of those parameters. In this situation, the experience and judgement of subject matter experts become essential. Structured expert elicitation (SEE) is one of the methods that allows collection of expert judgement quantitatively on the uncertain parameters [187]. Thus, SEE was used to characterise the uncertainty of the parameters that most influenced the outcomes of our decision tree model selected by univariate sensitivity analysis.

3.5.3.2 Protocol and procedure

To conduct expert elicitation, a standardised protocol was developed based on the Sheffield Elicitation Framework (SHELF), which provides documents, templates and a software tool to conduct elicitation of the probability distributions for uncertain parameters. We prepared an evidence dossier summarizing all available evidence related to the parameters of interest as part of the protocol. The dossier and SHELF expert briefing document were sent to the experts before the interview. The elicitation was conducted using a web-based MATCH Uncertainty Elicitation Tool

(http://optics.eee.nottingham.ac.uk/match/uncertainty.php), which is based on the SHELF framework [188]. The bisection method of elicitation was explained to the experts before the interview. This method allowed experts to set a plausible range, median, lower and upper quartile values for each parameter to build a probability distribution. Experts were informed before the elicitation that the purpose was not to obtain precise parameter estimates, but rather to quantify uncertainty. There was a discussion of how to avoid cognitive biases, as well as how to estimate parameters reliably. The elicitation was conducted remotely, and experts were asked to quantify their belief on the parameters. Fitted probability distributions were shown to the experts to check the fitted distributions match with their judgement.

3.5.3.3 Selection of experts

We selected experts based on three inclusion criteria: 1) PhD degree, 2) subject matter expertise in infectious disease (or) infectious disease epidemiology (or) medical microbiology and 3) having substantial experience of infectious diseases or febrile illness related research in the Southeast Asia region. Experts were identified through a review of authors of relevant publications in the field. Among 15 experts invited, six participated in the interview (two male, four female), with a 40% response rate.

3.5.3.4 Elicited parameters and interview

A total of ten parameters (questions) were asked to the experts during the interview (five for each age group). The parameters are listed in Table 3.6. I conducted one-on-one interviews with each expert, following the above protocol systematically to ensure uniformity. Microsoft Teams was used for the elicitation interviews, which took between 60 and 90 minutes each.

Table 3.6 Parameters selected for experts' elicitation interview

No	Description of parameters
Children	
1	Untreated mortality of bacterial LRTI
2	Prevalence of bacterial aetiology in LRTI
3	Untreated mortality of leptospirosis
4	Untreated mortality of rickettsioses
5	Untreated mortality of fever with watery diarrhoea
Adolescents and adults	
6	Untreated mortality of bacterial LRTI
7	Prevalence of bacterial aetiology in LRTI
8	Untreated mortality of leptospirosis
9	Untreated mortality of rickettsioses
10	Untreated mortality of bacterial URTI

3.5.3.5 Mathematical aggregation of elicited probability distributions

We aggregated elicited probabilities mathematically using linear opinion pooling (arithmetic averaging) method using the formula below.

$$p(\theta) = \sum_{i=1}^{n} w_i \, p_i(\theta)$$

where n is the number of experts, $p_i(\theta)$ represents expert i's probability distribution for parameter θ, $p(\theta)$ represents the combined probability distribution, and the weights w_i are non-negative and sum to one [189]. The linear opinion pooling method was used to combine probabilities because it is the most common approach used in the literature of elicitation in health care decision making [187]. Considering the variation among experts, we believed the broader distribution resulting from linear pooling was appropriate and preferable. We assigned equal weight to experts and pooled probabilities were fit to beta distributions.

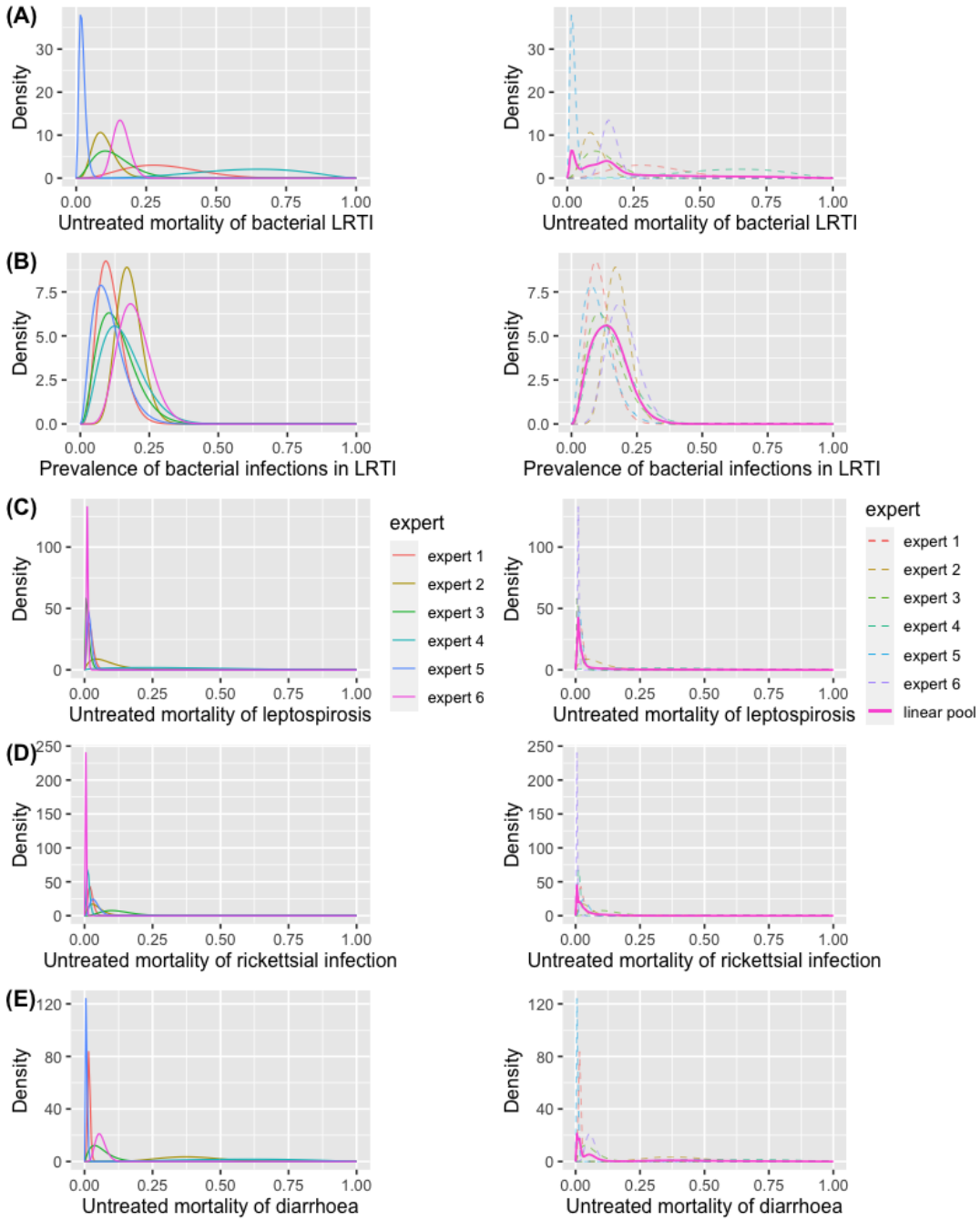


Figure 3.5 Results of elicited parameters for children. Row (A) to (E) represent probability distributions of each elicited parameter. Left column shows distributions from individual experts and right column shows pooled probabilities (purple lines).

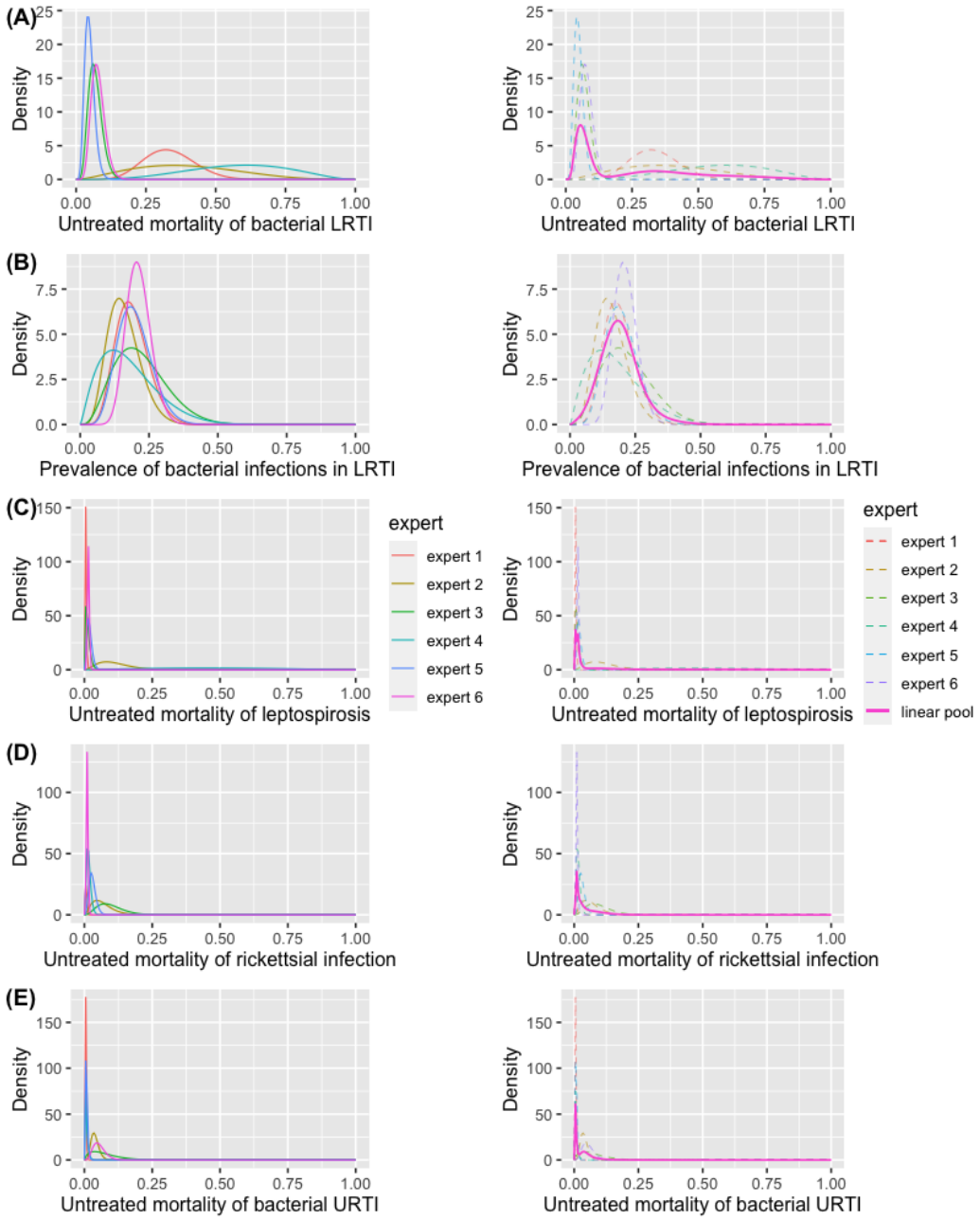


Figure 3.6 Results of elicited parameters for adolescents and adults. Row (A) to (E) represent probability distributions of each elicited parameter. Left column shows distributions from individual experts and right column shows pooled probabilities (purple lines).

3.5.4 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to characterise parameter uncertainty and test the robustness of the model outcomes to variation in parameter inputs. We ran Monte Carlo simulations 1,000 times by randomly selecting values from each parameter's distribution at each time. The incremental cost-effectiveness ratios

(ICERs) are presented in the cost-effectiveness plane, cost-effectiveness acceptability curves (CEAC) and cost-effectiveness acceptability frontiers (CEAF).

3.6 Results

3.6.1 Deterministic base case analysis

3.6.1.1 Predicted number of deaths

In the absence of treatment, the model predicts 39,564 deaths and 70,672 deaths due to non-malaria febrile illness per year in children, adolescents and adults in rural Myanmar (detail in Table 3.7). Current antibiotic prescription could avert 7,798 deaths in children and 19,985 deaths in adolescents and adults. In children, among the empirical treatments, the combined (amoxicillin plus azithromycin) treatment was predicted to avert most deaths achieving a reduction of 5854 deaths, whereas amoxicillin and azithromycin could avert 4398 deaths compared to current prescription practice. The corresponding figures with CRP guided empirical treatments were 5741, 4355 and 5587 deaths averted respectively.

A similar pattern of predicted effect was seen in adolescents and adults. Among empirical treatments, the combined treatment was predicted to avert most deaths having a reduction of 14214, followed by 8877, 12489 and 10945 for amoxicillin, azithromycin and doxycycline treatments respectively. The corresponding numbers for CRP guided treatment were predicted to be 14165, 9103, 12290 and 10891 respectively.

Table 3.7 Predicted number of deaths

Scenarios	Total no. of deaths
Children	
Untreated	39564
Current practice of care	31766
Empirical treatment	
Amoxicillin	27368
Azithromycin	26096
Combination treatment	25912
CRP guided empirical treatment	
Amoxicillin	27411
Azithromycin	26179
Combination treatment	26025
Adolescents and adults	
Untreated	70672
Current practice of care	50687
Empirical treatment	
Amoxicillin	41810
Azithromycin	38198
Combination treatment	36473
Doxycycline	39742
CRP guided empirical treatment	
Amoxicillin	41584
Azithromycin	38397
Combination treatment	36523
Doxycycline	39796

3.6.1.2 Predicted cost and effects

In both age groups, empirical treatment was cost saving and more effective (less DALYs) than current practice. CRP guided empirical treatment cost more but was still more effective (less DALYs) compared to the current practice. The predicted cost and DALYs

per every 10,000 febrile cases for current practice, empirical treatment and CRP guided empirical treatment for children are presented in Table 3.8 and for adolescents and adults in Table 3.9

Table 3.8 Deterministic model outcomes for children showing mean (90% Crl)

Treatment options	Cost (Thousand USD)	Outcomes (10,000 cases)		Comparison with the current practice		
		Deaths	DALYs	Incremental cost	DALYs averted	ICER
Current Practice	237	35	2226	**Reference**	**Reference**	
Amoxicillin	229	30	1919	- 8457	307	- 27.5
Azithromycin	227	28	1831	- 10231	395	- 25.9
Combination Tx	232	28	1818	- 5300	408	- 12.9
CRP guided Amoxicillin	254	30	1922	16738	304	55.1
CRP guided Azithromycin	250	29	1836	13008	390	33.3
CRP guided Combination Tx	259	28	1826	22300	400	55.7
ICER = Incremental cost-effectiveness ratio						

Table 3.9 Deterministic model outcomes for adolescents and adults showing mean (90% Crl)

Treatment options	Cost (Thousand USD)	Outcomes (10,000 cases)		Comparison with the current practice		
		Deaths	DALYs	Incremental cost	DALYs averted	ICER
Current Practice	245	93	1816	**Reference**	**Reference**	
Amoxicillin	233	77	1500	-11835	316	-37.4
Azithromycin	228	55	1076	-16812	740	-22.7
Combination Tx	234	46	899	-10399	917	-11.3
Doxycycline	229	67	1308	-15707	508	-30.9
CRP guided Amoxicillin	260	74	1456	14709	360	40.8
CRP guided Azithromycin	251	55	1078	6252	738	8.5
CRP guided Combination Tx	266	45	880	20735	936	22.2
CRP guided Doxycycline	252	66	1291	6993	525	13.3
ICER = Incremental cost-effectiveness ratio						

3.6.1.3 Predicted overtreated cases

The model predicts that there could be 6128 overtreated cases (non-bacterial infection getting antibiotics) per 10,000 febrile cases with the current practice of care. Empirical treatment and CRP guided empirical treatment were predicted to avoid 4105 and 1409 overtreated cases compared to the current prescribing practice in children. The corresponding figures for adolescents and adults were 4127 and 1351 respectively (Table 3.10).

Table 3.10 Predicted number of overtreated cases from the deterministic analysis

No	Scenarios	Overtreated cases (10000 febrile cases)	Reduction in overtreated cases (10000 febrile cases)
Children			
1	**Current practice**	6128	**Reference**
2	**Empirical treatment**	2023	4105
3	**CRP guided empirical treatment**	4719	1409
Adolescents and adults			
1	**Current practice**	5827	**Reference**
2	**Empirical treatment**	1698	4127
3	**CRP guided empirical treatment**	4476	1351

3.6.2 Deterministic sensitivity analysis

One-way (Univariate) sensitivity analysis was carried out comparing each antibiotic in empirical treatment and CRP guided empirical treatment versus the current practice of care. The top 15 parameters with the biggest influence on the ICERs are shown in Figure 3.7 and Figure 3.8 for children. In all comparisons, similar results were found. Parameters with the biggest effect on the ICERs were those related to respiratory tract infection: probability of beta-lactam antibiotic prescription and probability of azithromycin antibiotic prescription in respiratory tract infection, probability of

antibiotic prescription in respiratory infection, probability of bacterial aetiology in LRTI and probability of untreated mortality of bacterial aetiology in LRTI.

In children, lower prescription rate of beta-lactam antibiotics, azithromycin and overall antibiotics in acute respiratory tract infection in the current practice increased the ICER (meaning that the treatment of interest will be less-cost effective than the current practice). A higher probability of bacterial aetiology in LRTI and untreated mortality of bacterial LRTI lowered the ICER (meaning making treatment of interest more cost effective) Figure 3.7. When comparing CRP guided empirical treatments with current practice, the lower value of sensitivity of CRP test and the higher value of CRP testing cost increased ICER. Details on the output of one-way sensitivity analysis are shown in tornado diagrams in Figure 3.7 (empirical treatments vs current practice) and Figure 3.8 (CRP guided empirical treatment vs current practice).

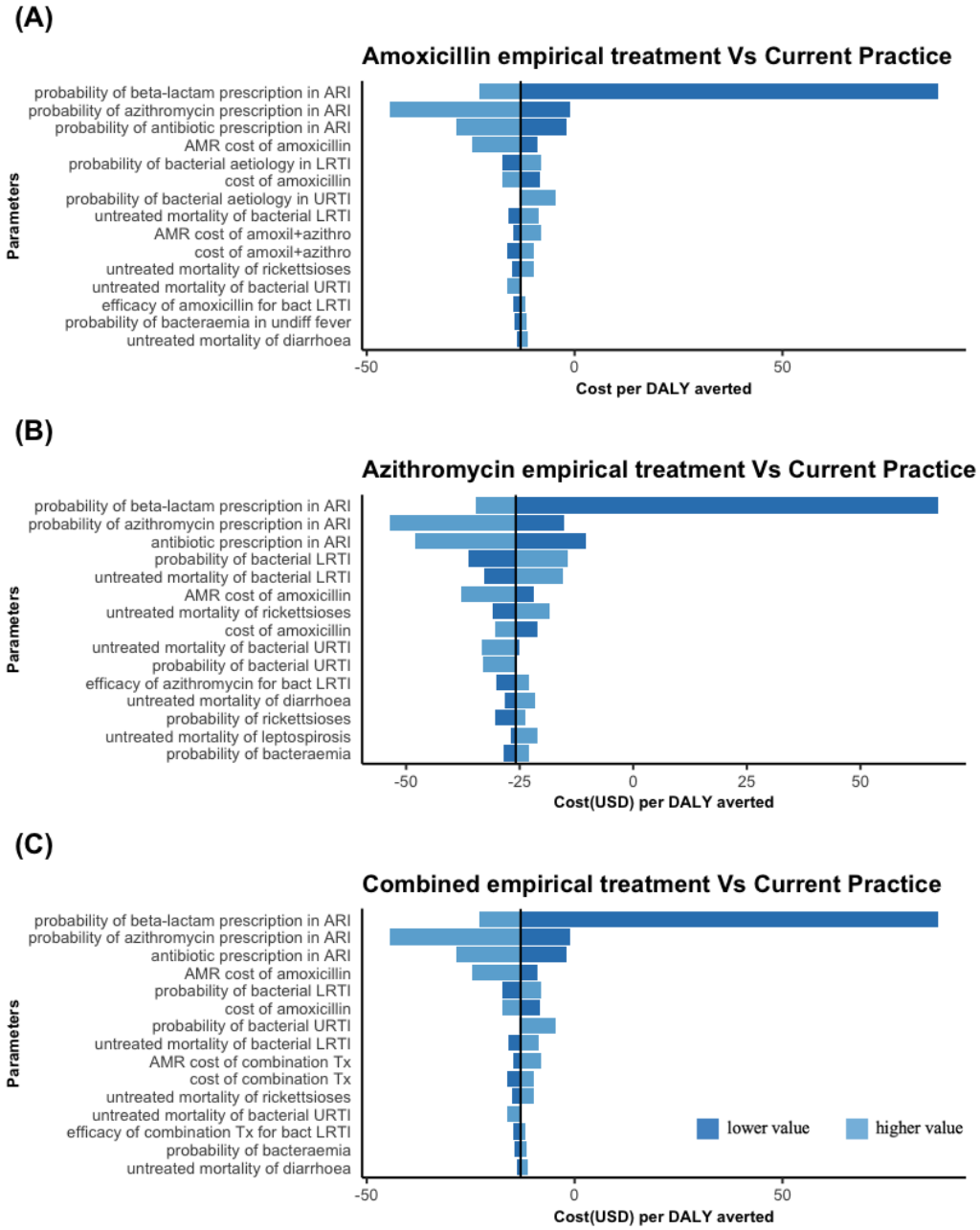


Figure 3.7 Deterministic one-way sensitivity analysis for empirical treatments against current practice of care in children. The vertical line represents the base case ICER.

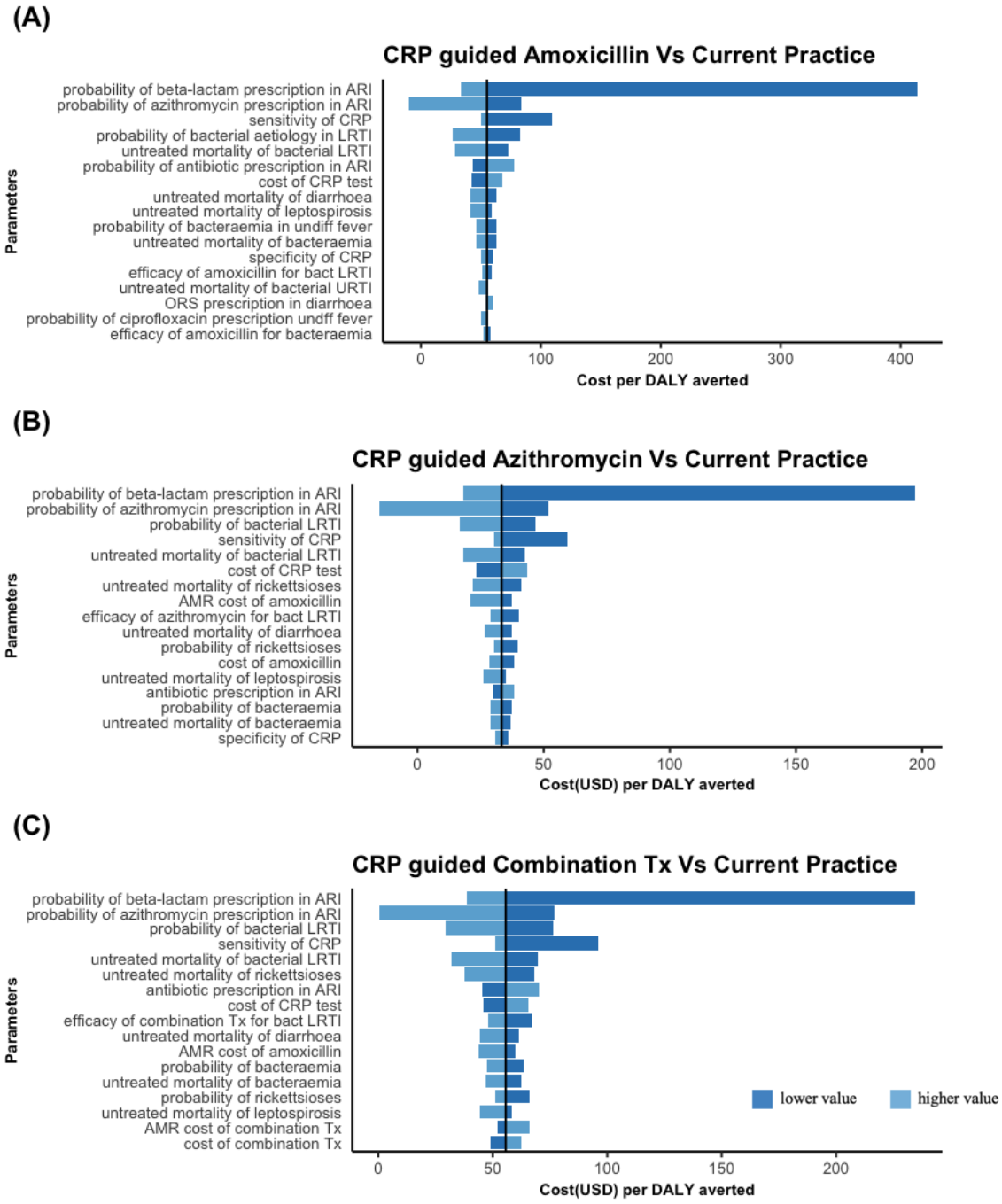


Figure 3.8 Deterministic sensitivity analysis for CRP guided empirical treatments against the current practice of care in children. The vertical line represents the base case ICER.

In the adolescents and adults age group, parameters related to respiratory tract infection had the most influence on the ICER. The top parameters that increased ICER were lower prescription of beta-lactam antibiotics, azithromycin and overall prescription rate in

acute respiratory infection. A higher probability of bacterial aetiology in LRTI and untreated mortality of bacterial LRTI decreased ICER making empirical treatment more cost-effective. A higher untreated mortality of bacterial URTI and probability of bacteria aetiology in URTI are associated with decreased ICER. Similar results are found when comparing CRP guided empirical treatment against current practice except the sensitivity of CRP test was included in the top five parameters. The lower sensitivity of CRP testing is associated with increased ICER making the CRP guided treatment less cost-effective compared to current practice. The top fifteen parameters that had the most influence on the ICER are shown in tornado diagrams in Figure 3.9 and Figure 3.10.

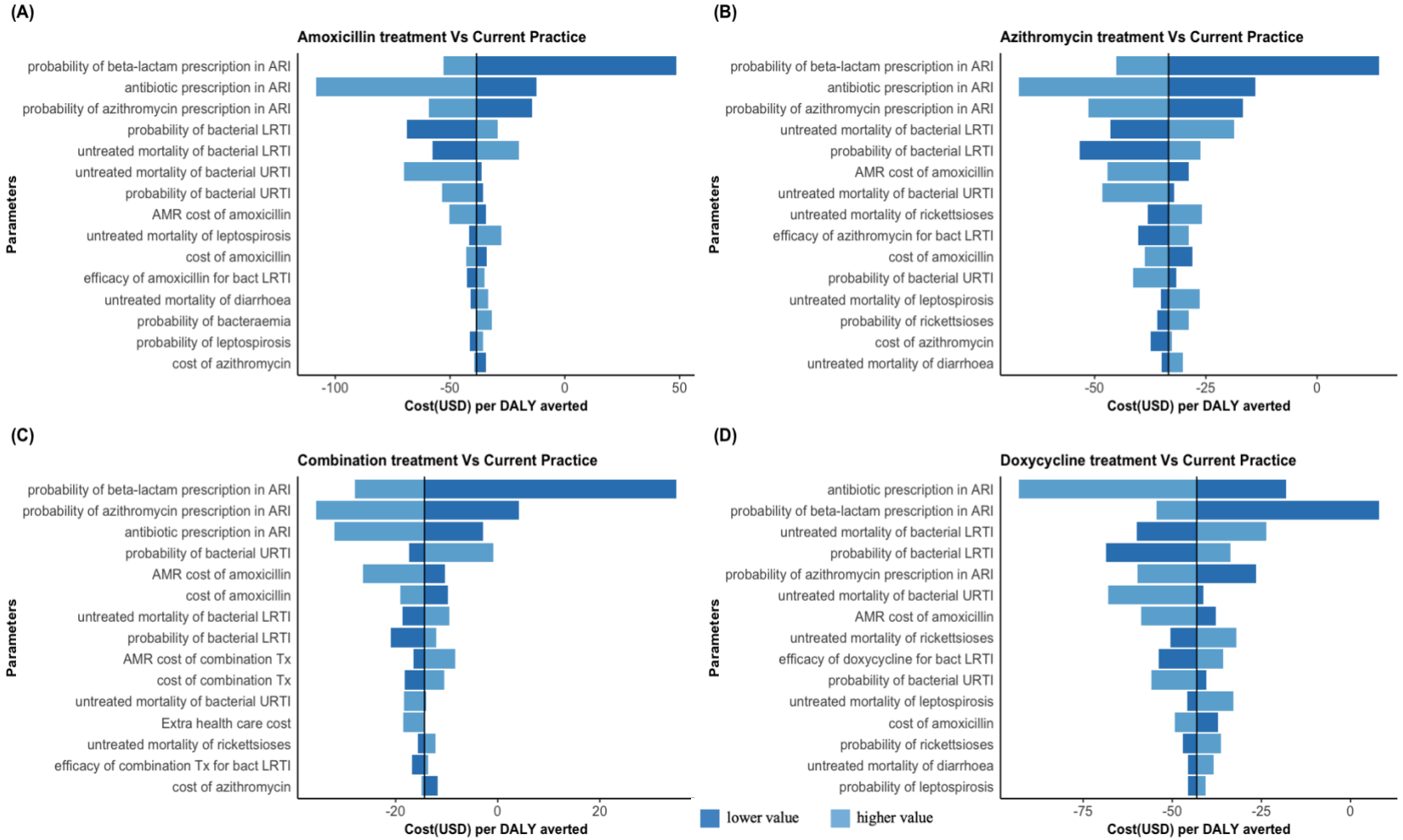


Figure 3.9 Deterministic sensitivity analysis for empirical treatments against the current practice of care in adolescents and adults. The vertical line represents the base case ICER.

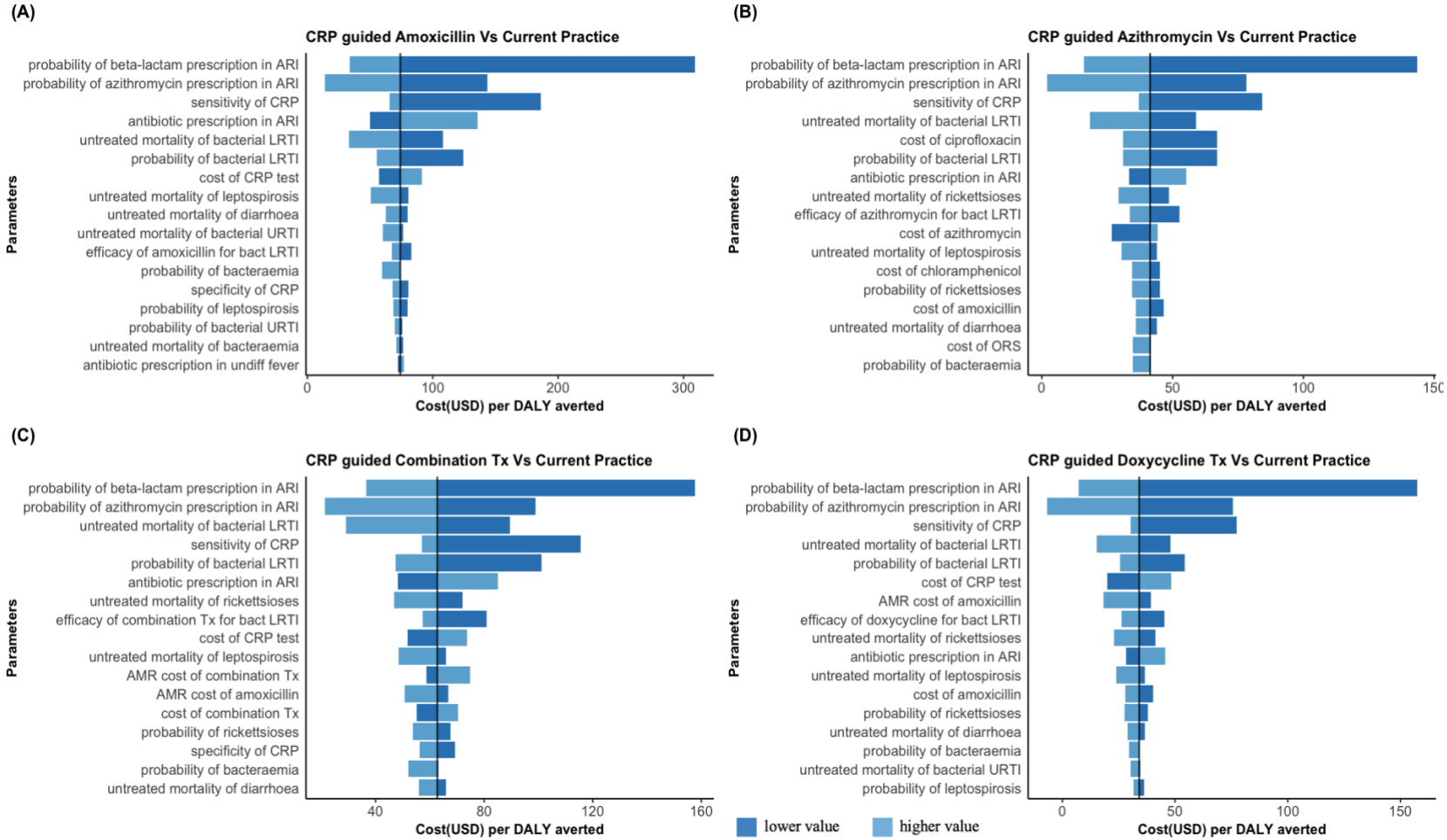


Figure 3.10 Deterministic sensitivity analysis for CRP guided empirical treatments against the current practice of care in adolescents and adults. The vertical line represents the base case ICER

3.6.3 Probabilistic sensitivity analysis

Both empirical treatment and CRP guided empirical treatment led to a reduction in mortality compared to the current practice of care in both age groups.

In children, the largest mortality reduction was seen in empirical treatment with azithromycin and combined antibiotics, and the smallest was seen in CRP guided amoxicillin treatment (Table 3.11). All three empirical treatments were cost saving with the largest cost saving seen in azithromycin empirical treatment (Figure 3.11). All CRP guided empirical treatments were highly cost-effective. Summarizing these results on the cost-effectiveness plane shows that all three CRP guided empirical treatment have a very high probability of being highly cost-effective at WHO-recommended threshold (cost per DALY averted less than gross domestic product per capita) compared with the current practice (Figure 3.12).

In adolescents and adults, the largest mortality reduction was seen in CRP guided combination treatment and the smallest was seen in empirical treatment with amoxicillin (Table 3.12). All four empirical treatments were cost saving with the largest cost saving seen in azithromycin treatment. All four CRP guided empirical guided treatments were highly cost-effective. Summarizing these results on the cost-effectiveness plane shows that all four CRP guided empirical treatments have a very high probability of being highly cost-effective (Figure 3.14).

However, there were large uncertainties regarding the reduction of mortality in empirical treatment and DALYs averted partly reflected by the uncertainty of parameters.

Table 3.11 Probabilistic model outcomes for children showing mean (90% Crl)

Treatment options	Cost (Thousand USD)	Outcomes (10,000 cases)		Comparison with the current practice		
		Deaths	DALYs	Incremental cost	DALYs averted	Mean ICER
Current Practice	197 (158, 243)	70 (34, 136)	4,464 (2164, 8711)	**Reference**	**Reference**	**Reference**
Amoxicillin	184 (146, 227)	38 (27, 54)	2,423 (1735, 3477)	-13,255 (-23736, -7089)	2,042 (278, 5272)	- 6.5
Azithromycin	182 (144, 224)	36 (26, 52)	2,322 (1652, 3309)	-15,101 (-26274 - 8140)	2,142 (324, 5454)	- 7.0
Combination Rx	187 (150, 230)	36 (26, 51)	2,317 (1646, 3287)	-9,972 (-21,598 - 2419)	2,147 (348, 5434)	- 4.6
CRP guided Amoxicillin	210 (171, 255)	40 (27, 62)	2,573 (1742, 3972)	12,797 (2132, 21995)	1,892 (280, 4786)	6.8
CRP guided Azithromycin	206 (167, 250)	39 (26, 59)	2,475 (1671, 3805)	8,908 (-2946, 19134)	1,989 (320, 5102)	4.4
CRP guided Combination Rx	216 (177, 260)	38 (26, 59)	2,472 (1658, 3809)	18,555 (6184, 30292)	1,992 (336, 5024)	9.3

Table 3.12 Probabilistic model outcomes for adolescents and adults showing mean (90% Crl)

Treatment options	Cost (Thousand USD)	Outcomes (10,000 cases)		Comparison with the current practice		
		Deaths	DALYs	Incremental cost	DALYs averted	Mean ICER
Current Practice	200 (159, 251)	81 (35, 170)	2,968 (812, 7,227)	**Reference**	**Reference**	
Amoxicillin	189 (149 , 237)	63 (31, 119)	2,319 (711, 5,292)	-10,519 (-22,191, -2,001)	650 (-939, 3,172)	- 16.2
Azithromycin	186 (146, 234)	56 (28, 108)	2,090 (631, 4,848)	-13,337 (-27,691, -4,102)	879 (-831, 3,908)	- 15.2
Combination Tx	191 (152, 240)	51 (26, 101)	1,877 (555, 4,549)	-8,513 (-24,979, 1,798)	1,091 (-788, 4,482)	- 7.8
Doxycycline	186 (146, 234)	61 (29, 117)	2,266 (694, 5,255)	-13,949 (-26,409, -5,247)	703 (-918, 3,481)	- 19.8
CRP guided Amoxicillin	212 (172, 260)	49 (27, 91)	1,776 (573, 3,872)	12,457 (1,020, 21,973)	1,193 (144, 3,433)	10.4
CRP guided Azithromycin	207 (167, 255)	45 (27, 76)	1,659 (566, 3,313)	7,698 (-6,039, 18,281)	1,310 (165, 3,934)	5.9
CRP guided Combination Rx	216 (177, 265)	37 (24, 57)	1,354 (507, 2,606)	16,389 (1,096, 29,261)	1,614 (214, 4,704)	10.2
CRP guided Doxycycline	205 (164, 253)	49 (27, 87)	1,799 (583, 3,855)	5,065 (-7,084, 15,030)	1,169 (164, 3,566)	4.3

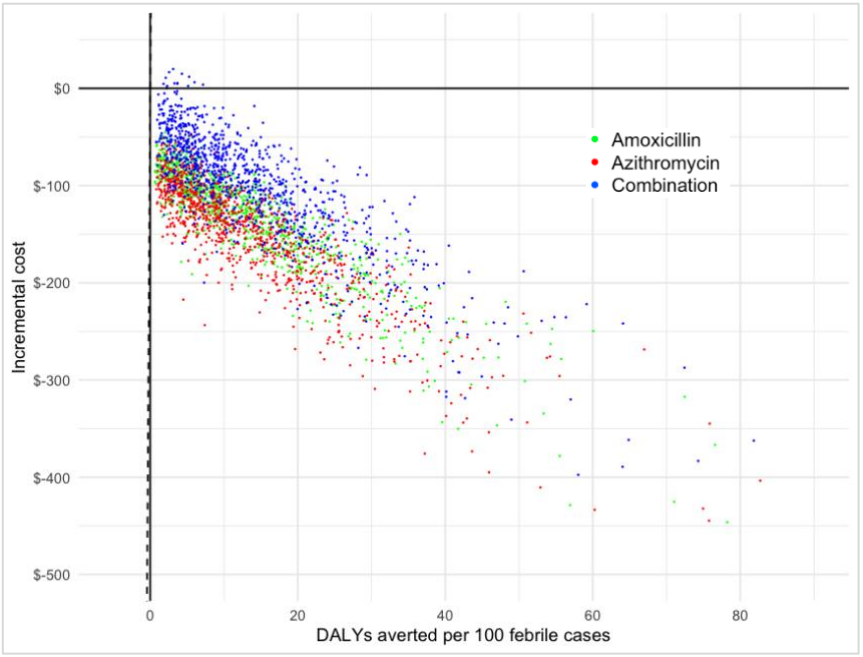


Figure 3.11 Cost-effectiveness plane showing simulated samples of DALYs averted and incremental costs for the three empirical treatments in children. Points to the right of the dashed line (which corresponds to a threshold of US$1200 per DALY averted) would be considered highly cost-effective compared with the current practice in Myanmar

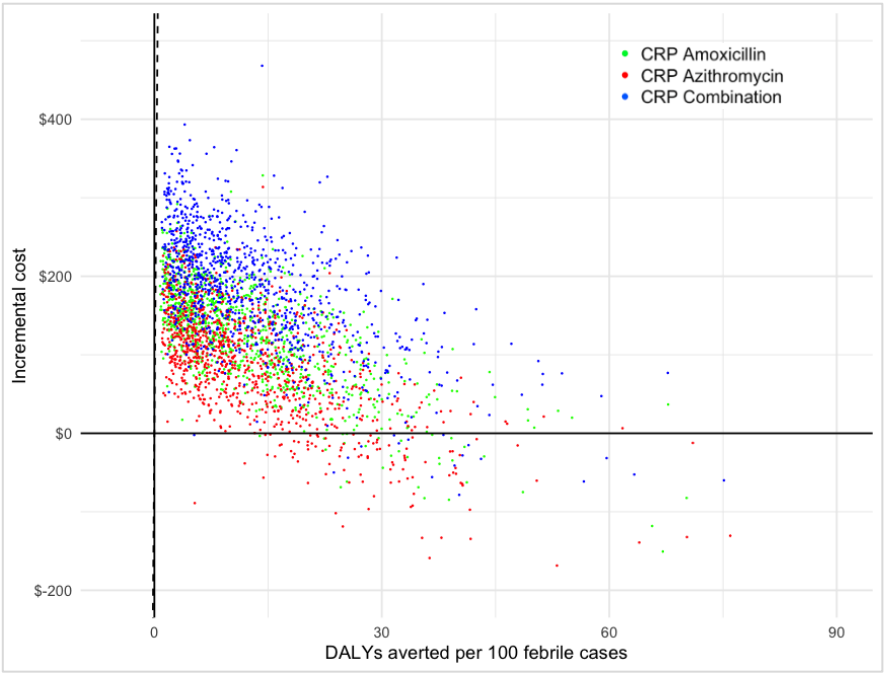


Figure 3.12 Cost-effectiveness plane showing simulated samples of DALYs averted and incremental costs for the three CRP guided empirical treatments in children. Points to the right of the dashed line (which corresponds to a threshold of US$1200 per DALY averted) would be considered highly cost-effective compared with the current practice in Myanmar.

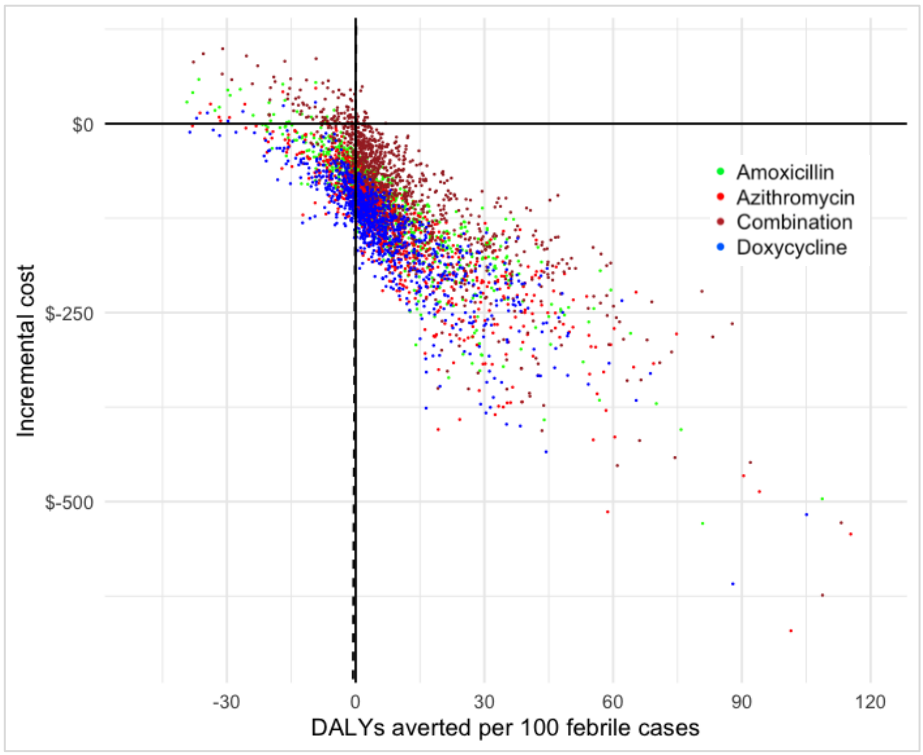


Figure 3.13 Cost-effectiveness plane showing simulated samples of DALYs averted and incremental costs for the four empirical treatments in adolescents and adults. Points to the right of the dashed line (which corresponds to a threshold of US$1200 per DALY averted) would be considered highly cost-effective compared with the current practice in Myanmar.

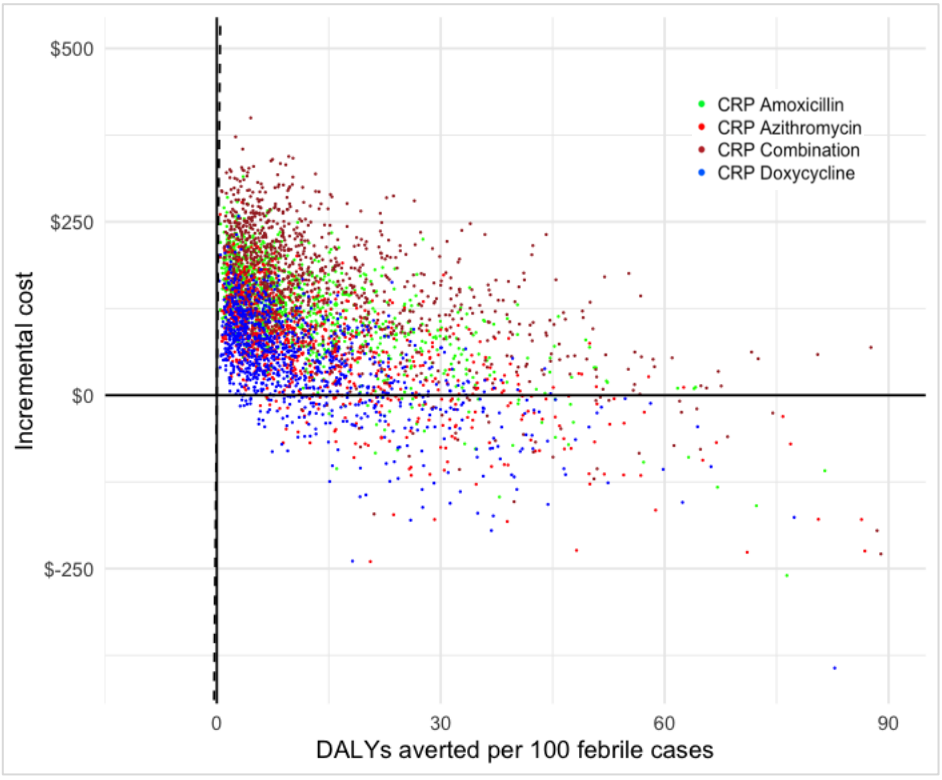


Figure 3.14 Cost-effectiveness plane showing simulated samples of DALYs averted and incremental costs for the four CRP guided empirical treatments in adolescents and adults. Points to the right of the dashed line (which corresponds to a threshold of US$1200 per DALY averted) would be considered highly cost-effective compared with the current in Myanmar.

The cost-effectiveness acceptability curves for the seven treatment options for children are shown in Figure 3.15. This shows that when the willingness to pay (WTP) threshold is less than 600 US$, empirical combined antibiotic treatment is likely to have the highest incremental net benefit (INB). Increasing the cost-effectiveness threshold above 600 US$ leads to an increasing chance that more costly CRP guided amoxicillin treatment will have the highest INB. The CEAF shows that CRP guided amoxicillin treatment becomes optimal only at a threshold above 1000 US$ per DALY averted while empirical treatment with combined antibiotics was optimal at a threshold below

1000 US$ (Figure 3.16). None of the other treatment options were optimal below a threshold of 1200 US$ per DALY averted.

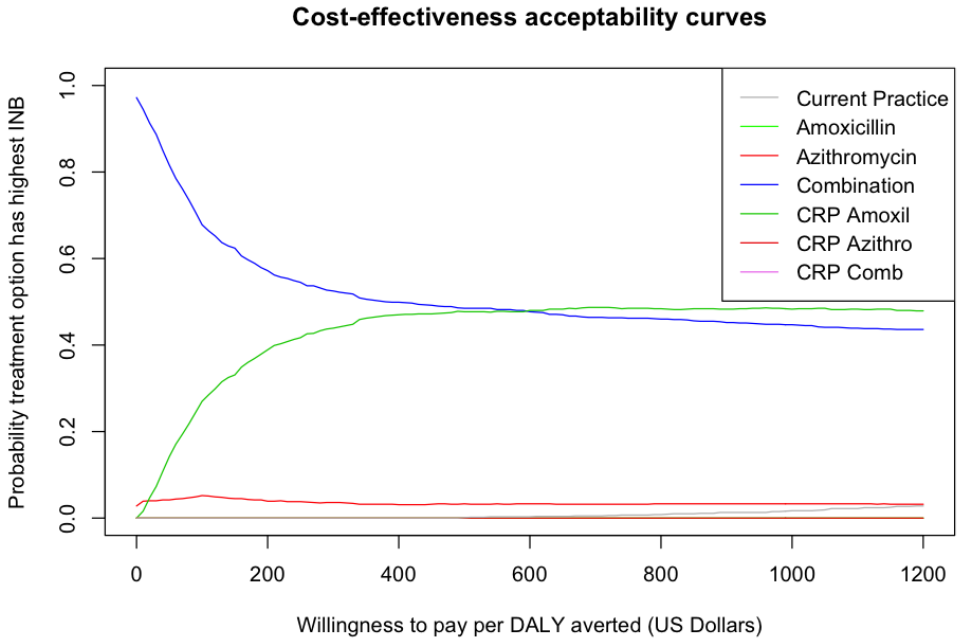


Figure 3.15 Cost-effectiveness acceptability curves showing all seven treatment options in children

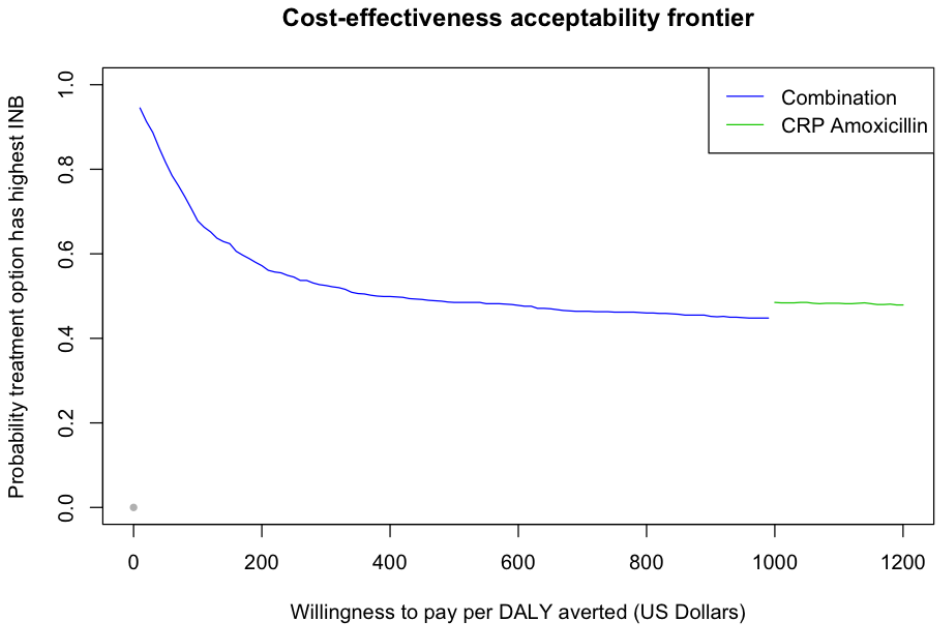


Figure 3.16 Cost-effectiveness acceptability frontier showing optimal treatment strategies at different willingness to pay per DALY averted in children.

The cost-effectiveness acceptability curves for the nine treatment options for adolescents and adults are shown in Figure 3.17. This shows that at a very low willingness to pay (WTP) threshold of below 100 US$ per DALY averted, doxycycline empirical treatment is likely to have the highest incremental net benefit (INB). However, the probability that this had the highest INB never reached above 0.4. With a WTP threshold of above 100 US$, CRP guided doxycycline treatment is likely to have the highest INB. The CEAF shows that at a very low level of WTP (< 50 US$), the current practice of care was optimal. CRP guided doxycycline treatment was optimal when the WTP threshold was above 50 US$ (Figure 3.18).

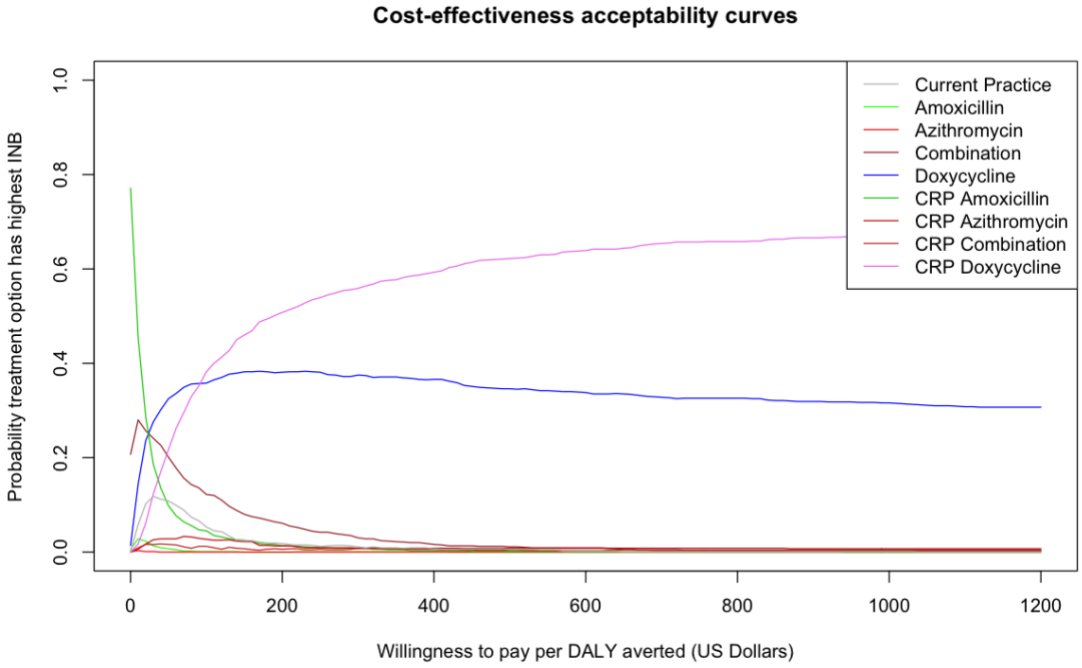


Figure 3.17 Cost-effectiveness acceptability curves showing all nine treatment strategies in adolescents and adults

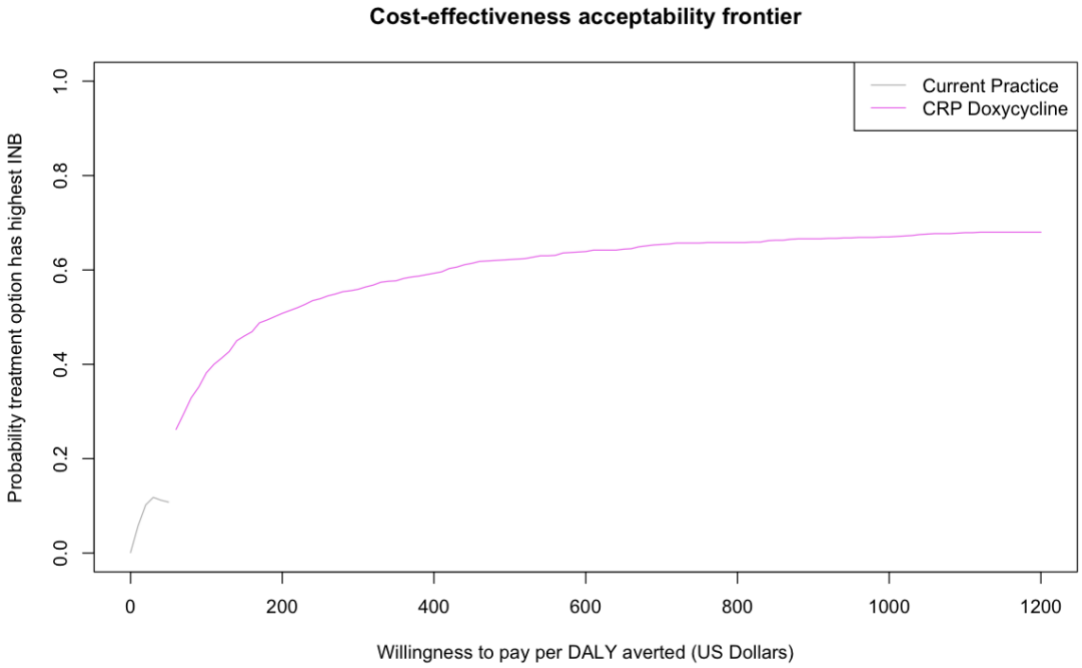


Figure 3.18 Cost- effectiveness acceptability frontier showing optimal treatment strategies at different willingness to pay per DALY averted in adolescents and adults.

Table 3.13 Predicted number of overtreated cases per 10,000 febrile cases

No	Scenarios	Overtreated cases	Reduction in overtreated cases
Children			
1	**Current practice**	5957 (4808, 7113)	**Reference**
2	**Empirical treatment**	1947 (1708, 2155)	4,010 (2,843, 5,139)
3	**CRP guided empirical treatment**	4686 (3959, 5439)	1,271 (-112, 2,616)
Adolescents and adults			
1	**Current practice**	5,730 (4,579, 6,816)	**Reference**
2	**Empirical treatment**	1,724 (1,445, 1,948)	4,005 (2,834, 5,081)
3	**CRP guided empirical treatment**	4,467 (3,730, 5,229)	1,263 (-84, 2,514)
The data are presented as mean (90% CrI)			

For every 10,000 febrile cases, empirical treatment strategy and CRP guided empirical treatment could avoid 4010 and 1271 overtreated cases with antibiotics (Table 3.13). There was a similar number of reductions in adolescents and adults. The corresponding numbers were 4005 and 1263 respectively.

3.7 Discussion

The declining malaria burden in rural Myanmar and the widespread availability of malaria RDTs pose challenges for health care workers when treating acute febrile patients who have negative malaria tests. We used the decision tree model to estimate the impact and cost-effectiveness of empirical treatment with different antibiotics for treatment of non-malaria acute febrile illness in rural Myanmar. We also conducted an expert elicitation exercise to quantify the uncertain parameters.

Our model estimates that both empirical treatment and CRP guided empirical treatment strategies could reduce mortality associated with non-malaria acute febrile illness

compared to the current prescribing practice. Both strategies can represent good value for money in rural settings in Myanmar. All antibiotics considered under the empirical treatment strategy were cost saving while achieving more DALYs averted compared to the current prescribing practice in both age groups. In contrast, CRP guided empirical treatments were not cost saving, but they were found to be highly cost-effective against the current practice. Our model also predicts a reduction of 67% and 22% unnecessary antibiotic prescription, as defined by prescription of antibiotics to patients with non-bacterial infections, with empirical treatment and CRP guided empirical treatment strategies respectively. A lesser reduction of unnecessary prescription with CRP guided treatment could be explained by the fact that testing of CRP for patients with URTI (most of them are viral infections) and a threshold of 10 mg/L has a specificity of 49%, meaning that half of the viral URTIs would receive empirical treatment [60]. In children, combined empirical treatment was optimal when WTP threshold was below 1000 US$ and CRP guided amoxicillin became optimal once WTP was over 1000 US$. In adolescents and adults, CRP guided doxycycline treatment was optimal once the WTP threshold is over 50 US$.

We are not aware of any similar cost-effectiveness analysis of oral empirical antibiotics treatment for non-malaria acute febrile illness in Myanmar. However, there are a few studies in the region. A modelling study that evaluated different prescription strategies in rural Laos found that surveillance guided treatment which informs the choice of empirical antibiotics as well as CRP guided antibiotic treatment are associated with reduction in mortality and are cost-effective in managing non-malaria febrile illness compared with the standard practice [190]; a finding broadly in agreement with our own. However, instead of surveillance guided treatment, we considered antibiotics that

are effective against common diseases and pathogens associated with acute febrile illness in the region informed by the literature. A 44% reduction in antibiotic prescription with CRP guided treatment was observed in the same study.

Another modelling study which evaluated the different types of point of care tests for management of acute undifferentiated fever in remote tropical settings demonstrated that CRP testing was superior to rapid tests targeted to bacterial and viral infections in terms of cost-effectiveness and identifying patients who could benefit from antibiotics [63]. Since most health expenditures are largely incurred by patients out of pocket in Myanmar, we did not consider pathogen-specific rapid tests in our study. However, the cost-effectiveness finding of CRP testing is in accordance with our study finding.

The cost-effectiveness of CRP testing for non-malaria febrile patients has also been modelled in Afghanistan. In that study, the ICER for an additional correctly treated case was 11.4 US$ from a societal perspective against the current practice [191]. Similarly, our study predicts that ICERs of CRP guided empirical treatment against current practice to be less than 11 US$ per DALY averted for all types of antibiotics considered in both age groups.

A modelling study based on the Vietnam context explored the impact of spatial heterogeneity of aetiology of febrile illness on national empirical treatment and demonstrated that a spatially explicit treatment algorithm could lead to an improvement in the number of appropriate treatments by 50% even with intermediate levels of spatial variation. However, we didn't explicitly model spatial heterogeneity of aetiologies since the available data are sparse. To better inform national empirical treatment policy for acute febrile illness, future work is required to set up fever surveillance study sites in multiple rural areas in Myanmar.

Antibiotics considered for empirical treatment were informed by fever studies in the region. A fever study among pregnant women along the Thailand-Myanmar border showed that one third of febrile cases were caused by rickettsia or leptospirosis after excluding malaria, pyelonephritis and respiratory infection [26]. Another fever study in rural Laos also revealed that scrub typhus and leptospirosis were among the top five aetiologies among febrile patients [28]. A systemic review of aetiologies of undifferentiated fever also confirmed that leptospirosis, typhoid and scrub typhus were common causes of treatable undifferentiated fever in South and Southeast Asia regions [21]. Doxycycline or azithromycin are appropriate antibiotics for those infections and amoxicillin is a commonly used empirical antibiotic to treat bacterial respiratory tract infection. Also, the choice of antibiotics considered for empirical treatment in our study is largely in accordance with the 2021 WHO AWaRe classification [192]. None of the empirical antibiotics are from the "Reserve" class, amoxicillin and doxycycline are from the "Access" class whereas azithromycin is listed under the "Watch" class. In the era of rapid emergence of AMR, it is crucial to balance access and overuse of antibiotics.

Integration of health services to treat other common illnesses in the community could improve on the malaria testing among community health workers. This has been demonstrated by the introduction of a basic health care package in four cohorts of community health workers (CHWs) in Myanmar [193]. As malaria is now only responsible for a small fraction of illness among febrile patients, it would be good to integrate services with selected antibiotics to treat non-malaria febrile illness in primary care. However, whether non-medically trained CHW should be allowed to use antibiotics is still debated in Myanmar.

Strengths of our study includes detailed accounting for health and economic impacts as well as the societal cost of AMR per a single course of empirical treatment. We also performed expert elicitation, which is a growing field where limited or unavailable parameters in health care intervention analysis are elicited from a group of experts. Additionally, uncertainty of parameters was propagated throughout the decision tree by probabilistic sensitivity analysis. Moreover, distribution of febrile syndromes was derived from a large community health worker (CHW) database from various regions of Myanmar.

3.8 Limitations

There are also a number of limitations in our analysis. First, parameters for distribution of aetiologies were referenced from a number of sources in the region rather than studies conducted inside Myanmar given a limited literature and lack of proper aetiological studies in the country. It is possible that these estimates may not reflect the distribution of aetiologies in Myanmar. As a consequence, if there is a substantial regional variation in distribution of aetiologies, the estimation on the impact of different empirical antibiotics could be changed. As a third point, we did not explicitly model the deteriorating patients after treatment who could be referred to higher centres, as we considered only binary health outcomes (alive or dead). In terms of generalizability, the findings could be applicable to LMICs with similar distributions of febrile syndromes and underlying aetiologies.

3.9 Conclusion

Treatment of patients with acute febrile illness after malaria is ruled out by rapid test is challenging even for experienced clinicians. There is limited training for frontline health care workers, lack of diagnostic facilities and poor knowledge on antibiotic targeting common infections. Under these circumstances, the decision to prescribe antibiotics and choice of antibiotics is difficult. The cost-effectiveness of CRP-guided antibiotic therapy has been demonstrated by previous modelling studies. In our analysis, we found that empirical antibiotic treatment was cost saving and CRP guided empirical treatment with selected antibiotics was highly cost-effective compared to the current prescribing practice in rural Myanmar.

Chapter 4

Variability of antibiotic prescription for patients with acute fever among primary care doctors

4.1 Abstract

Background

Antibiotics are commonly prescribed in primary care. Prescribing doctors may have different tendencies to prescribe antibiotics simply because of their prescribing style or behaviour. Overall prescription data may mask differences in prescribing rate among prescribers, even within a single health facility. We assessed the variation of antibiotic prescription for febrile patients among prescribers working within the same organization.

Methods

We performed a secondary analysis of prescribing data from a trial in Yangon that investigated the role of C-reactive protein (CRP) testing on antimicrobial prescribing in patients with acute fever [19]. Multilevel logistic regression analysis was used to quantify between-prescriber variation in antibiotic prescription. Variance, Variance Partition Coefficient (VPC) and Median Odds Ratio (MOR) were presented.

Results

The analysis consisted of 1090 patient consultations and 40 prescribers. We found substantial between-prescriber variation in antibiotic prescription. The MOR from the unadjusted model was 1.82 (95% CI:1.47–2.56) implying that if two prescribers were randomly selected from this population, then in 50% of these pairs the odds of antibiotic prescription by one clinician will be 1.82 times greater than the other. The between-prescriber variability remained even after accounting for patient characteristics and

CRP information (p-value < 0.001). Four patient characteristics (prior antibiotic use, fever on presentation, duration of fever > 2 days and presence of respiratory symptoms) and high CRP value were found to be associated with increased odds of the prescribing doctor's decision to prescribe antibiotics.

Conclusion

Even though all prescribers supposedly followed the same management guidelines, there was substantial variation in antibiotic prescription for patients with acute fever. Between-prescriber variation should be considered when designing and analysing the trials that aim to influence behaviour of prescribers. Policy makers and antibiotic stewardship programmes should target prescribers with high prescription rates as well as trying to reduce the overall prescription rate.

4.2 Introduction

Antimicrobial resistance (AMR) is an increasing problem worldwide that poses a serious threat to global health and hinders the achievement of Sustainable Development Goals (SDGs). If no action is taken now, it is estimated that AMR attributable deaths will increase to 10 million annually by 2050, costing the global economy a cumulative 100 trillion dollars in economic output [194]. A global burden of bacterial antimicrobial resistance study estimated that there were 4.9 million bacterial AMR related deaths and 1.27 million bacterial AMR attributable deaths in 2019 alone [195]. Infections with antibiotic resistant bacteria are usually associated with longer hospital stays, the need to use reserved antibiotics, higher medical costs, and increased risk of death.

Although bacteria can develop antibiotic resistance naturally, misuse and overuse of antibiotics in humans and livestock are accelerating the process [196]. In LMICs, antibiotics are easily available without a prescription, which exacerbates the problem of antimicrobial resistance. There has been a substantial increase in the global consumption of antibiotics in the last 20 years. Between 2000 and 2018, global antibiotic consumption in humans increased by 65%, but the trend varied greatly by geographical region [69]. Antibiotic use is associated not only with the development of resistant bacteria, but also with increased carriage of resistant bacteria and the use of second line antibiotics in the community [197].

Nonetheless, antibiotics are commonly prescribed in primary care to patients with febrile illness or acute respiratory infections [198-200]. In malaria endemic regions, antibiotics are often prescribed to febrile patients, especially when malaria tests are found to be negative or when the tests are not available or performed [68, 201]. Those prescriptions are largely unnecessary since most febrile illnesses are self-limiting and

patients recover without treatment unless they have serious bacterial infections. However, it is challenging for healthcare workers to identify patients who could benefit from antibiotic treatment, especially in resource-poor settings where diagnostic facilities are scarce. In 2014, a situational analysis by WHO in Myanmar reported a high rate of antibiotic prescription in primary care. On average, antibiotics were prescribed to half of outpatients, with rates ranging from 34% to 54%. A higher prescription rate was reported for upper respiratory tract infections with an average prescription rate of 87% ranging from 73% to 96% across health facilities [202].

Although antibiotics are commonly prescribed, there is a substantial variation in prescription among primary care prescribers across different countries[203]. It has been observed that prescribers at a single health facility may prescribe antibiotics differently despite sharing a common health facility and the same management guideline [204, 205]. As a result, a health facility's summary data could mask differences between prescribers' antibiotic prescription rates. If there are significant differences in prescribing rates among doctors, a health facility may have doctors who prescribe at the optimum as well as doctors who overprescribe and under prescribe. Using peer-to-peer comparison and feedback programs to encourage higher prescribers to limit antibiotic use could potentially reduce antibiotic overuse where there is a substantial variation of antibiotic prescription between doctors [206, 207]. Various studies have shown variations in antibiotic prescription by general practitioners and primary care physicians in developed countries across Europe and America [203, 208, 209]. However, few studies have been conducted in low- and middle-income settings and Southeast Asia. Studies on antimicrobial stewardship that neglect to account for

variation of antibiotic prescription between prescribers may produce inefficient study designs, incorrect analyses, and premature conclusions.

4.3 Objectives

The main objective of this study was to quantify the amount of variation in antibiotic prescription among prescribing doctors for patients with acute febrile illness in primary cares. Secondary objectives were:

1. To investigate whether the variation can be explained by differences in patient characteristics
2. To quantify the association between patient characteristics and the clinician decision to prescribe antibiotics

4.4 Methods

4.4.1 Study Dataset

This is a secondary analysis of data derived from a clinical trial that investigated the impact of point of care (POC) C-reactive protein (CRP) testing on antibiotic prescription and clinical outcomes in patients who presented with acute fever [19]. In the original trial, POC-CRP testing with a cut-off of 40 mg/L was found to reduce antibiotic prescriptions compared with the routine practice. It was an open label, randomized, controlled trial carried out in Yangon in three primary care clinics and one outpatient department of a nearby Township hospital (Hlaing Thar Yar hospital). In brief, patients over one year of age who presented with fever or history of fever of less than two weeks' duration were recruited. Fever was defined as tympanic membrane temperature of > 37.5°C or axillary temperature of > 37°C on presentation. The following patients were excluded: infants (less than 1 year old), a positive malaria test,

bleeding manifestations, symptoms suggestive of tuberculosis, urinary tract infection or skin/ soft tissue infection or dental abscess as a possible cause of fever; any associated symptoms lasting longer than 2 weeks; severely ill patients who needed hospital referral (either having convulsion, impaired conscious level, inability to take oral medication); not being able to comply with trial procedure including follow-up visits. After getting informed consent, patients were randomly assigned into one of the three groups: two CRP-guided intervention groups and one control group. Trial staff on site took capillary blood to test CRP using CRP reader (NycoCard II Reader, Axis Shield, Oslo, Norway) before the patients in intervention groups consulted with clinic doctors. A cut-off value of 20 mg/L was used for intervention group A and 40 mg/L for intervention group B. The CRP results were informed to the consulting doctors as 'high CRP' or 'low CRP' depending on the cut-off values of the allocated intervention groups. CRP tests were not performed for patients in the control group and the consulting doctors were advised to manage them according to their routine practice. Intervention was not masked to the consulting doctors due to the nature of the intervention. Patients were followed up at day-5 and day-14 with allowable range of +/- 2 days to assess outcomes and recovery. The primary outcomes of the trial were antibiotic prescription rate from day-0 up to day-5 and the proportion of patients prescribed antibiotics if they had 'high CRP' and 'low CRP'.

The analysis was restricted to antibiotic prescription at the first consultation (day 0) in three primary care clinics because the aim of this analysis was to estimate the variability of antibiotic prescription among clinic doctors working in a single organisation (under uniform management guideline) who are providing care to the same patient population. Patients recruited at the outpatient department of the adjacent hospital were not

included because the hospital had a management guideline that was different from the other three clinics and served a different population.

The three clinics included in the analysis were operated by a non-governmental organisation, Medical Action Myanmar (https://mam.org.mm/what-we-do/healthcare). They are located in poor industrial slum areas at the outskirt of downtown Yangon. The clinics open seven days a week from 9 am to 5 pm and provide a range of healthcare services including but not limited to general medical care, antenatal care, reproductive health care including family planning and treatment of sexually transmitted infections, counselling, testing, treatment, and care for people living with HIV/ AIDS and tuberculosis. All services are provided free of charge. Patients are seen by the next available general doctor in the clinics.

4.4.2 Statistical analysis

Clustering of patient consultations within doctors

The data had a two-level hierarchical structure as patients' consultations were nested within prescribing doctors. In other words, a single doctor could have multiple patient consultations. This kind of hierarchical structure could result in correlated data as the likelihood of being prescribed an antibiotic is similar for patients seen by the same doctor. In traditional statistical models, data are assumed to be uncorrelated or independent. Multilevel models, however, recognize correlated data and explicitly model it.

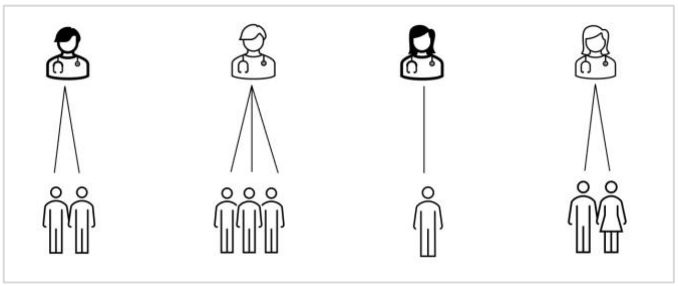


Figure 4.1 Schematic diagram showing patient consultations nested within doctors

Multilevel logistic regression model

Probabilities can be used to determine the likelihood of a particular event, in our case the decision to prescribe an antibiotic. Alternatively, we can use odds, defined as the ratio of the probability that an event occurs (Y = 1) and the probability that the event does not occur (Y = 0). To model clustering of patients within doctors, a multilevel logistic regression model was used as illustrated below:

$$\mathbf{logit}(\boldsymbol{p_{ij}}) = \boldsymbol{\alpha_0} + \boldsymbol{\beta X_{ij}} + \boldsymbol{\alpha_j}$$

where, p_{ij} was the probability of the occurrence of the binary outcome, the decision to prescribe antibiotics in our case, for the i^{th} patient by the j^{th} prescriber, X_{ij}denoted a vector of patient's explanatory variables, α_0 denoted the overall intercept, β denoted the vector of associated regression coefficients, and α_j denoted the prescriber-specific random effects which was assumed to follow a normal distribution with a mean of 0 and variance of σ^2: $\alpha_j \sim \mathrm{N}(0, \sigma^2)$. The variance ($\sigma^2$) can referred to as between-prescriber variance or prescriber residual variance.

Variance partition coefficient (VPC)

Clustering of patients by prescriber in our data made partition of total residual variance into two components: a between-prescriber component (variance of prescriber-level

residuals) and a within-prescriber component (variance of patient-level residuals). The prescriber residuals, called 'prescriber effects', represent unobserved prescribing doctor characteristics that affect the decision to prescribe antibiotic. The VPC that measured the proportion of total residual variance that was due to between-prescriber variation was estimated as illustrated below:

$$\text{VPC} = \frac{\sigma^2}{\sigma^2 + \sigma_{e^*}^2}$$

where σ^2 was the variance of prescriber-level residuals and $\sigma_{e^*}^2$ was the variance of patient-level residuals which followed a standard logistic distribution and equated to, $\sigma_{e^*}^2 = \frac{pi^2}{3} \sim 3.29$.

Median Odds Ratio (MOR)

To translate the prescriber level variance into commonly used odds ratio (OR) scale, which has a clear and understandable interpretation, MOR was calculated as described in Merlo et al using the following equation [210]:

$$\text{MOR} = \exp\left(\sqrt{2\sigma^2}(0.6745)\right)$$

where σ^2 denoted prescriber residual variance. MOR can be interpreted as the median of the odds ratios obtained by comparing the odds of antibiotic prescription in a patient seen by a randomly selected prescriber with another patient seen by a randomly selected but different prescriber in the study population.

Estimation of between-prescriber variation in the decision to prescribe antibiotics

Patient characteristics are presented as frequency (percentage) unless stated otherwise. First, a multilevel logistic regression model (without any patient characteristics) was fitted to quantify the amount of variation of antibiotic prescription between prescribers. This model will be referred to as 'prescriber only model' hereafter. In this model, the

decision to prescribe an antibiotic was fitted as a binary outcome (yes/ no) and the prescribing doctors were fitted as random effects allowing intercept to vary with each prescriber. Point estimates and 95% confidence intervals were calculated for the between-prescriber variance together with corresponding VPC and MOR. A likelihood ratio test was performed comparing the multilevel logistic regression model with an ordinary logistic regression model. Prescriber residuals were assessed graphically using a caterpillar plot. A population of prescribers with a distribution of prescription probability was simulated using the intercept and variance estimated from the model. Then, implied percentiles of prescription probability among prescribing doctors were calculated and visualized graphically.

Next, patient characteristics were incorporated into a multilevel logistic regression model to investigate whether the variation in antibiotic prescribing could be explained by differences in clinical presentations of patients. This model will be referred to as the 'patient characteristics adjusted model'. In this model, eight patient characteristics and study site were fitted as fixed effects together with prescriber as random effects. The patients' characteristics were selected a priori as covariates that had potential to be associated with antibiotic prescription informed by literature. The following eight patient covariates were adjusted in the model: age (categorical: < 12 and ≥ 12 years); gender (male or female); presence of comorbidities (yes or no); prior antibiotic use (yes or no); fever on presentation (yes or no); self-reported duration of fever (categorical: ≤ 2 and > 2 days); CRP information (categorical: no CRP test, low CRP, high CRP); self-reported duration of respiratory symptoms at presentation (categorical: no respiratory symptoms, ≤ 3 days and > 3 days). Point estimates and 95% confidence intervals were estimated for the between-prescriber variance together with

corresponding VPC and MOR as in the first model. Adjusted OR estimates and 95% CI were calculated for association between patient characteristics and the prescriber decision to prescribe antibiotic. Data analysis was done using STATA Version 17 (StataCorp, TX, USA).

4.4.3 Ethics approval

The original trial protocol and all related documents were approved by the Oxford Tropical Research Ethics Committee (OxTREC) and the Department of Medical Research (DMR) Ethics Committee, Myanmar. The trial was registered in ClinicalTrials.gov (registration no. NCT02758821).

4.5 Results

4.5.1 Patient characteristics

Between November 2016 and June 2017, a total of 1090 patients were recruited into the trial in three clinics in Yangon, Myanmar. Of these, 561 were children and 529 were adults. Details of patient characteristics and proportion of patients who received antibiotics are shown in Table 4.1.Proportions of children and adults were similar as randomization was stratified by age groups in the original trial. Of the recruited patients, 45% (487) were male, 6.5% (71) had comorbidities, 5.2% (57) had history of prior antibiotic use, 56% (604) had fever on presentation, 47% (508) had duration of fever of more than 2 days, 55% (598) had respiratory symptoms ≤ 3 days and 16% (179) had respiratory symptom > 3 days. In terms of CRP testing information, almost half of the patients (521, 48%) had a low CRP test result, 19% (204) had a high CRP result and 33% (356) had no CRP test information (patients in the control group).

Table 4.1 Characteristics of patients and study sites

Characteristics	Patients	Proportion of patients prescribed antibiotics
Total patients	1090	372 (34%)
Subgroups		
Study sites		
Clinic A (HTY A clinic)	416 (38%)	135 (32%)
Clinic B (HTY B clinic)	343 (32%)	125 (36%)
Clinic C (SPT clinic)	331 (30%)	112 (34%)
Age of patients		
≥ 12 years	529 (49%)	191 (36%)
< 12 years	561 (51%)	181 (32%)
Gender		
Male	487 (45%)	171 (35%)
Female	603 (55%)	201 (33%)
Presence of comorbid diseases[1]		
No	1,019 (93%)	343 (34%)
Yes	71 (6.5%)	29 (41%)
Prior antibiotic use		
No	1,033 (95%)	344 (33%)
Yes	57 (5.2%)	28 (49%)
Fever at presentation[2]		
No	480 (44%)	138 (29%)
Yes	604 (56%)	234 (39%)
Reported duration of fever[3]		
≤ 2 days	565 (53%)	147 (26%)
> 2 days	508 (47%)	224 (44%)
Respiratory symptoms duration[4]		
No respiratory symptoms	311 (29%)	72 (23%)
≤ 3 days	598 (55%)	202 (34%)
> 3 days	179 (16%)	97 (54%)
CRP information		
No CRP test	365 (33%)	137 (38%)
CRP test - Low	521 (48%)	80 (15%)
CRP test - High	204 (19%)	155 (76%)

Footnote: Data are presented as frequency (%). [1] Diabetes, Hypertension, Asthma, Hepatitis B/C infection, HIV. [2] Data not recorded in six patients. [3] Data not recorded for 16 consultations with antibiotics prescribed and 1 consultation without antibiotics prescribed. [4] Data not recorded in two patients.

Overall, the doctors prescribed antibiotics to 34% (372/ 1090) of patients. There were similar antibiotic prescription rates among the three study sites: 32%, 36% and 34% for clinic A, clinic B and clinic C respectively. Antibiotics were prescribed more frequently to patients with comorbid diseases (41%) than those without (34%) (X^2 p-value = 0.217) , and patients with a history of prior antibiotic use (49%) than those without (33%) (X^2 p-value = 0.014).

Furthermore, the doctors prescribed antibiotics more frequently to patients who were febrile at presentation (39%) than those without fever (29%) (X^2 p-value = 0.001); patients with fever that lasted more than two days (44%) compared to those with less than two days (26%) (X^2 p-value < 0.001); patients who had respiratory symptoms (54% for more than three days and 34% for less than or equal to three days) than those who did not (23%) (X^2 p-value < 0.001).

4.5.2 Variability of antibiotic prescription among prescribing doctors

There were 40 prescribing doctors in three clinics over the study period. The median number of consultations per prescriber was ten ranging from a minimum of one to a maximum of 125. Observed percentage of antibiotic prescription among prescribers stratified by clinic is shown is Appendix Figure 1. Distribution of age and gender of patient consultations grouped by prescribing doctor is shown in Appendix Figure 2.

Observed percentage of antibiotic prescriptions is shown in Figure 4.2. There was variation of observed antibiotic prescription among prescribing doctors (Figure 4.2a). The variability still existed after stratifying the patient consultations by CRP test information (Figure 4.2b-d). A higher prescription rate was observed in patients with high CRP test results compared to patients with no CRP test and low CRP test.

The variance components of two multilevel logistic regression models (a prescriber only model and a patient characteristic adjusted model) are shown in

Table 4.2. In the prescriber-only model, there was strong evidence of inter-prescriber variation which was supported by a p-value of 0.001 from the likelihood ratio test that compared the multilevel logistic regression model with the ordinary logistic regression model. The variance was 0.39 (95% CI: 0.16 - 0.97), the VPC was 0.11 (95% CI: 0.05 - 0.23) and the MOR was 1.82 (95% CI: 1.47 - 2.56). The VPC of 0.11 implied that 11% of residual variation in the decision to prescribe an antibiotic was due to between-prescriber variation (differences in unobserved characteristics of prescribing doctors). The MOR of 1.82 can be interpreted as when two prescribers are randomly selected from this population, there is a 50% probability that the odds of prescription in one prescriber will be more than 1.82 times the other prescriber.

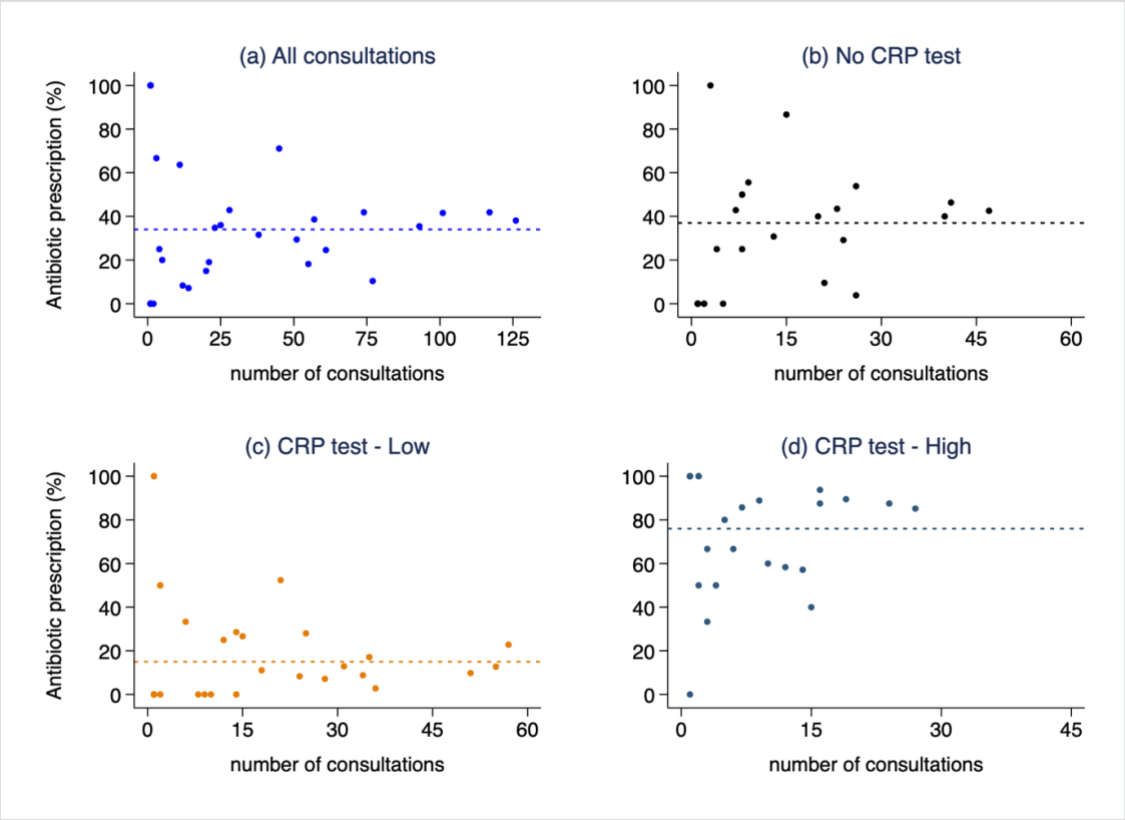


Figure 4.2. Scatter plots showing observed percentage of patient consultation prescribed antibiotics. (a) All consultations, (b) consultations with no CRP information, (c) consultations with CRP test- low and (d) consultations with CRP test - high. A dashed horizontal line represents the percentage of patients receiving antibiotics in the respective category. Each dot represents a prescribing doctor with corresponding number of consultations in x-axis and corresponding antibiotic prescription rate in y-axis.

Table 4.2. Variance components of prescriber-only model and patient characteristics adjusted model

	Estimate (95% CI)		
	Prescriber only model		**Patient characteristics adjusted model**
Variance	0.39 (0.16 - 0.97)		0.73 (0.30 - 1.75)
Variance partition coefficient (VPC)	0.11 (0.05 - 0.23)		0.18 (0.08 - 0.35)
Median odds ratio (MOR)	1.82 (1.47 - 2.56)		2.25 (1.69 - 3.54)

The prescriber residuals from the prescriber-only model are displayed in Figure 4.3. Although we did not have enough power to show the effect of gender on variation in prescription, prescriber residuals by gender are shown in Appendix Figure 2.

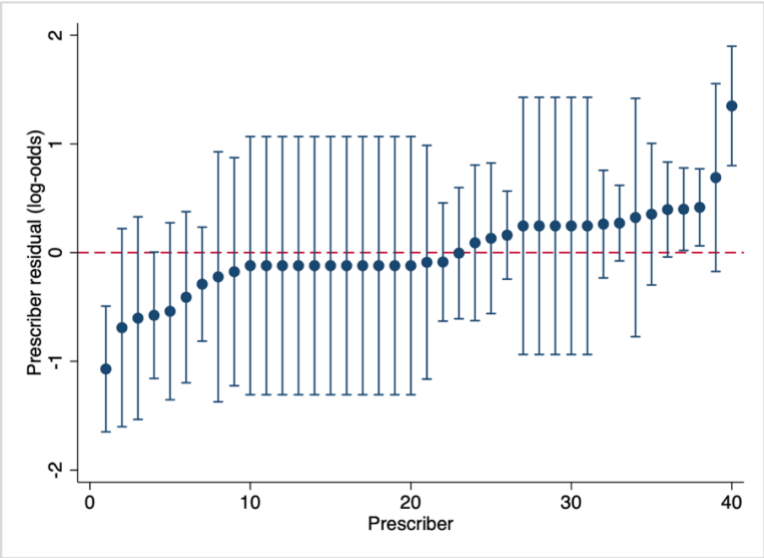


Figure 4.3. Caterpillar plot showing prescriber residual with 95% confidence intervals for log-odds of prescribing antibiotic for prescriber-only model. A horizontal dashed line represents no difference from the main intercept and each dot represents a prescribing doctor. If a prescriber's residual is above the zero line, they prescribe antibiotic more often than the main intercept, and if it is below the zero line, they prescribe antibiotic less often. All 40 prescribing doctors are displayed in the plot.

Using the variance and intercept from the model, a distribution of probability of antibiotic prescription among the prescriber population was simulated and displayed graphically (Figure 4.4). According to the distribution of prescriber population, the doctors in the top 5% prescribe antibiotics more than 56 times for every 100 patient consultations. In contrast, the doctors in the bottom 5% prescribe antibiotics in fewer than 13 of every 100 patient consultations.

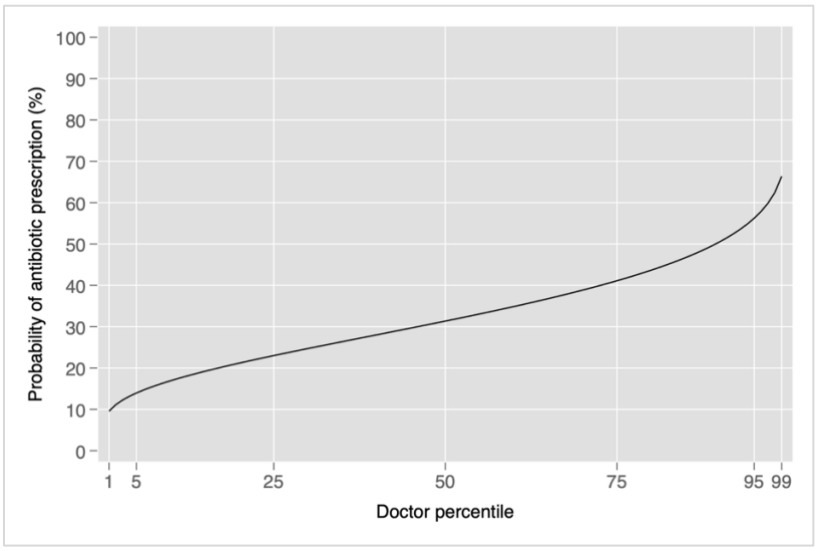


Figure 4.4. Predicted variability of antibiotic prescription among doctors. Distribution function of predicted prescribing probability of doctors is presented as a percentage. Under this distribution, a doctor at the 75th percentile prescribes antibiotics to 41% of their consultations whereas a clinician at the 25th percentile prescribes antibiotics to 23%. The distribution is derived from the estimate of the intercept (-0.784) and estimate of the variance (0.396) from the prescriber-only model.

To determine if patient characteristics can explain between-prescriber variation, as well as to investigate the influence of patient characteristics on antibiotic prescribing decisions, a multilevel logistic regression model was fitted adjusting for eight patient characteristics and study site. The likelihood ratio test that compared prescriber-only model and patient characteristic adjusted model gave a p-value of 0.001 indicating strong evidence of inter-prescriber variation even after accounting for patient clinical presentations. The variance, VPC and MOR were not reduced after patient characteristics were adjusted for (Table 4.2).

This suggests variation of antibiotic prescription among prescribing doctors is not explained by differences in patients' clinical presentations. The prescriber residuals

from the patient characteristics adjusted model are displayed graphically (Figure 4.5)

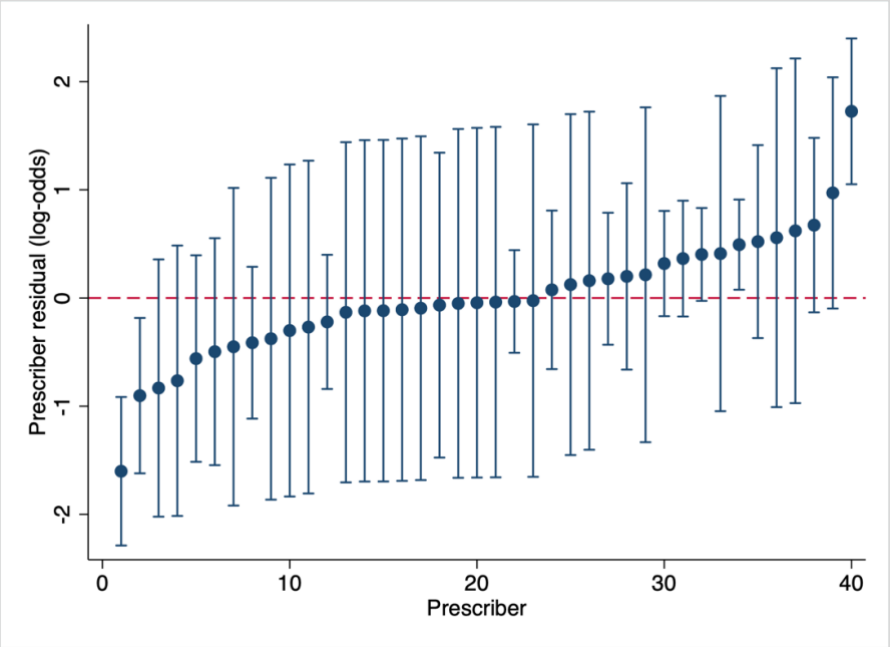


Figure 4.5. Caterpillar plot showing prescriber residuals with 95% confidence intervals for log-odds of prescribing antibiotic of adjusted model. A horizontal dashed line presents no difference from the main intercept and each dot represents a prescriber. If a prescriber's residual is above the zero line, they prescribe antibiotics more often than the main intercept, and if it is below the zero line, they prescribe antibiotics less often. All 40 prescribers are displayed in the plot.

4.5.3 Relationship between patient characteristics and decision to prescribe antibiotics

The estimated odds ratios and 95% CIs from the adjusted multilevel model are shown in Table 4.3. Several patient characteristics were found to be associated with the prescriber decision to prescribe antibiotic. Prescribing doctors prescribed antibiotics more frequently to patients with duration of fever > 2 days than patients with duration of fever ≤ 2 days [OR - 2.00 (95% CI: 1.42–2.82)] and to patients with respiratory symptoms than those without [OR - 1.85 (95% CI: 1.25–2.75) for respiratory symptoms duration > 3 days and OR - 3.56 (95% CI: 2.13–5.94) for ≤ 3 days]. Doctors prescribed antibiotics more often to patients with prior antibiotic use [OR - 2.82 (95% CI: 1.40–

5.69)] and patients who had fever on presentation [OR - 1.65 (95% CI: 1.17–2.33)]. Prescribers were more likely to prescribe antibiotics to patients with high CRP than those with no CRP [OR - 5.98 (95% CI: 3.84–9.32)] and less likely to prescribe antibiotics to patients with low CRP [OR - 0.24 (95% CI: 0.16–0.34)] than patients with no CRP information.

Table 4.3. Adjusted odds ratio from a multilevel logistic regression model with patient characteristics and study site

Patient characteristic	Adjusted OR (95% CI)	p-value
Study sites		
Clinic A (HTY A)	**Reference**	
Clinic B (HTY B)	1.58 (0.72 -3.47)	0.25
Clinic C (HTY C)	1.18 (0.56–2.49)	0.67
Age		
≥ 12 years	Reference	
< 12 years	0.76 (0.51 – 1.11)	0.16
Gender		
Male	Reference	
Female	1.04 (0.76 - 1.44)	0.79
Presence of comorbid diseases		
No	Reference	
Yes	1.20 (0.74 – 1.95)	0.46
Prior antibiotic use		
No	Reference	
Yes	2.82 (1.40–5.69)	0.004
Fever on presentation		
No	Reference	
Yes	1.65 (1.17–2.32)	0.004
Reported duration of fever		
≤ 2 days	Reference	
> 2 days	2.00 (1.42 - 2.82)	< 0.001
Respiratory symptoms duration		
No symptoms	Reference	
≤ 3 days	1.85 (1.25 – 2.75)	0.002
> 3 days	3.56 (2.13 - 5.94)	< 0.001
CRP information		
No CRP	Reference	
CRP test - Low	0.24 (0.16 - 0.34)	< 0.001
CRP test - High	5.98 (3.84 - 9.32)	< 0.001

4.6 Discussion

In this secondary data analysis, we examined variation of antibiotic prescription among prescribing doctors using a dataset derived from a previous clinical trial that investigated the impact of point of care CRP testing on the antibiotic prescription for

patients with acute fever. Multilevel logistic regression models were used to quantify the amount of variation among prescribing doctors and explore whether differences in patients' characteristics were behind this variation.

We found substantial variation of antibiotic prescription among prescribers and the variation still existed after accounting for differences in patient characteristics, CRP test result and study site. This finding suggests that variation in prescription was largely unaffected by differences in patients' clinical presentations and CRP result. Additionally, we found several patient's characteristics that were associated with the prescriber's decision to prescribe antibiotics.

In this regard, it is worth mentioning that the dataset contained a relatively homogeneous patient population, as participants were selected by a set of eligibility criteria in the original trial [19]. Moreover, all prescribing doctors are part of the same organization and practicing under a uniform management system and seeing the same patient population. It further supports our findings that the decision to prescribe antibiotics or not is largely determined by the preference of the prescribing doctors, rather than solely by the patient's clinical presentations and CRP value.

Variation of antibiotic prescription in primary care settings has been described before. In this study, the estimated MOR was 1.8 from the prescriber-only model indicating that for a given patient, seeing two different prescribing doctors could increase the odds of receiving an antibiotic by 1.8 times. Other studies investigating the use of antibiotics in primary care have found similar results. For instance, a study that investigated the inter-prescriber variability of antibiotic prescriptions among primary care physicians in Canada found that consulting with two different physicians resulted in 1.7-fold difference in the odds of receiving an antibiotic for the same patient [209]. A similar

finding of 3-fold difference in the odds of receiving antibiotic for acute rhinopharyngitis was observed among general practitioners in France [211].

We demonstrated that between-prescriber variation remained after accounting for differences in patient characteristics. It is likely that the prescribing style of individual doctors plays an important role in variation of antibiotic prescription in addition to differences in patient clinical presentations. This claim is supported by a cross-sectional study conducted among GPs across six European countries where variation of antibiotic prescription for sore throat still remained after accounting for patient and GP characteristics [212]. A similar finding was reported in a population-based study in Canada where they investigated antibiotic prescription in children with respiratory infections. A high variation in prescription was not explained after accounting for patient, physician, and regional covariates [204]. Although antibiotics are commonly prescribed in primary care, variation of prescription has also been reported in inpatient and hospital settings [213].

In addition to high CRP result, we found a significant association between four patient characteristics (prior antibiotic use, fever on presentation, fever lasting more than two days, and duration of respiratory symptoms) and increased odds of antibiotic prescription. Age of patient, duration of fever, CRP value, findings on chest radiograph and presence of focal abnormal signs have been reported as predictors of antibiotic prescription in a large study which involved over 5000 children with fever in 28 outpatient departments across 11 European countries [198]. However, we did not find a significant association between age of patient and antibiotic prescription. It may be beneficial to conduct further studies with a larger sample size to obtain a more precise estimate. In addition to duration of fever (> 7 days) and high temperature (> 38°C),

consultations in private clinics compared with public primary care was associated with an increased odds of receiving antibiotics in a study in Malaysia [144]. Although it is important to prescribe empirical antibiotics when a patient is suspected of having a bacterial infection, prescribers face difficulties due to uncertainty and imperfect sensitivity of clinical presentations. There have been reports of disagreements between infectious disease specialists regarding the prescription of antimicrobial regimens for hospitalized patients [214].

One important strength of our study is that the dataset contained a homogeneous patient population and all prescribing doctors worked under one organisation. This supports our conclusion that the estimated between-prescriber variability was unlikely to be affected by differences in clinical settings and management guideline. The variation in prescription is also graphically displayed and presented as MOR which are easily understandable by policy makers and prescribers.

In this study, we were not able to estimate the relationship between prescriber characteristics and antibiotic prescribing tendency because prescribers' demographic and other characteristics were not collected in the original trial. Consequently, we were unable to explore the prescription characteristics of the prescriber, such as gender, age, years of experience, previous training, and practice, which might explain some of the variation in antibiotic prescription. Since this study was conducted in the context of a clinical trial, generalizability of these findings is limited to the patient population recruited.

There are several implications of substantial variation in antibiotic prescriptions among prescribers. Since high levels of antibiotic use lead to the emergence of antibiotic-resistant bacteria, antibiotic stewardship programs try to limit antibiotic prescription

rates. However, policy makers should be aware that a hospital's or practice's prescription rate is just a summary measure of all prescription rates of several prescribers with different prescribing styles. The antimicrobial stewardship programme should aim to target prescribers with a high prescribing rate instead of trying to reduce overall prescribing of a setting especially with a high inter-prescriber variation in antibiotic prescription. Otherwise, there is a risk of unnecessarily reduction in prescription of prescribers who already have a low prescription rate.

Another important implication is related to designing trials that examine how an intervention impacts the prescription decision of healthcare professionals. In this context, investigators should be aware of the clustered nature of patient consultations within prescribers, and this should be considered in planning of trials. If clustering of patient consultations is ignored and independent patient consultations are assumed, the power of the study will be overestimated, and the expected effect will be underestimated. In addition, there is a risk of unintentionally running of cluster randomised trial if prescribers are assigned to intervention and control arms in the study [215]. A failure to consider the variation between prescribers in the analysis of such trials can result in inflation of type I error with subsequent tight confidence intervals, thereby causing wrong conclusions to be drawn [215-217].

4.7 Conclusion

In this study, we observed substantial inter-prescriber variation of antibiotic prescription among primary care doctors managing patients with febrile illness. The variability was not explained fully by differences in patient clinical presentations and CRP test result. This finding provides further evidence of variability of prescription in primary care in LMICs in Southeast Asia. It is important for researchers to be aware of

the clustered nature of doctor-patient consultations when designing and analysing a trial that aims to influence the prescribing behaviour of prescribers. Policy makers and antimicrobial stewardship leads should acknowledge the existence of different prescribing tendencies among prescribers when implementing antimicrobial stewardship programmes.

Chapter 5

Distribution of *Burkholderia pseudomallei* in environmental soil in Myanmar

5.1 Abstract

Background

Burkholderia pseudomallei are gram negative environmental saprophytes, which cause melioidosis, a disease with high mortality. Melioidosis is prevalent in Southeast Asia, but it has rarely been reported in Myanmar since it was first described in 1911. The true burden of melioidosis is unknown because of lack of awareness among clinicians and limited diagnostic facilities to identify *B. pseudomallei*.

Methods

We carried out a nationwide environmental soil study in all 15 states and regions of Myanmar from 2017 to 2019. We selected 387 sites for soil sample collection across the country. At each site, we made nine holes at three different depths (three each at 30 cm, 60 cm and 90 cm). We collected ten soil samples: nine individual samples from each hole and one pooled sample. All samples were cultured within 48 hours using Ashdown's agar and suspected isolates were confirmed by latex agglutination test and Analytical Profile Index (API) 20 NE. We explored associations between environmental factors and the isolation of *B. pseudomallei*.

Results

B. pseudomallei was isolated from 103 soil samples in 31 sites in seven states and regions. The majority of positive sites were located in the southern coastal region and the delta region which have a tropical monsoon climate. We isolated *B. pseudomallei* in all three seasons, all three depths, all types of soil and all types of land use. A higher

isolation rate was found in the tropical monsoon climate zone [RR-2.26; 95% CI (0.21-6.21)] compared to the tropical dry winter zone, and more often during the rainy season [RR-2.28 (95% CI: 0.70-7.38)] compared to the winter. Isolation was also more common in agricultural land [RR-5.11;95%CI (0.32 - 81.69)] and pastureland [RR-19.46;95%CI (0.46 - 816.13)] compared to residential areas. A higher isolation rate was found in samples collected at deeper depths in the winter and at more superficial depths in the rainy season.

Conclusion

B. pseudomallei is common in soil in Myanmar. Clinicians should be aware of the risk of melioidosis, in particular among high-risk populations such as people engaging in agriculture work and people with diabetes mellitus. In regions where *B. pseudomallei* was isolated in environmental soil, clinical and surveillance studies should be conducted to get a better understanding of the epidemiology and the burden of the disease.

5.2 Introduction

Burkholderia pseudomallei causes melioidosis, a serious tropical disease, in both humans and animals. They are gram negative bacilli living as saprophytes in the environmental soil, surface, and ground water [218]. They can survive in the environment for many years even in nutrient depleted conditions. Melioidosis is endemic in Southeast Asia, the northern part of Australia and the Indian subcontinent [219, 220]. However, the disease has been increasingly reported in other parts of the world including America and Africa [221, 222]. According to a modelling study, it was estimated that 3280 million population were at risk, 165,000 cases of human melioidosis occurred worldwide per year, and 89,000 people died as a result in 2015 [127]. The same study also predicted that more than 99% of all deaths due to melioidosis was in low- and middle-income countries, and only less than 1% in high-income countries [127].

Melioidosis was first described in Yangon (formerly "Rangoon"), Myanmar, in 1911 by Alfred Whitmore and Krishnaswami in post-mortem examination of morphine addicts [223]. The disease was later described in other countries. For instance, the first case of melioidosis was reported in Malaysia in 1913, Singapore in 1920, Australia in 1949 and Thailand in 1955 [224-227]. It is a potentially fatal disease and case fatality could be as high as 70% [228]. The usual mode of transmission incudes direct inoculation with contaminated soil, inhalation or ingestion of contaminated water or aerosolised dust [218]. The incubation period usually ranges from 1 to 21 days, but on average it takes 9 days [229]. A long incubation period of several decades has been

reported in rare cases [230]. Transmission is seasonal, with a higher incidence of cases during the rainy season [231].

Melioidosis has a wide spectrum of clinical presentations, depending not only on the route of transmission, i.e., inoculation, inhalation, and ingestion (rarely), but also on the bacteria load, the strain virulence, and host factors [232]. The majority of patients present as an acute infection, with fever, pulmonary infection, sepsis and deep abscesses in internal organs but it is often difficult to diagnose due to non-specific symptoms [233]. A number of risk factors have been described, which include male sex, diabetes mellitus, occupational exposure, chronic kidney disease, alcohol misuse and immunosuppressed health conditions [218, 234-237].

Diagnosis is usually made by culture and isolation of the organisms from clinical specimens including blood, pus, swabs, respiratory secretions, and urine [218]. The majority of laboratory culture media are suitable for their growth. However, it is possible to isolate organisms more efficiently from nonsterile sites by using selective media, such as Ashdown's media and selective enrichment broths [238]. Furthermore, identifying suspect colonies and making laboratory diagnoses are not easy tasks especially when laboratory staff are not familiar with the organisms. As a result, these organisms are often discarded as contaminants or mis-identified [239, 240]. Other methods of diagnosis include polymerase chain reaction (PCR), gene sequencing, mass spectrometry, serology, and antigen detection. However, these methods are not cheap and not widely available in endemic regions in low- and middle-income countries.

Standard treatment for melioidosis includes an initial intensive phase with intravenous antibiotics followed by a prolonged eradication phase with oral antibiotics for several months [228, 241]. The organism is intrinsically resistant to several antibiotics such as

penicillin, ampicillin, first- and second-generation cephalosporins, aminoglycosides, macrolides and polymyxins [218]. As a consequence, antibiotics recommended in most empirical treatment guidelines for management of sepsis and pneumonia do not cover melioidosis. Until the late 1980s, melioidosis was conventionally treated with parenteral chloramphenicol, doxycycline, trimethoprim-sulfamethoxazole, and kanamycin [242]. In 1989, a landmark trial showed a 50% reduction in mortality related to severe melioidosis treated by a new treatment regimen, which included ceftazidime, compared with the conventional therapy [243]. The current standard treatment includes intravenous ceftazidime or meropenem for at least two weeks followed by oral trimethoprim-sulfamethoxazole for three to five months depending on the site of infection [244]. Despite treatment with effective antimicrobial therapy, there is still a risk of death. A study in Thailand showed mortality of 41% in hospitalized melioidosis patients with a positive blood culture in 2006 [234].

The Southeast Asia region has a high burden of melioidosis. In Thailand, melioidosis is endemic throughout the country and more than 2500 culture-confirmed cases are reported annually. It is the second most common cause of community-acquired bacteraemia in Northeast Thailand [245]. At present, Malaysia is ranked second in the region for the frequency of melioidosis cases reported [237]. In Cambodia, a retrospective study identified 173 cases of culture-confirmed paediatric melioidosis cases in a single hospital between 2009 and 2013 [246]. In contrast, only 298 melioidosis cases have been reported in Myanmar over a 100 year-period since its first discovery in 1911 and most of them were reported before 1948 [247]. It is highly likely that the burden of melioidosis has been underestimated in Myanmar given the high prevalence of the disease in neighbouring countries. The burden of melioidosis in

Myanmar is believed to be high, with an estimated annual incidence of 6000 cases and 3000 deaths [127].

B. pseudomallei has been identified in several environmental studies in Southeast Asia. An isolation rate of 32% in soil samples and 60% in paddy field water samples was reported in Northeast Thailand [248]. Similarly, presence of *B. pseudomallei* in the soil collected from 39% of paddy fields has been confirmed in Vietnam and 44% in Laos [249, 250]. In recent years, two small studies confirmed the existence of *B. pseudomallei* in environmental soil in three regions of Myanmar [251, 252]. However, the distribution of *B. pseudomallei* in the remaining regions and at the national level is unknown. Detecting *B. pseudomallei* in environmental samples is vital for defining geographic areas where humans and animals are at risk of contracting melioidosis. Thus, it is important to map the geographic distribution of *B. pseudomallei* in all regions of Myanmar. This information can be used as the basis for further research to provide a more comprehensive understanding of melioidosis in Myanmar as a public health issue.

5.3 Objectives

1) To map the geographic distribution of *B. pseudomallei* in the environmental soil in all regions of Myanmar
2) To explore the association between environmental factors and isolation of *B. pseudomallei* in environmental soil

5.4 Methods

5.4.1 Study location

Myanmar is a lower-middle income country located in the northwest part of the Southeast Asia region. It has a border with China in the north and northeast, Laos in the east and Thailand in the southeast, India and Bangladesh in the northwest, Bay of Bengal in the west and Andaman Sea in the south. The 2019 census estimated Myanmar's population at 51.1 million, with approximately 70% living in rural areas [83]. Myanmar is an agriculture-based economy with the majority of its gross domestic product (GDP) contributed by agriculture, providing jobs to upwards of 70% of its labour force [253]. Landscapes in the country are diverse, with central lowlands encircled by mountains in the north, east, and west, and coastline along the south. The climate is largely tropical, although some areas in the north are temperate and a small area in the centre of the country is dry steppe [254]. Myanmar has three seasons: the summer ("hot and dry") season from March to mid-May, the rainy ("monsoon") season from mid-May to October, and the winter ("cool and dry") season from November to February [254].

5.4.2 Selection of sample sites

We generated 800 random points throughout the country using Geographic Information System (QGIS version 3.4.9 https://qgis.org/). The random points were subsequently evaluated based on whether they were located in geographically inaccessible areas, unsafe locations and extreme remote areas. Among them, 413 points were located in uninhabited forest, lakes, mountains, armed conflict areas, and extreme remote areas (inaccessible by nearby main roads) and they were regarded as inaccessible locations for the study and excluded. The remaining 387 points were considered suitable for soil

sample collection. A nearby location was selected at each point based on factors informed by literature as associated with *B. pseudomallei* such as agriculture field, pastureland, and unused land in proximity to villages. We collected information on type of land use at the time of soil sample collection and they were categorised into agricultural land (paddy field and other crops), pastureland, unused land and residential areas. The physical texture of collected soil was recorded as sandy, silt or clay. We collected soil samples from 161 out of 330 townships throughout the country.

5.4.3 Soil sampling method

At each selected location, three holes were drilled at 30 cm, three at 60 cm, and three at 90 cm with a distance of 5 metres between each hole. Although the consensus guideline for *B. pseudomallei* environmental sampling recommends collecting 100 samples per location, our sampling method collected ten samples per site in order to cover a wider geographical area with limited resources [255]. Coordinates (latitude and longitude) at each sampling site were recorded using GPS GARMIN72H. We used a mechanical auger to dig the holes. To prevent cross contamination of sample collection between the holes, the auger and shovel were thoroughly cleaned with plenty of water and 70% alcohol between diggings. Two soil samples (10 gm each) were collected from each hole. For individual cultures, the first sample was kept separately, while the second sample from each hole was mixed together on site to make a pooled sample. Thus, a total of nine individual samples (10 gm each) and a pooled sample (90 g) were collected from each selected location. The purpose of making the pooled sample was to investigate sensitivity of isolation of *B. pseudomallei* compared to testing individual samples. The soil samples collected were kept in sealed plastic bags and transported in a cool box, protected from direct sunlight. All samples were transported as quickly as

possible to the Department of Medical Research (Yangon) for bacterial culture. All soil cultures were performed within 48 hours of the time of sample collection.

5.4.4 Culture of soil samples

First, individual soil samples and pooled soil samples were mixed with enrichment medium (threonine-basal salt solution plus colistin 50mg/L (TBSS-C50)) in sterile universal tubes. We used 10 ml of TBSS-C50 solution mixed with each 10 g individual soil sample and 90 ml of TBSS-C50 solution mixed with 90 g of pooled samples as per the consensus guideline [255]. Afterwards, the tubes were capped securely, vortexed for 30 seconds and incubated at 40°C in air for 48 hours. Next, 10 µl of the upper layer of the medium was sub-cultured on an Ashdown agar plate streaking to achieve single colonies inside a biosafety cabinet (BSC). The agar plates were then incubated at 40°C in air and examined daily in a BSC for the next 5 days. Bacterial colonies suspected to be *B. pseudomallei* were identified by the following morphological characteristics: pinpoint size, clear and pale pink colonies at 24 hours, turning into pinkish-purple, flat, and slightly dry colonies in the next 48 hours, characteristic colonies with a metallic sheen that gradually turns into a dry and wrinkled appearance at 96 hours [255]. Other common types of colonial variants such as smooth and shiny, mucoid or dry, or purple in shade were also considered as suspected colonies of *B. pseudomallei*.

5.4.5 Identification of *Burkholderia pseudomallei*

We performed oxidase and three-disc antibiotic (gentamicin, colistin and co-amoxiclav) screening tests on all colonies suspected of being *B. pseudomallei* [256]. The colonies with positive oxidase test and compatible antibiogram (resistance to gentamicin and colistin but susceptible to co-amoxiclav) were further tested with

confirmatory tests (*B. pseudomallei* specific latex agglutination test and Analytical Profile Index (API) 20NE) [257, 258]. Polymerase chain reaction (PCR) targeting the Type III Secretion System of *B. pseudomallei* was performed on a subset of 17 isolates that were confirmed by latex agglutination test and API 20NE.[259] The PCR method was validated at the Lao-Oxford- Mahosot Hospital-Wellcome Trust Research Unit [260]. Seven isolates also underwent Whole Genome Sequencing (WGS) [261].

Burkholderia thailandensis was also identified in our study. The profile of *B. thailandensis* is not included in the API20NE database, which gives similar results to *B. pseudomallei*, except that *B. thailandensis* tests positive for arabinose assimilation [255]. Therefore, isolates with a compatible colonial appearance and antibiogram that were negative for latex agglutination and positive for arabinose assimilation in the API 20NE were identified as *B. thailandensis*.

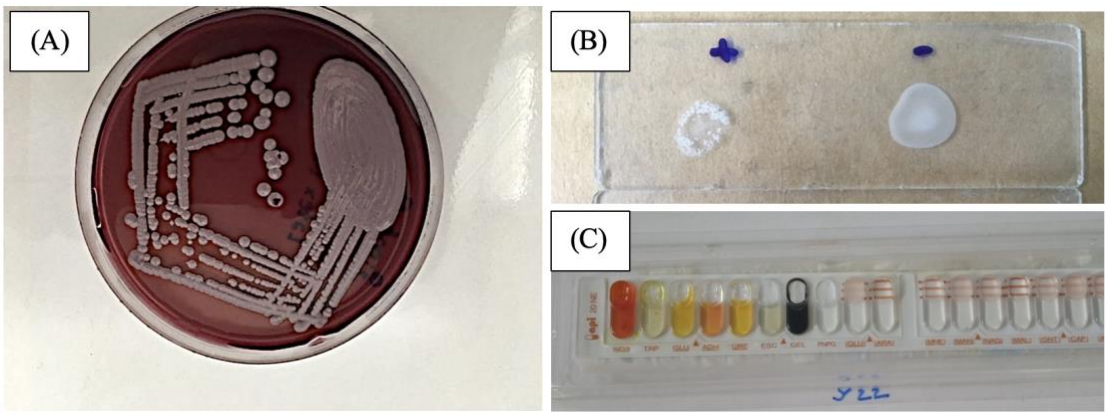


Figure 5.1 Identification of *Burkholderia pseudomallei*. (A) *B. pseudomallei* colonies on Ashdown's agar plate. (B) Positive and negative *B. pseudomallei* specific latex agglutination test (C) Analytical Profile Index (API) 20NE (Photo courtesy: *Dr Mo Mo Win*)

5.4.6 Statistical Analysis

Data are summarised as frequency and percentage unless stated otherwise. Due to overly dispersed count data, a negative binomial regression model was used for data

analysis. We defined outcome as the number of positive *B. pseudomallei* samples across all depths at each site. The following environmental factors were considered for the analysis: climate zone, seasons, soil type, soil depth and current land use status. Geographic locations of sampling sites across Myanmar were categorized into three climate zones according to Koppen Geiger climate classification: the tropical monsoon climate along the coastal region in the south, the tropical dry winter/dry steppe in the central plain region and the temperate dry winter in the north and eastern mountainous region [262].

To investigate the association between environmental factors and isolation of *B. pseudomallei*, the univariable negative binomial regression model was fitted. The environmental factors were treated as follows for the univariable analysis: climate zones (categorical: tropical monsoon, tropical dry winter/dry steppe and temperate dry winter), seasons (categorical: summer, monsoon and winter), soil type (categorical: clay, silt and sand), current land use status (categorical: residential, agriculture, pastureland and disused land). Multivariable analysis was not performed because only a few sites were positive for *B. pseudomallei* (31 out of 387 sites). This prevented adjusting for all variables in the model.

To explore the association between soil depth (three different depths at each site) and isolation of *B. pseudomallei*, we treated the outcome as the number of positive samples at site-depth level and fitted site as a random effect in the model to account for clustering of depths within each site. Interaction between season and soil depths was performed in a sub-group analysis.

5.5 Results

Between September 2017 and June 2019, we collected a total of 3870 soil samples from 387 sites throughout the country. The sampling sites covered 161 townships across all 15 states and regions of Myanmar.

5.5.1 Geographic distribution of *Burkholderia pseudomallei*

Details of the sampling periods (year, seasons) across all states and regions together with site and sample positivity are shown in Table 5.1 and Figure 5.2. In total, we isolated *B. pseudomallei* from 103 samples (3%) at 31 (8%) sites across three calendar years. A site was defined as positive if at least one of the samples was positive for *B. pseudomallei*. The positive sites were spread across 21 townships in 7 states and regions: Yangon, Kayin, Mon, Ayeyarwady, Bago, Magway and Rakhine (Table 5.1 and Appendix Table 1). The site positivity rate varied from 7% to 25% among positive states and regions. Ayeyarwady had the highest site positivity (25%), followed by Kayin (21%), Bago (16%) and Rakhine (15%) whereas the site positivity rates in Mon, Yangon and Magway were 12%, 11% and 7% respectively. Among the positive sites, the number of positive samples per site ranged from 1 to 9 with the median (interquartile range) of 3 (1 – 4). The number of positive samples per site are shown in Figure 5.2.

Table 5.1 Summary of sampling years and seasons together with population density in each state and region with site and sample positivity for *Burkholderia pseudomallei*

Year	Seasons	States and Regions	Population density (per km^2)	Site positivity	Sample positivity
2017	Rainy	Yangon	716	4/36 (11%)	13/360 (4%)
	Winter	Kayin	51	5/24 (21%)	11/240 (5%)
2018	Winter	Mon	167	3/26 (12%)	7/260 (3%)
	Winter	Kachin	18	0/28	0/280
	Summer	Sagaing	56	0/42	0/420
	Summer	Chin	13	0/18	0/180
	Rainy	Ayeyawady	176	9/36 (25%)	34 /360 (9%)
	Rainy	Bago	123	6/37 (16%)	18/370 (5%)
	Winter	Mandalay	199	0/24	0/240
	Winter	Magway	87	2/29 (7%)	5/290 (2%)
2019	Winter	Tanintharyi	32	0/20	0/200
	Summer	Rakhine	86	2/13 (15%)	15/130 (12%)
	Summer	Kayar	24	0/9	0/90
	Summer	Shan	37	0/36	0/360
	Rainy	Naypyitaw	164	0/9	0/90
Grand total			76	31/387 (8%)	103/3870 (3%)

The sample positivity rate, which was defined as the number of positive *B. pseudomallei* samples out of total samples collected in each state and region, was highest in Rakhine (12%), followed by Ayeyarwaddy (9%) , Kayin (5%) and Bago (5%). We did not identify *B. pseudomallei* in eight states and regions: Kachin, Sagaing, Chin, Mandalay, Tanintharyi, Kayar, Shan and Naypyitaw. The positive sites were located in all states and regions in the lower half of Myanmar except Tanintharyi which is located in the lowest and southernmost part of the country (Figure 5.2).

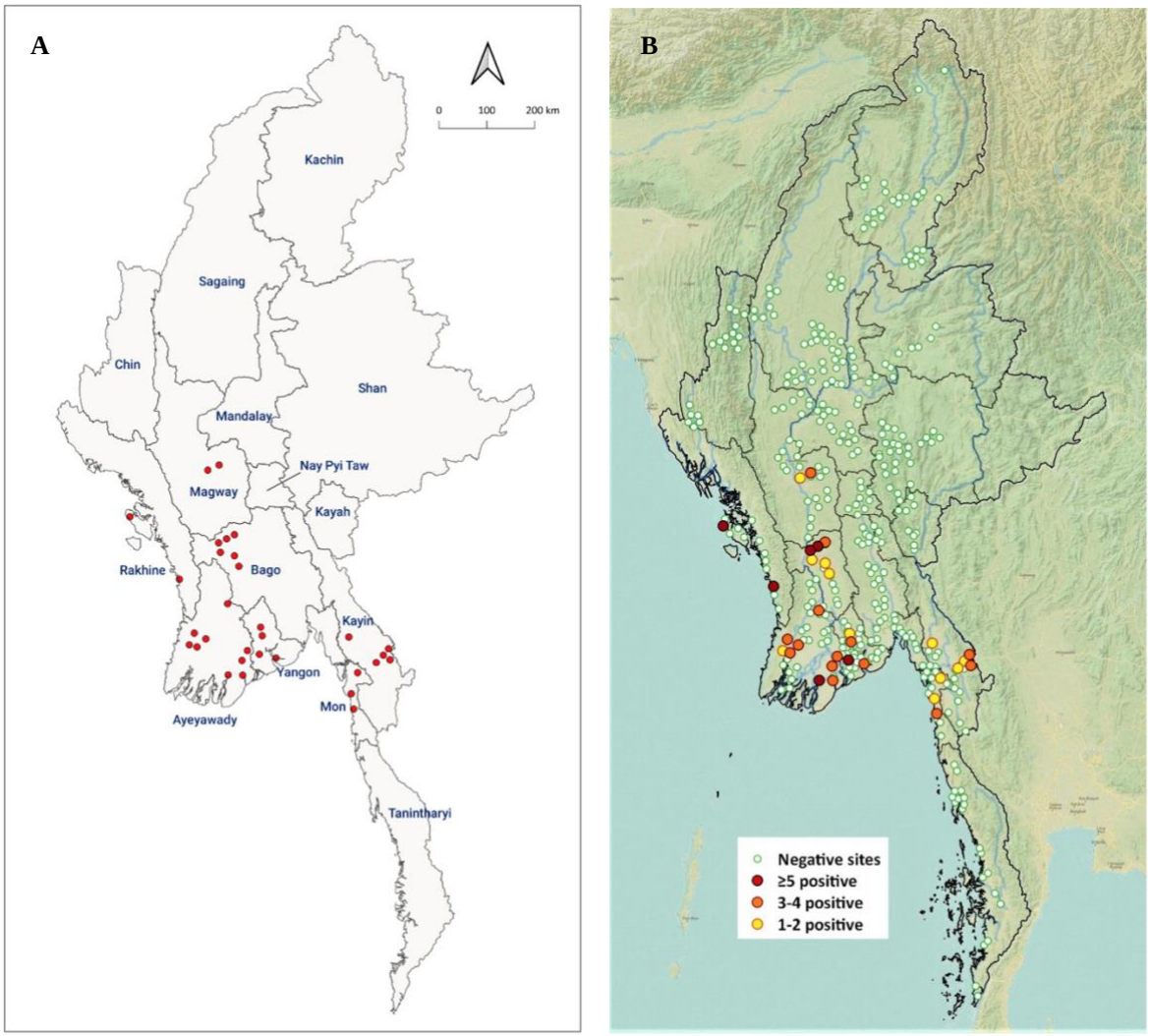


Figure 5.2. Distribution of *B. pseudomallei* positive sites across the country. (A) Map showing distribution of *B. pseudomallei* positive sites in 15 states and regions of Myanmar. Each red dot represents a *B. pseudomallei* positive site. (B) Map showing the number of positive samples among positive sites. Dark-red dot represent site with ≥ 5 positive samples, red dot represent site with 3-4 positive samples, yellow dot represent site with 1-2 positive sample and small white dot represent site negative for *B. pseudomallei*.

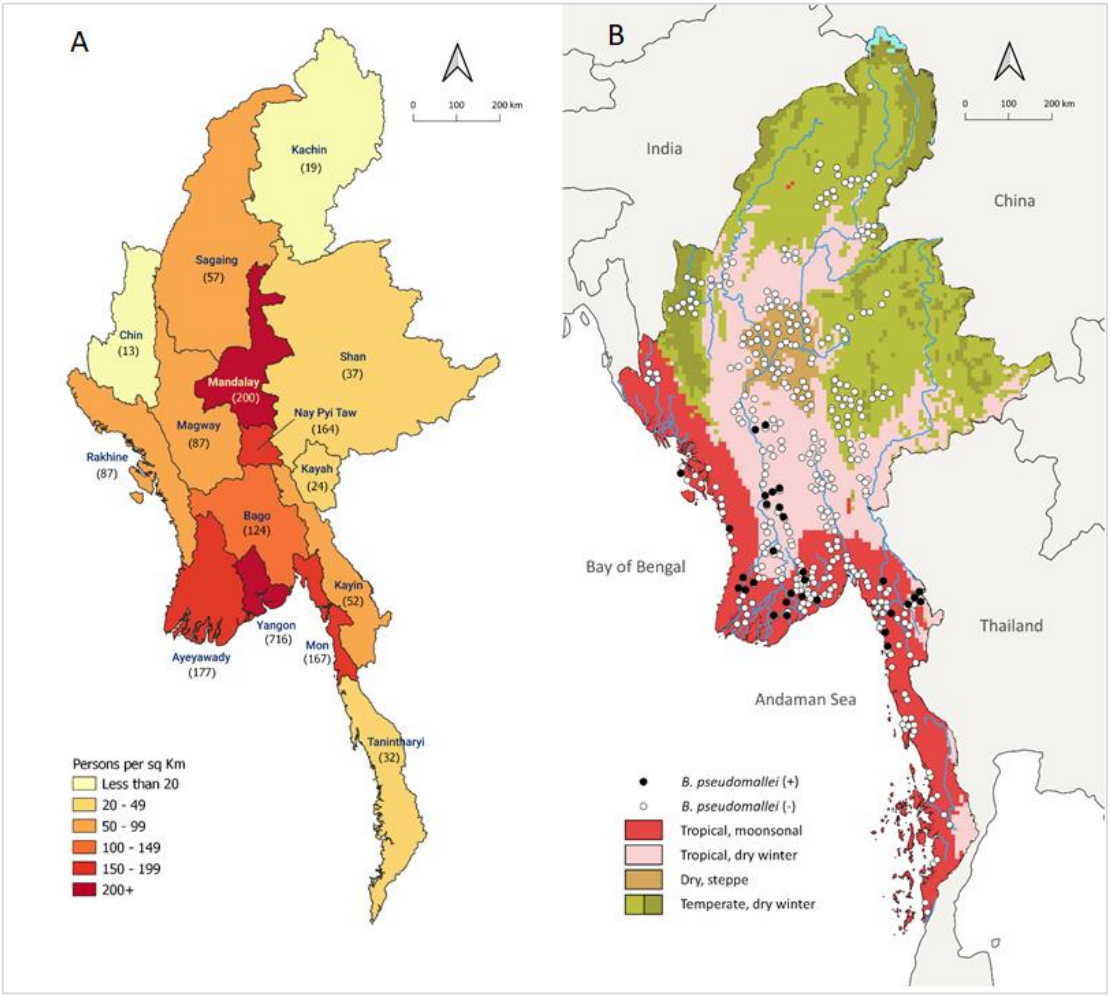


Figure 5.3. Population density and distribution *of B. pseudomallei* across Myanmar. A. Map of the states and regions of Myanmar with corresponding population density (person per square km). B. Map of Myanmar climate zones based on the Koppen Geiger climate classification (Source: http://koeppen-geiger.vu-wien.ac.at/present.htm). Black dots represent *B. pseudomallei*-positive sites (at least one sample positive for *B. pseudomallei*) and white dots represent *B. pseudomallei*-negative sites). [reproduced from the paper published under CC BY license][117]

5.5.2 Environmental factors and characteristics of collected soil samples

Characteristics of collected soil together with isolation of *B. pseudomallei* and *B. thailandensis* are shown in Table 5.2. Regarding the climate zones, most soil samples were collected from tropical dry winter (1700, 43.9%), followed by tropical monsoon (1400, 36.2%) whereas only 770 samples (19.9%) were from the temperate dry winter. In terms of season, most soil samples were collected in the winter (1550, 40.1%), one-

third in the rainy (1250, 32.3%) and the rest in the summer season. In regard to type of soil, the most common type was silt (2590, 66.9%), followed by clay (1200, 31%) whereas only 2% (80) of soil were sandy type. Almost 80% of collected soil samples were from agriculture land. The remaining were from disused land (360, 9.3%), residential areas (230, 5.9%) and pastureland (130, 3.4%).

B. pseudomallei was more frequently isolated in samples collected from tropical monsoon (4.8%) than tropical dry winter climate zone (2.1%). None of the samples collected from the temperate dry winter climate zone were positive for *B. pseudomallei* (Table 5.2 and Figure 5.3). A higher proportion of *B. pseudomallei* was isolated in samples collected during the rainy season (4.6%) compared to those collected during the winter (2%) and the summer (1.4%). Across all three depths, *B. pseudomallei* was isolated in similar proportions (2.4% each in 30 and 60 cm depth, and 2.6% in 90 cm depth). There were 6.3% of positive samples in sandy soil, 3% in clay soil and 2.4% in slit soil. *B. pseudomallei* isolation was highest in pastureland (8.5%), followed by disused land (5.8%) and agriculture land (2.2%). In residential areas, only 0.4% of soil samples was positive for *B. pseudomallei*.

Table 5.2. Environmental and soil characteristics together with *B. pseudomallei* and *B. thailandensis* positivity

Characteristics	Total N=3870	*B. pseudomallei* n=103	*B. thailandensis* n=135
Climate zones			
Tropical dry winter/ dry steppe	1700 (43.9%)	36/1700 (2.1%)	48/1700 (2.8%)
Tropical monsoon	1400 (36.2%)	67/1400 (4.8%)	76/1400 (5.4%)
Temperate dry winter	770 (19.9%)	0/770	11/770 (1.4%)
Season			
Winter (cool, dry)	1550 (40.1%)	31/1550 (2.0%)	70/1550 (4.5%)
Summer (hot, dry)	1070 (27.6%)	15/1070 (1.4%)	17/1070 (1.6%)
Rainy (monsoon)	1250 (32.3%)	57/1250 (4.6%)	48/1250 (3.8%)
Soil depth			
30 cm	1161 (30.0%)	28/1161 (2.4%)	41/1161 (3.5%)
60 cm	1161 (30.0%)	28/1161 (2.4%)	36/1161 (3.1%)
90 cm	1161 (30.0%)	30/1161 (2.6%)	43/1161 (3.7%)
pooled sample	387 (10.0%)	17/387 (4.4%)	15/387 (3.9%)
Soil type			
Silt	2590 (66.9%)	62/2590 (2.4%)	93/2590 (3.6%)
Sand	80 (2.1%)	5/80 (6.3%)	2/80 (2.5%)
Clay	1200 (31.0%)	36/1200 (3.0%)	40/1200 (3.3%)
Current land use			
Residential area	230 (5.9%)	1/230 (0.4%)	7/230 (3.0%)
Agriculture	3150 (81.4%)	70/3150 (2.2%)	112/3150 (3.6%)
Pastureland	130 (3.4%)	11/130 (8.5%)	2/130 (1.5%)
Disused land	360 (9.3%)	21/360 (5.8%)	14/360 (3.9%)

5.5.3 Association between environmental factors and isolation of *B. pseudomallei*

Rate ratios from the negative binomial regression analysis are shown in Table 5.3. Soil collected from the tropical monsoon climate zone had increased rate of *B. pseudomallei* isolation compared to those collected from tropical dry winter/ dry steppe zone [RR- 2.26; 95% CI (0.21 - 6.21), p-value=0.11]. Soil collected during the rainy season had increased rate [RR- 2.28; 95% CI (0.70 - 7.38), p-value=0.11] and summer season had

decreased rate [RR- 0.70; 95% CI (0.19 - 2.56), p-value=0.59] of *B. pseudomallei* isolation compared to those collected in the winter season. There was no association between the soil depth and isolation of *B. pseudomallei*, the rate ratios for 60 cm [RR- 1.03; 95% CI (0.49 - 2.17), p-value=0.95] and 90 cm [RR- 1.12; 95% CI (0.54 - 2.33), p-value=0.77] were not significantly different compared to 30 cm depth. Sandy type [RR- 2.61; 95% CI (0.08 – 86.86), p-value=0.59] and clay type of soil [RR- 1.25; 95% CI (0.41 – 3.84), p-value=0.69] had increased rate of isolation compared to the silt type. A higher rate of *B. pseudomallei* isolation was seen soil collected from agriculture fields [RR- 5.11; 95% CI (0.32 – 81.69), p-value=0.25], pastureland [RR- 19.46; 95% CI (0.46 – 816.13), p-value=0.12] and disused land [RR- 13.42; 95% CI (0.59 - 307.30), p-value=0.10] compared to those collected from residential areas. All 95% confidence intervals were wide and crossed the null value of one. Thus, associations between environmental factors and isolation of *B. pseudomallei* were not statistically significant in our study.

Table 5.3. Association between environmental factors (climate zones, season, soil type, soil depth and current land use status) and isolation of *B. pseudomallei*

Environmental factors	Unadjusted rate ratio (95% CI)	p-value
Climate zones		
Tropical dry winter/ dry steppe	*Reference*	
Tropical monsoon	2.26 (0.21 - 6.21)	0.11
Temperate dry winter[1]	NA	
Season		
Winter	*Reference*	
Summer	0.70 (0.19 – 2.56)	0.59
Rainy	2.28 (0.70 – 7.38)	0.17
Soil depth		
30 cm	*Reference*	
60 cm	1.03 (0.49 - 2.17)	0.95
90 cm	1.12 (0.54 - 2.33)	0.77
Soil type		
Silt	*Reference*	
Sand	2.61 (0.08 - 86.86)	0.59
Clay	1.25 (0.41 - 3.84)	0.69
Current land use		
Residential area	*Reference*	
Rice/ agriculture field	5.11 (0.32 - 81.69)	0.25
Pastureland	19.46 (0.46 - 816.13)	0.12
Disused land	13.42 (0.59 - 307.30)	0.10

[1] *B. pseudomallei* was not isolated in any of soil samples collected in "temperate dry winter" climate zone

5.5.4 Relation between seasons and soil depth on isolation of *B. pseudomallei*

The joint effect of seasons and soil depths on isolation of *B. pseudomallei* is shown in the Table 5.4. We observed variation in rate of isolation of *B. pseudomallei* in different soil depths by seasons. In the winter season, the rate of *B. pseudomallei* isolation was higher in soil collected from depths of 60 cm [RR- 2.51; 95% CI (0.64 - 9.83), p-value=0.19] and 90 cm [RR-3.30; 95%CI (0.86 - 12.65), p-value=0.08] compared to

those collected from 30 cm. In contrast, *B. pseudomallei* was less frequently isolated in these depths: 60 cm [RR-0.66; 95%CI (0.25 - 1.76), p-value=0.41] and 90 cm [RR-0.67;95%CI (0.26 - 1.75), p-value=0.43] compared to the shallow depth 30 cm in the rainy season. However, the effect of season on soil depth for isolation of *B. pseudomallei* was not statistically significant given wide confident intervals and large p-values.

Table 5.4. Joint effect of season and soil depth on isolation of *B. pseudomallei*

Characteristics	Proportion of sample positive for *B. pseudomallei*	Rate Ratio (95% CI)	p-value
Winter season			
30 cm	4/ 465 (0.9%)	1 (*Reference*)	
60 cm	10/ 465 (2.3%)	2.51 (0.64 - 9.83)	0.19
90 cm	12/ 465 (2.6%)	3.30 (0.86 - 12.65)	0.08
Summer season			
30 cm	5/321 (1.6%)	1 (*Reference*)	
60 cm	5/321 (1.6%)	1.00 (0.16 - 6.33)	1.00
90 cm	4/321 (1.3%)	0.77 (0.11- 5.22)	0.79
Rainy season			
30 cm	19/375 (5.1%)	1 (*Reference*)	
60 cm	13/375 (3.5%)	0.66 (0.25 - 1.76)	0.41
90 cm	14/375 (3.7%)	0.67 (0.26 - 1.75)	0.43

5.5.5 Isolation of *B. pseudomallei* in pooled samples

Among the 387 pooled samples, *B. pseudomallei* was isolated in only 17. The overall isolation rate among pooled samples was 4.4%. Among 31 positive sites, *B. pseudomallei* was isolated in only half of the pooled samples. In one site, *B. pseudomallei* was isolated in the pooled sample but not in any of the individual samples.

5.5.6 Isolation of *Burkholderia thailandensis*

The presence of *B. thailandensis*, a close relative of *B. pseudomallei*, was also detected in 72 out of 387 sites (19%) and 135 out of 3870 soil samples (4%) from 13 states and regions (Appendix Table 2 and Appendix Figure 1). Both species were identified in 4 out of 387 sites but they were not isolated together in any single soil sample.

5.6 Discussion

This is the largest environmental soil study to date that looked at distribution of *B. pseudomallei* in Myanmar in terms of geographic coverage and sample size. This study aimed to identify the presence of *B. pseudomallei* in environmental soil and map the areas where humans and animals are at risk of melioidosis. This study confirmed a widespread distribution of *B. pseudomallei* in environmental soil in several states and regions of Myanmar.

B. pseudomallei was isolated in 103 samples from 31 sampling sites across seven states and regions. The regions with positive sites were located in the lower half of Myanmar along the coast in the south and central plains, where population density is high. A recently published surveillance study that was carried out between 2017 -2019 in four tertiary hospitals in Yangon found 21 cases of melioidosis, and all of them were from four regions where *B. pseudomallei* was isolated in our study. This finding implies that residents in those regions are at risk of contracting melioidosis [116].

In our study, we did not identify *B. pseudomallei* in samples collected from Kachin, Sagaing, Chin and Shan states in the northern part and Tanintharyi region in the southernmost part of the country despite environmental conditions that have been predicted to be favourable for existence of *B. pseudomallei* in those areas by a modelling study [127]. The southernmost part is the coastal region located between

Andaman Sea in the west and western part of Thailand in the east. In the neighbouring province of Thailand, there have been reports of human and animal melioidosis cases since 2006, and presence of *B. pseudomallei* in the environment [263, 264]. There are several reasons that could explain not isolating the organisms in our study. One of them is the imperfect sensitivity of culture methods in isolating *B pseudomallei* from environmental soil compared to molecular detection methods such as real-time PCR [265]. Also, there has been report of random distribution of *B. pseudomallei* in the environment [266]. Our soil samples were collected at a single point in time, which might have coincided with the dry season. All those factors suggest possibility of the presence of *B. pseudomallei* in the soil in those regions of Myanmar but simply they were not identified in our study.

In addition, many positive sites were located in close proximity to rivers and tributaries in the Ayeyarwady delta region. It has been suggested that rivers may act as carriers and sentinels for *B. pseudomallei* [267]. The finding of a high number of positive sites in the delta region in our study could be explained by the fact that heavy rainfall could erode contaminated soils, which are then transported downstream by the rivers and deposited in the delta region.

Many of the positive sites were located in the coastal region of Myanmar which has a tropical monsoon climate with heavy rainfall each year [81]. In contrast, *B. pseudomallei* was less frequently isolated in central plain regions with tropical dry winter climate having a low annual rainfall [81]. The north and eastern parts of Myanmar are mountainous regions having a temperate dry winter climate and none of the soil samples collected from those regions were positive for *B. pseudomallei*. The effect of climate on melioidosis epidemiology has been documented and heavy rainfall

has been shown to predict presence of *B. pseudomallei* in the environmental soil probably due to high moisture levels in the soils [268, 269].

Furthermore, a higher proportion of soil samples collected during the rainy season was positive for *B. pseudomallei* (RR - 2.28; 95% CI 0.70 - 7.38, p-value = 0.17). A similar finding, abundance of *B. pseudomallei* in the soils during the rainy season, has been reported from India [270]. Additionally, Thailand, Cambodia and Laos have reported a high incidence of melioidosis cases during the rainy season [271, 272]. Therefore, clinicians in Myanmar should be aware that melioidosis could present as community acquired pneumonia and sepsis, especially during the rainy season. Findings from our study also provide further evidence on the effect of climate and rainfall on environmental distribution of *B. pseudomallei*.

B. pseudomallei was isolated in all types of soil (sand, silt and clay) but more frequently in the sandy type (RR - 2.61; 95% CI 0.08 - 86.86, p-value = 0.69). This finding is in line with an earlier study reporting isolation of *B. pseudomallei* in soil with predominant sandy type [273]. *B. pseudomallei* was isolated in soils collected from all types of land use. However, a higher isolation rate was observed in the soil collected from agriculture land (RR - 5.11; 95% CI 0.32 - 81.69, p-value = 0.25), pastureland (RR - 19.46; 95% CI 0.46 - 816.13, p-value = 0.12), disused land (RR - 13.42; 95% CI 0.59 - 307.3, p-value = 0.10) compared to those collected from the residential areas. Isolation of *B. pseudomallei* in agricultural land especially rice fields has been well reported in previous studies carried out in the region. For instance, *B. pseudomallei* was isolated in 32% of paddy field soils and 60% of paddy field water samples in Thailand, and 36% of paddy field soil samples in Laos [274]. Thus, people engaging in agriculture and rice farmers are particularly at risk of contracting melioidosis because it is the place where

the most contact occurs between humans and contaminated soil. Not wearing protective footwear and gloves could further increase the risk of melioidosis. Additionally, cattle and buffalo are commonly used as draft animals in the agricultural sector in Myanmar and these animals could also be at risk.

B. pseudomallei was isolated in soil collected from all three depths (30 cm, 60 cm and 90 cm) with similar isolation rates. However, the rate of isolation among the three different depths varied by season. In the winter season, *B. pseudomallei* was isolated more often in soil collected from 60 (RR - 2.51; 95% CI 0.64 - 9.83, p-value = 0.19)or 90 cm (RR - 3.30; 95% CI 0.86 - 12.65, p-value = 0.08) than those collected from 30 cm. The reverse finding was observed in the rainy season. This finding may support the hypothesis of vertical migration of *B. pseudomallei* together with the elevation of the water table after heavy rainfall and the proliferation of the organisms in the soil during the dry seasons [275, 276]. Although this finding in our study is not conclusive, it is likely that the organisms migrate to deeper soil and thrive there during dry months. Therefore, it might be good practice to collect soil samples from different depths for environmental surveys and deeper than 30 cm in the dry months.

In this study, we also assessed utility of pooling of multiple soil samples compared to individual samples in regard to isolation of *B. pseudomallei.* Only 17 of the 31 pooled samples from the positive sites yielded positive isolates, whereas 14 failed to isolate the organisms. In contrast, the pooled sample from one site was positive for *B. pseudomallei*, whereas the nine individual samples were all negative. This finding suggests that pooling of multiple soil samples worked partially. It also points out how difficult it is to isolate *B. pseudomallei* from environmental soil samples and the possibility of false negative results by culture method. For this reason, it would be

worthwhile to collect multiple soil samples and use different methods for identification of *B. pseudomallei* before concluding that a particular site is negative [277].

We also identified *B. thailandensis,* a close relative of *B. pseudomallei,* but they are believed to be non-pathogenic to human and animals, in 72 (19%) sites and 135 soil samples (4%) in this study. These two closely related species were not found together in a single soil sample, but in four sites, they were isolated from different soil samples. This finding may be related to the fact that the two species compete with each other, as evidenced by a previous study that showed inhibition of growth and motility of *B. thailandensis* by a compound secreted by *B. pseudomallei* [278]. The presence of both species in a single field has also been reported by a study in Thailand [279].

5.7 Limitations

There are several limitations in the study. First, we collected only 10 samples from each sampling site instead of 100 as suggested by an international consensus guideline [255]. This is because we aimed to explore a large geographic area throughout the country with limited resources. Second, soil samples from armed conflict and remote areas were not included in this study due to safety and logistic reasons. Third, soil samples were collected at each site at one time point rather than at different time points throughout the year. Fourth, the consensus culture method used in this study is less sensitive than other methods such as initial screening with PCR after enrichment followed by different culture methods on PCR-positive samples [277]. Finally, failure to isolate *B. pseudomallei* in pooled samples including positive sites and a positive pooled sample with negative individual samples may suggest inconsistent isolation of the organisms by the culture method. All the above limitations may contribute to reduction in the chance of isolating *B. pseudomallei* and underestimate the geographic distribution in

Myanmar. Therefore, study findings should be interpreted in the light of these limitations, and it should be noted that negative findings in some regions do not necessarily indicate that *B. pseudomallei* is absent.

5.8 Implications

A widespread distribution of *B. pseudomallei* in several regions and a historically low incidence of melioidosis in Myanmar suggest the disease is under-recognized in the country. As an agriculture-based economy, most of the workforce is engaged in agriculture-related jobs in rural areas and they are particularly at increased risk [280, 281]. Additionally, diabetes mellitus, a well-documented risk factor for melioidosis, is on the rise in Myanmar, further increasing its burden [282]. Therefore, it is also important for practising clinicians to be aware that melioidosis is still around and can present with a variety of clinical presentations such as pneumonia, sepsis or abscesses in internal organs.

Another issue related to diagnosis of melioidosis is the difficulty in picking up suspected colonies especially when the laboratory staff are not familiar with isolation of *B. pseudomallei* [240, 283]. Thus, it is advisable to strengthen laboratory systems and provide necessary training to staff especially in the regions where *B. pseudomallei* is endemic. In Cambodia, a recent training initiative has raised awareness of this disease, and similar events should be considered in Myanmar [284].

In Thailand and Laos, incidence of melioidosis was consistently low and under-recognized before the disease was actively looked for during the 1990s [124, 285, 286]. The situation in Myanmar is likely to be similar. In addition, whole genome sequencing of *B. pseudomallei* isolates from Myanmar showed genetic diversity suggesting long-term endemicity of melioidosis in Myanmar [261].

5.9 Conclusion

Melioidosis is a serious and potentially fatal disease caused by saprophytic bacilli living in environmental soil and water in the tropics. This nationwide study confirmed a widespread distribution of *B. pseudomallei* in environmental soil in several states and regions of Myanmar. A lack of awareness among clinicians and very limited diagnostic facilities in rural areas are likely to lead to under-recognition of this disease in Myanmar, where melioidosis is expected to be prevalent. Findings from this study inform that clinicians should be aware of possibility of melioidosis in patients with pneumonia, sepsis and abscesses, especially if they have a history of contact with soil and occupational exposure during the rainy season. Clinical and surveillance studies should be initiated in regions where *B. pseudomallei* was isolated to get a better understanding of the epidemiology and true burden of melioidosis in Myanmar.

Chapter 6

A forum theatre public engagement project on "Fever and Antibiotic use"

6.1 Abstract

Background

Myanmar is in the Southeast Asia region where the risk of emergence and spread of antibiotic resistant bacteria in humans is high. Antibiotics are accessible without prescription and practice of self-medication with antibiotics is common in Myanmar and likely to be a major driver of antimicrobial resistance. We organized and evaluated a forum theatre public engagement about antibiotic use for febrile illness.

Method

The engagement activities took place in slum areas of a peri-urban township in Yangon. To develop storylines for the forum theatre performances, story gathering workshops were conducted in the preparatory stage. Between September and October 2018, forum theatre plays were organised in the selected areas. After each play, the organizers delivered four simple keys messages from the WHO's world antibiotic awareness week (2017) materials: 1) Antibiotics are medicines used to treat bacterial infections 2) Antibiotics are not useful for coughs and colds 3) Never use leftover antibiotics or share antibiotics with others, 4) Prevent infections by regularly washing hands, preparing food hygienically, avoiding close contact with sick people, and keeping vaccinations up to date. We evaluated the engagement activities using pre- and post-theatre focus group discussions (FGDs) with attendees.

Results

Two themes: “Fever and antibiotics” and “Mixed medicine”, derived from five story gathering workshops were used to develop storylines for the forum theatre plays. A total of ten forum theatre plays were organized and the engagement activities reached 1175 community members. Four themes emerged from the content analysis of FGDs after the performances: 1) Dissemination of knowledge, 2) Enjoyment and fun, 3) Willingness to support and suggestions for future engagement activities, and 4) preference over traditional health talks. The analysis showed improvement of knowledge related to antibiotic use, attendees’ enjoyment of the plays, community support and useful suggestions for future engagement activities.

Conclusion

Forum theatre could be used as an innovative, fun and participatory approach in public engagement to raise awareness about antibiotic use in the community.

6.2 Introduction

Bacterial infection was a major cause of morbidity and mortality worldwide during the pre-antibiotic era. The discovery of penicillin in 1928 followed by mass production in the 1950s have contributed to a substantial reduction in mortality associated with bacterial infections and improved overall life expectancy [64]. Global under-five mortality dropped from 216 deaths per 1000 livebirths in 1950 to 39 deaths per 1000 livebirths in 2017 [287]. Over the same period, global life expectancy increased from 48 years to 70 years for men and from 53 years to 76 years for women [287]. This positive impact has also been contributed to by improvements in nutrition, access to clean water, sanitation, and vaccine provision. The efficacy of antibiotics has, however, been compromised by an increase in antimicrobial resistance (AMR) worldwide, which threatens to erode the benefits of antibiotics.

Global antibiotic consumption increased by 65% between 2000 and 2015, mainly attributed to increased usage in LMICs. Without any intervention, it is projected that antibiotic consumption will increase by 200% by 2030 compared to 2015 [288]. A recent spatial modelling study using multiple data sources estimated that there was a 46% increase in global antibiotic consumption in humans between 2000 and 2018 [69]. Inappropriate use of antibiotics is widespread in Asia and WHO country situational analyses in the region have highlighted misuse of antibiotics in primary care as a major issue in some countries, for example antibiotic prescription for upper respiratory tract infection (URTI) varied from 34% in Bhutan to 94% in India [47].

Self-medication with antibiotics, often regarded as inappropriate use, is common practice in Asia [74]. The prevalence of such practice varied across the countries in Asia ranging from 7.3% in Indonesia to 85.6% in India [73]. This suggests a lack of

understanding about antibiotics and awareness of AMR in the community as well as poor governance and policy on antimicrobial use.

Myanmar is a developing country in the WHO Southeast Asia region where the risk of emergence and spread of antibiotic resistant bacteria in humans is high [289]. A WHO survey on usage of medicine across public health facilities in Myanmar reported prescription of antibiotics in 87% of patients with URTI in primary care [290]. Likewise, a fever study in a peri-urban region of Myanmar found antibiotic prescription in almost 70% of febrile outpatients in hospital setting and 41% of general patients in medical NGO-led primary care clinics[19].

Although Myanmar has a National Action Plan (NAP) for containment of AMR which was released in 2017, policy and regulation for antimicrobial use is still in its infancy [47, 291]. Nevertheless, the country is already facing the problem of AMR. The national AMR surveillance data in 2017 reported a high level of antibiotic resistance in bacterial isolates; methicillin-resistant *Staphylococcus aureus* (40%), extended spectrum beta-lactamase producing *Enterobacteriaceae* (48%), carbapenem-resistant *Acinetobacter* species (9%) and *Pseudomonas* species (19%), and vancomycin-resistant *Enterococcus* species (15%) [75]. A similar but a higher level of antibiotic resistant and multi-drug resistant bacteria isolated from paediatric patients was reported in a recent study [292]. Although antibiotics are listed as prescription-only medicines in Myanmar, they are accessible without prescription from pharmacies and local drug shops [293]. Drug shop surveys done in two cities of Myanmar confirmed that antibiotics including amoxicillin, cotrimoxazole, erythromycin, metronidazole, tinidazole, ciprofloxacin, norfloxacin and neomycin were sold without prescription [294, 295]. Furthermore, drug shops sell mixed medicine packets (called "***set say***" in the local language), which contain an

assortment of 4 -5 tablets or capsules, usually contain antibiotics and sometime steroids [293]. As such people are taking those packets available from the local drug stores with or without realizing that they are taking antibiotics.

Additionally, the practice of self-medication with antibiotics is common in Myanmar. A recent nationwide survey on public knowledge, practices and awareness of antibiotics and AMR reported that more than half of participants gave a history of taking antibiotics without prescription purchased mainly from drug stores or pharmacies [75]. The survey on treatment-seeking behaviour of acute fever in the malaria endemic regions of Myanmar found that about one-fourth of patients treated their illness by self-medication [182].

In line with WHO-endorsed Global Action Plan to tackle AMR, one of the objectives of Myanmar's NAP is to raise awareness and understanding of AMR through effective communication, education and training [291]. A recent qualitative study examining patients' perceptions on febrile illness and medicines in the context of point of care CRP testing in Chiang Rai, Thailand and Yangon, Myanmar, showed that treatment seeking behaviour was likely to be influenced by their perceptions of illness [296]. Given the accessibility of antibiotics without prescription in Myanmar, it is crucial to understand how communities make health seeking decisions and how they use antibiotics for febrile illnesses. We developed a public engagement initiative using a forum theatre approach to get a better understanding of antibiotic use for acute fever and to raise awareness about appropriate use of antibiotics in the community.

Forum theatre (also known as "Boal's Theatre, 'Theatre of the Oppressed' or 'Theatre for Development') was invented by a Brazilian theatre director, Augusto Boal in the 1970s. In forum theatre the audience can interact with the actors and explore different

solutions to a given problem [297]. The plays are performed twice with some oppressed characters in the plays. Typically, the first play ends with an unresolved problem or a tragic ending. In the replay, audience members (also known as 'spectactors') are invited to take on the roles of the oppressed characters and they are given opportunities to solve the problems to reach a better outcome. An important requirement of forum theatre is that good facilitation is needed to ensure smooth flow of the plays and active participation of audience members [297].

The forum theatre technique has been used as an engagement activity in different areas of biomedical science such as in clinical trials, health promotion, health education and training of health professionals [298-303]. The reason for choosing forum theatre for our public engagement was that it is entertaining, interactive, does not rely on the literacy of the audience and encourages active participation of the audience to share their knowledge with others.

6.3 Objectives

The main objective of this engagement project was to understand antibiotic use for febrile illness and to raise awareness about appropriate use of antibiotics in the community. We evaluated the engagement activities in order to:

1) assess whether the engagement project fulfilled its objective
2) identify what knowledge was disseminated through the engagement
3) provide feedback to researchers for future engagement activities

6.4 Methods

We collaborated with an established local theatre group, “Art for All”, who had received training on “forum theatre performance” from Pan Intercultural Arts (London).

The group was started as a community-led performance group in 2011 and has been involved in a number of engagement projects to raise awareness and implement behavioural change related to health issues such as reproductive health, HIV/ AIDS, and social and justice issues such as human trafficking, gender equality, gender-based violence among young people and their communities across Myanmar (https://www.britishcouncil.org.mm/programmes/arts/human-drama). We obtained permission to carry out the engagement project from the Yangon regional health department. Project plans were discussed with administrative authorities in the project area.

6.4.1 Project location

The engagement project was carried out in Hlaing Thar Yar (HTY) Township located in the western part of Yangon (former capital of Myanmar). It is one of the biggest townships in the country with an estimated population of over half a million (678,867) according to the 2019 inter-censal survey. Within the township, five locations were selected for the engagement activities after discussion with township administrative authorities. These locations were purposively selected because they were overcrowded with poor living standards, insufficient access to clean water and lack of basic sanitary conditions. All these conditions are well documented to be associated with a high burden of infectious diseases. Most residents living in these areas are manual labourers and factory workers with below average socio-economic status.



Figure 6.1 The map shows the location of Hlaing Thar Yar township in Yangon region (engagement project location)

6.4.2 Designing the forum theatre performance

Story-gathering workshops

As forum theatre uses real-life scenarios, we arranged story gathering workshops to identify common health concerns related to febrile illnesses in the community. Community members from different backgrounds were invited to the workshops, including community leaders, housewives, manual workers, and members of civil society organizations. Common illnesses, access to antibiotics, use of mixed medicine packets, and treatment-seeking for acute fever were discussed during the workshop. We

carried out five story gathering workshops in the selected areas in July and August 2018. Between 25 and 35 community members participated in each workshop, which lasted approximately one hour. Consensus was used to prioritize the issues raised during the workshops. For the forum theatre play, two topics related to febrile illness were chosen: "Fever and antibiotic use" and "Mixed medicines".

Table 6.1 Timeline of public engagement activities

No	Engagement activities	Timeline
1	Consultative meeting with health and general administrative authorities	April - May 2018
2	Story-gathering workshops	July - August 2018
3	Development of storyline, scripts and songs	July - August 2018
4	Forum theatre performance	September - October 2018
5	Evaluation of engagement activities	September - October 2018



Figure 6.2. Pictures of story gathering workshops at preparatory stage

Storylines

Together with the project team, the theatre group developed songs and scripts for the forum theatre plays on the topics chosen following the workshops. To provide a sense

of familiarity, we used colloquial language in the script. The storylines centred on a sick febrile person (a protagonist) self-medicated with antibiotics bought over the counter or who took a "mixed medicine" packet purchased from local shops. At various scenes in the play, members of the family, neighbours, and community tried to persuade the sick person not to take antibiotics without prescription. In both storylines, the sick person ended up in the hospital due to the side effects of antibiotics or mixed medicine, and failure to seek proper medical advice from health professionals.



Figure 6.3. Pictures of development of scripts and song (left), and rehearsal of forum theatre play (right)

Forum theatre plays

The theatre group that consisted of 10 youth actors from both genders was led by a project manager. The plays were performed by seven actors over five or six scenes and lasted about 45–60 minutes, including the replay which was assisted by a facilitator. Before the start of the play, a facilitator explained the nature of the forum theatre to the audience and encouraged them to participate actively in the replay. At certain scenes during the replay when there was a chance to persuade the main character not to take antibiotics without prescription, the facilitator paused the replay and asked the audience whether they would like to make alternative suggestions. Then the audience members were invited to the stage to take the role of a family member, neighbour or community

member of the main character. In the replay, alternative endings were possible, including convincing the sick individual to seek medical attention instead of self-medicating with antibiotics and taking “mixed medicine” bags. In each replay, two to four audience members actively participated and took of the role of the actors. Four key messages were delivered after each play. These were based on the WHO’s World Antibiotic Awareness week advocacy materials: 1) Antibiotics are medicines used to treat bacterial infections 2) Antibiotics are not useful for coughs and colds 3) Never use leftover antibiotics or share antibiotics with others 4) Prevent infections by regularly washing hands, preparing food hygienically, avoiding close contact with sick people, and keeping vaccinations up to date. We conducted pre and post focus group discussions (FGD) on the same day. We made a short film to document engagement activities and the film can be accessed here (https://www.youtube.com/watch?v=4dC4PLygsHM&t=7s).



Figure 6.4. Pictures of scenes from the forum theatre plays

6.4.3 Evaluation

We recorded the number of audience members for each performance and collected qualitative information from a subset to capture the perspectives of the people we engaged. To achieve our objectives, we used four main evaluation questions to guide

the evaluation process. The questions and data collection methods were outlined in Table 6.2.

Table 6.2. Evaluation questions and data collection methods

Evaluation questions	Data collection method
1. What is the community's understanding about the role of antibiotics to treat febrile illness?	Pre- and post-performance FGDs, intervention action of audience members in the replay
2. Have the engagement activities improved the community's understanding of antibiotics and their appropriate usage?	Pre- and post-performance FGDs
3. What did the community think about the forum theatre approach for public engagement?	Pre- and post-performance FGDs
4. What were the challenges during the process of conducting these activities?	Field notes and reflective analysis throughout the engagement process with different level of authorities

Qualitative data collection: Qualitative interviews were done by two researchers: an experienced qualitative researcher led the interviews assisted by a research assistant. Both are Myanmar nationals, and the lead researcher has several years of qualitative research experience and is familiar with the local context.

Focus group discussions

In total, four FGDs (pre- and post-performance) were carried out in four out of ten plays. The guideline questions for FGDs were developed and they are outlined in Table 6.3.Three questions were discussed for pre-performance FGD: 1) What are antibiotics? 2) What are they used for? 3) Does all fever need antibiotics? For the post-performance FGD, five additional questions were discussed to capture what they learned, their opinion on the replay part of the performance engaging with some of the audience, their feedback and suggestions on the forum theatre engagement activity.

Table 6.3. Questions used in pre- and post-performance focus group discussion for evaluation

Pre-performance questions	Post-performance questions
1) What are antibiotics?	1) What are antibiotics?
2) What are they used for?	2) What are they used for?
3) Does all febrile illness need antibiotics?	3) Does all febrile illness need antibiotics?
	4) What did you learn from the performances?
	5) What do you think about the replays with audience interventions?
	6) If you had a chance to intervene, would you have done it and why?
	7) What are the things you dislike about the performance?
	8) Do you have any general recommendations for the performance/project (place, timing, etc.)?

FGD participants: A total of 40 individuals took part in four FGDs before and after the performance. We selected the participants based on their availability and willingness to participate for both pre- and post-performance FGDs. In addition, individuals who actively interacted with the actors during the replay part of the performance were also invited to join the post-performance FGDs.

Procedure: All FGDs were conducted on the same day and same location of the engagement performance activity. Burmese language ("official language" of Myanmar) was used to communicate and discuss with the participants during the FGDs. During the FGDs, all discussions were recorded on audiotape. Before the start of the FGDs, the lead researcher explained about the general purpose of the engagement activity, asked

their consent to participate in the FGDs informing them that their identities would not be revealed when analysing the audio recordings, and advised them of the importance of keeping confidentiality in regard to the discussion within the group. The guideline questions outlined in the Table 6.3 were used to probe the discussion during the FGDs. Each FGD lasted approximately 40 to 60 minutes.

Data analysis: All the recorded audio tapes were transcribed verbatim. The transcripts in Burmese were then translated into English which were analysed by the content analysis method. The method involved determining the presence of certain words, themes, or concepts and grouping them into similar categories (identifying categories). After that, various major and minor categories were compared and contrasted. As a final step, the original transcripts were reviewed and checked to make sure all the information that needed to be categorised had been covered. We also performed triangulation of the findings within the project team to verify the integrity of the references drawn from the discussion in the FGDs. We recorded the number of audiences for each theatre play including individuals who actively engaged during the replays of the performance.



Figure 6.5. Pictures of pre- and post-performance focus group discussion

6.4.4 Ethical consideration

For this implementation and evaluation of a public engagement activity using forum theatre we obtained permission from the Yangon regional health department and general administrative authorities of the township where the engagement activities happened. We also discussed evaluation of the project with the Oxford Tropical Research Ethics Committee (OxTREC) who granted a waiver from ethics committee review. We obtained verbal consent from those who participated in FGDs. We did not record participants' names, addresses and all other information that might identify participants were removed from the transcripts.

6.5 Results

Between September and October 2018, we organized ten forum theatre plays on two themes: "Fever and antibiotics" and "Mixed medicines". The engagement activities reached 1175 community members. Thirty-six individuals actively engaged and interacted with the actors during the replays. Detailed information on the date, location and number of audiences for each play are shown in Table 6.4.

Table 6.4. Date, location, theme of the plays and number of audiences members for the forum theatre performance

No	Date	Location of engagement	Theme	No of audience	No of audience who engaged in the replays
1	8/9/18	Ward 1	Fever and antibiotics	106	4
2	9/9/18	Shwe Lin Pan	Fever and antibiotics	110	4
3	22/9/18	Ward 6	Mixed medicines	126	4
4	23/9/18	Ward 1	Mixed medicines	136	4
5	23/9/18	Shwe Lin Pan	Mixed medicines	83	4
6	6/10/18	Ward 6	Mixed medicines	104	3
7	7/10/18	Ward 5	Fever and antibiotics	132	3
8	14/10/18	Ward 5	Mixed medicines	132	2
9	18/10/18	Ward 19	Fever and antibiotics	123	4
10	18/10/18	Ward 19	Mixed medicines	123	4
Total				**1175**	**36**

Four themes emerged from the analysis of qualitative data collected during the FGDs: 1) Dissemination of knowledge 2) Having fun and enjoyment, 3) Willingness to support and suggestion for future engagement activities, 4) Preference of forum theatre over traditional methods of engagement e.g., health talks.

Dissemination of knowledge

Before the engagement, most participants had only heard the term "antibiotics", but they were unclear about what antibiotics were and when these antibiotics should or should not be taken.

Following are some quotes from participants about their understanding about antibiotics:

"I know antibiotic such as amoxicillin and they are used when fever is very high" (FGD 2)

"Antibiotics needed to be taken when you get dog bites, or attacked by any poisonous animals like snakes" (FGD 1)

"Antibiotics can also be used when we have pains in arms and legs with high fever" (FGD 3)

"I heard antibiotics are used for diarrhoea" (FGD 4)

"I know that we use antibiotics to stop spreading the diseases" (FGD 4)

"We can use antibiotics to prevent seasonal flu" (FGD 1)

"I think antibiotics are used for TB (tuberculosis) and I don't think we should use for other diseases" (FGD 3)

"I also heard that antibiotics are used to help other medicine's effects" (FGD 2)

"Different antibiotics need to be used for children. They must not be the same with antibiotics for adults" (FGD 2)

There are some quotes above that illustrate a correct understanding of antibiotics, while others illustrate common misconceptions about the use of antibiotics.

After the forum theatre engagement activity, most FGD participants said that antibiotics are medicine used to kill bacteria: '***poe tat say* (germ killer)**' in Burmese language.

"Now I know antibiotics are medicines which kill bacteria" (FGD 2)

"Now I know that antibiotics are used to kill bacteria and we shouldn't take them every time we have symptoms like sneezing and headache" (FGD 1)

"We learnt that we shouldn't take mixed medicines on our own without doctors' prescription" (FGD 2)

"We should not take antibiotics and analgesic all the time" (FGD 3)

"And we learned that being superstitious is not good" (FGD 2)

"We should stop people from using antibiotics carelessly" (FGD 1)

"We realized that we should go to clinics/hospitals rather we go the drug store and get random drugs" (FGD 1)

Having fun and enjoyment

It was evident from our observations and FGDs that audience members enjoyed the performances. In addition to expressing their overall satisfaction with the engagement, FGD participants commented on specific parts of the plays that they enjoyed.

"I really enjoyed the part of the play where May Thu (a sick character in the play) resisted to go to the hospital" (FGD 4)

"I like those kinds of short plays. They are interesting and very informative" (FGD 2)

"Kids are happy as well" (FGD 1)

Willingness to support and suggestions for future activities

It was noted that many participants were willing to support similar events in the future and wanted to see other different health related issues.

"We will support if you are doing more project like this" (FGD 2)

"We would like to see more plays on TB (tuberculosis), Hepatitis C and also women topics like using contraceptives" (FGD 2)

"For next time, please do health education talk on TB, we also have a lot of immigrants, who need to see this kind of show" (FGD 2)

"We also want to see plays on drugs use, especially for kids. We have kids who use drugs in school, we don't know what we should do about that" (FGD 2)

Additionally, they offered some practical suggestions for future engagement events.

"Performance overall was good, but we think the performers could have paid more attention the background settings to look more realistic e.g., the pharmacy, they could have built a small shop on stage or something similar a separate dispensing room" (FGD 2)

"Regarding the timing, we prefer Sundays because we have to go work on Saturday as well" (FGD 4)

Preference of forum theatre over traditional methods of health education delivery

During the FGD, participants also expressed their comparison between forum theatre and conventional health education.

"We prefer this kind of health education compared with the formal health talks. This one is more interesting" (FGD 2)

"And this kind of performance is more fun and enjoyable and also more informative" (FGD 2)

In addition to data derived from the FGDs, we obtained additional insights from actions by participants during the replay. By witnessing actions of audience members who intervened during replay, we noted and learnt the following:

1. Most of the audience members who actively engaged in the replays seemed to not exactly know in what ways self-medication with antibiotics was inappropriate. The advice that they gave when persuading the main character was to go and get proper treatment from medical doctors.

2. Myanmar culture has a strong hierarchy within the family and the engaged person who took the role of younger family members faced more challenges. At some points, they almost failed when trying to convince senior family members not to self-medicate with antibiotics.

3. In most cases, audience members who played the role of neighbours were willing to assist financially if the sick person had financial hardship to seek medical care.

Challenges during organization of the engagement activities and lessons learnt

Due to heavy rain during the late monsoon season, we had to postpone and reschedule the forum theatre plays several times. The problem was compounded by flooding shortly after the rain due to the poor drainage systems in the selected areas. In addition, the rain before the plays discouraged members of the community from coming to the plays. Several of the play venues offered by the administrative authorities were Buddhist religious buildings, which may have excluded people from other religions. In the weekdays, most residents were at work, so we could only organize engagement activities at the weekends.

We noted that it was important to establish a good relationship with community leaders and administrative authorities from the start in order to get their active participation for the smooth operation of all engagement activities. The ward administrators and community leaders were invited to all engagement activities, which partly contributed to getting community trust.

6.6 Discussion

In this public engagement project, we used the forum theatre technique to engage with the marginalized communities in a peri-urban area of former capital city, Yangon.

As part of our engagement activities, we successfully organized ten forum theatre plays on two themes: “Fever and antibiotics” and “Mixed medicine”. We also made a short film to document overall activities of the engagement project. We evaluated the project to capture the information conveyed and the participants’ impressions of our

engagement activities. Additionally, we provided insights into potential challenges that we encountered during the different stages of the engagement. Overall, the engagement activities reached over 1000 community members with active participation in all stages. Public engagement has been increasingly used in science and research to actively engage and inform the general public about the latest research and developments in science. Most engagement activities are usually held in non-academic venues like cafés, local pubs and theatres in order to provide a friendly and lively atmosphere to the public[304]. For example, the first "Science Café" was introduced in Laos in 2016 and the first "Pint of Science" was launched in Thailand in 2017 [304, 305]. Also, drama and film have been used in neighbouring countries for engagement activities such as "Village Drama Against Malaria" in rural Cambodia and "Under the Mask" film about tuberculosis in Thailand-Myanmar border [306, 307] but none of these engagement activities deployed the forum theatre technique.

Formal health education is common in the community, but it is traditionally one way communication and interaction with audience is minimal. By contrast, our public engagement was a two-way communication, which involved listening to what the engaged community had to say through story gathering workshops as well as giving them information on the topic of interest. Furthermore, members of the engaged community, including community leaders, were invited to participate in all stages of engagement from the initial story gathering stage to theatre plays and evaluation. The importance of community involvement throughout the engagement project was also highlighted by a community engagement about malaria using village drama in rural Cambodia [308].

Forum theatre is an audio-visual interactive type of activity in which the audience can actively engage during the replay part to change the direction of the storyline. This encouraged them to use their reasoning ability to make a rational decision. In addition, the audience were able to express their own ideas and experience related to the topic of the engagement with others. This gave them a unique and creative experience while learning new things on the topics. Furthermore, forum theatre engagement empowered the audience by giving them the feeling of being able to influence the storyline to reach a positive outcome.

Considering the prevalence of inappropriate use of antibiotics and self-medication with antibiotics in developing countries, raising awareness about appropriate antibiotic use could be a useful strategy to tackle the problem of AMR. Findings from pre- and post-performance FGDs in our evaluation showed that there was an improvement in their knowledge about antibiotic use. A similar finding was demonstrated by a community engagement project using a film about tuberculosis along Thailand-Myanmar border. An evaluation of questionnaires before and after watching the film showed a significant improvement in self-perceived knowledge about tuberculosis among attendees [307]. In another study, theatre-based educational initiatives were used to raise awareness and knowledge about eclampsia in rural Bangladesh [300].

The findings of our study might be applicable to peri-urban slum areas of other low- and middle-income countries, particularly in terms of active community participation, interactive communication, and community empowerment. However, it is important to note that the characteristics of forum theatre groups played an important role in achieving the active participation of audience members. Our theatre group was made up of enthusiastic youth performers who had several years' experience in theatre plays

for raising awareness and implementation of behavioural changes related to a variety of health and social issues.

The audience also expressed enjoyment of forum theatre engagement and their willingness to support such kind of activities in the future. This highlights the importance of a participatory and entertaining approach in campaigning to disseminate and raise awareness about important health-related issues. A participatory approach which used forum theatre technique to raise awareness about importance of flu vaccination among health care workers in Italy also demonstrated a positive impact on the message delivered [299].

Based on our observation, field notes and the number of attendees at each event, we conclude that the preparatory phases were important in establishing effective communication with both authorities and local communities. Through audience participation in the replay part, we were able to learn how the community made decisions regarding antibiotic use. Targeting behaviour change at all levels of the community, such as at the individual, the family, the neighbours, and the wider community, might have a lasting effect on appropriate antibiotic use especially in the context of over-the-counter availability of antibiotics.

To the best of our knowledge, this is the first public engagement project which deployed the forum theatre technique to raise awareness about appropriate antibiotic use in Myanmar. Instead of using simple questionnaires, we did our evaluation qualitatively through a series of before and after engagement FGDs to capture the audience's impression and immediate impact of the engagement activities. The number of attendees in each performance reflected the people reached by the forum theatre performance.

6.7 Limitations

There are some limitations in evaluation of our public engagement project. First, evaluation was done by the organizers who arranged the engagement activities; therefore, it was not independent. Second, there might have been selection bias as we were only able to interview the audience members who agreed to take part in FGDs. Third, the evaluation was done at a single time point on the same day as the plays. Therefore, the findings might reflect their immediate impression of the engagement activities and we were not able to assess the retention of knowledge or behavioural change after the engagement. Fourth, the engagement was done in peri-urban slum areas and future activities should involve rural communities as the majority of the Myanmar population are rural dwellers. Thus, findings from the evaluation should be interpreted in light of the limitations outlined above.

6.8 Conclusion

Forum theatre could be an effective and fun way for interactive public engagement around health-related topics. This engagement project met its aims of understanding antibiotic use in the community and raising awareness about appropriate use. The audience expressed their willingness to support future engagement activities. In addition to improving knowledge about antibiotics, attendees were able to express and share their ways of tackling issues around the theme played by actively interacting with actors on stage. In summary, forum theatre could be an innovative approach of engaging and promoting health-related knowledge in the community.

Chapter 7

General conclusion

7.1 Overview

The main aim of this thesis is to propose suitable empirical antibiotic treatments and evaluate their cost-effectiveness for non-malaria febrile illness in rural Myanmar. Other factors will affect how antimicrobials are used to treat febrile illness in practice. Variation in antibiotic prescribing among primary care doctors was assessed and quantified from the prescriber perspective. Antibiotics are available over-the-counter in Myanmar. Perceptions and understanding about antibiotics use for acute fever in the community were explored through public engagement using the "forum theatre" technique. Other aims include systematic gathering of all reports of neglected tropical infectious diseases in Myanmar and investigating nationwide geographic distribution of *Burkholderia pseudomallei* in the environmental soil, a potentially important cause of febrile illness in the country.

Here each chapter is summarised, and the key findings are discussed in relation to the thesis aims, their implication to improve management of acute febrile illness in Myanmar. The results and limitations are discussed in the Myanmar context and directions for future work are identified.

7.2 Summary of chapters

In Chapter 2, a systematic review was undertaken to document all reported neglected tropical infectious diseases in Myanmar. Melioidosis and rickettsioses were added to the recognised list as neglected diseases of regional interest. A literature search was

done in four international databases and one national database in Myanmar (locally published studies). All the retrieved records were systematically screened, and the findings were summarised.

Chapter 3 defined empirical treatment with selected antibiotics considering common pathogens responsible for non-malaria febrile illness in Myanmar. A decision tree model was developed to evaluate the cost-effectiveness of different empirical antibiotic regimens for children (1 - 12 years) and adolescents and adults (> 12 years). As part of quantifying uncertainty of parameters, expert elicitation was carried out for a set of parameters that had the greatest influence on the model outcome. Probabilistic sensitivity analysis was carried out by propagating the uncertainty of parameters throughout the decision tree. The incremental cost-effectiveness ratios (ICERs) were presented in the cost-effective plane. The cost-effectiveness acceptability curves (CEAC) and cost-effectiveness acceptability frontier (CEAF) were used to identify the empirical antibiotics that have the highest probability of incremental net benefit compared with current practice.

Chapter 4 was a secondary analysis of the data derived from a clinical trial that investigated the impact of point of care C-reactive protein testing in the management of acute febrile illness in Myanmar. A multi-level model was used to assess the variation of antibiotic prescription among the primary care doctors. Patient-level covariates were selected a priori to adjust in the multivariable model. Variance partition coefficient (VPC) and median odds ratios (MOR) were used to express inter-prescriber variability of antibiotic prescription.

Chapter 5 investigated and mapped the geographic distribution of *B. pseudomallei*, a causal organism of melioidosis, in environmental soil in Myanmar. This is the first

study of its kind in Myanmar in terms of geographic coverage. A fixed interval sampling method was used to collect the soil sample from three different depths. Consensus culture method was used for culture and isolation of *B. pseudomallei.* All suspected colonies were confirmed by positive latex agglutination test and API 20NE. A negative binomial regression model was used to analyse the data.

Chapter 6 explored the community's understanding of antibiotic use for febrile illness through public engagement activities using the "forum theatre" technique. The engagement project was carried out in collaboration with a well-established "Arts for All" local theatre group. Storylines for "forum theatre" were developed through multiple story-gathering workshops with community members. The engagement activities were evaluated through focus group discussion (FGD) with audience members.

7.3 Key findings and implications to policy

7.3.1 Systematic review on neglected tropical infectious diseases in Myanmar

Studies from Myanmar are rarely included in international systematic reviews as most of them are published in local journals. This systematic review was carried out in accordance with the PRISMA guideline to collate all available information on neglected tropical diseases (NTDs) described in Myanmar in the past 100 years until 2021 for the first time including grey literature. Of 5573 records screened, 651 articles were included, 428 (65%) were published after 2000, 190 (30%) were locally published articles, theses or dissertations, 360 (55%) were from two regions (Yangon and Mandalay) of Myanmar. This finding suggests uneven geographic distribution of

included studies across the country and might reflect the interest of researchers and proximity to research institutions when selecting study sites.

Another important finding is that the review identified a range of viral and bacterial NTDs that are known to be associated with febrile illness and sepsis. These include arthropod-borne viral infections particularly dengue, salmonellosis, melioidosis, rickettsioses and leptospirosis. As reported by neighbouring countries in the region, it is highly likely that these diseases could also be common causes of acute febrile illness in Myanmar, with implications for the choice of antibiotics for empirical treatment strategies. This evidence could be further improved by setting up multiple fever aetiology surveillance sites in different regions of Myanmar.

7.3.2 Cost-effectiveness analysis of empirical antibiotic treatments for non-malaria febrile illness

Management of acute febrile illness after excluding malaria is challenging especially in resource-limited settings where diagnostic facilities are scarce; there is limited training available for basic healthcare workers and understanding is poor about likely underlying pathogens. With a substantial decline in malaria burden in the past decades, the majority of acute febrile illnesses are caused by non-malaria pathogens in Myanmar, although the current unstable situation and collapse of the healthcare system means this may be reversed again in the future [140]. A decision tree model was used for a cost-effectiveness analysis of different empirical antibiotic regimens for all non-malaria febrile syndromes. Four oral empirical antibiotic regimens (amoxicillin, azithromycin, combination of amoxicillin and azithromycin, and doxycycline) were considered; doxycycline treatment was only for patients over 12 years of age.

All empirical antibiotic regimens were found to be cost saving while achieving more DALYs averted compared to the current practice of care in both age groups. Empirical treatment with amoxicillin and azithromycin was found to save 6.5 US$ and 7 US$ per DALY averted in children whereas treatment with doxycycline, amoxicillin, azithromycin saved 19.8 US$, 16.2 US$ and 15.2 US$ per DALY averted in adolescents and adults compared to current practice. In both age groups, CRP guided empirical regimens were found to be highly cost-effective compared with the current practice. Among them, CRP guided azithromycin was the most cost-effective in children having 4.4 US$ per DALY averted and CRP guided doxycycline was the most cost-effective in adolescents and adults, having 4.3 US$ per DALY averted. These findings suggest that both strategies offer good value for money and may be considered as potential interventions to evaluate for the management of non-malaria febrile illness in rural Myanmar.

Additionally, empirical treatment and CRP guided empirical treatment could reduce about 67% and 22% unnecessary antibiotic treatments respectively compared with current practice. This finding implies that both strategies could cut costs related to unnecessary treatment as well as reducing the economic cost of AMR contributed by antibiotic treatment. A lesser reduction of unnecessary prescription with CRP guided treatment could be explained by the fact that testing of CRP for patients with URTI (most of them are viral infections) and a threshold of 10 mg/L has a specificity of 49%, meaning that half of the viral URTIs would receive empirical treatment. Nevertheless, both strategies are likely to reduce unnecessary antibiotic prescription in management of acute febrile illness.

To my knowledge, this is the first cost-effectiveness analysis of different empirical antibiotic treatments for non-malaria febrile illness in Myanmar. Findings from this study are broadly in agreement with findings from previous cost-effectiveness analyses of surveillance guided treatment and CRP guided treatment for acute febrile illness in the region [190, 309]. One of the limitations of this study is the uncertainty of the parameters as they derived from multiple different sources. However, uncertainty of parameters was captured by conducting expert elicitation.

7.3.3 Variability of antibiotic prescription for acute febrile illness among primary care doctors

Another angle that this thesis looked into is variation of antibiotic prescription among primary care doctors for management of acute fever. In particular, inter-prescriber variation was assessed and quantified. Patient characteristics known to be associated with antibiotic prescription were adjusted to check their influence on this variation. Our study found a substantial inter-prescriber variation in antibiotic prescription which remained after accounting for differences in patient clinical presentations and CRP test results. It is worthy noting that all prescribing doctors practised in the same organization under a uniform management guideline. This finding suggests that the decision to prescribe antibiotics depends mainly on individual prescriber preference rather than patients' clinical characteristics. But we were not able to take prescriber characteristics into account in the analysis as those variables were not captured in the original trial. This finding also contributes further evidence of variation in antibiotic prescription among primary care doctors in low- and middle-income countries for patients with acute fever.

An important implication of this study finding is that prescriber variation needs to be considered when designing trials that aim to reduce antibiotic prescription. Failure to account for this could lead to studies being underpowered, inappropriate analyses and subsequently render the risk of making incorrect conclusions [215, 216]. Furthermore, antibiotic stewardship programs should aim to target prescribers with a high prescribing rate rather than trying to reduce overall prescription of a clinic or hospital given the fact that overall prescription may be made up of over- and under-prescribers.

7.3.4 Geographic distribution of *Burkholderia pseudomallei* in environmental soil in Myanmar

B. pseudomallei causes melioidosis which was first described in Myanmar in 1911 but the disease has been rarely reported in the last 100 years. Our nationwide environmental soil study identified *B. pseudomallei* in seven out of fifteen states and regions. Of the 387 sampling sites, 31 (8%) had one or more positive samples and of the 3,870 samples cultured, 103 (2.7%) tested positive for *B. pseudomallei*. This finding implies that the causative organism of melioidosis is widely distributed in environmental soil in Myanmar. Although the consensus culture method was used in our study, it is known to have a low sensitivity of isolating *B. pseudomallei* compared to direct detection by PCR [265]. As a consequence, our study finding is likely to underestimate the true distribution.

We identified *B. pseudomallei* more frequently in soils collected during the monsoon season, from agricultural and pastureland. This suggests that people engaging in agricultural work are at risk of contracting melioidosis particularly if they have other predisposing factors such as diabetes or chronic renal disease. Clinicians practising in Myanmar should be aware of melioidosis as a potential cause of community acquired

sepsis and pneumonia especially in patients with occupational risk during the rainy season.

7.3.5 A forum theatre public engagement around "fever and antibiotic use"

In Myanmar, the national action plan to tackle AMR was released in 2017 and is in the early stages of development and implementation [291]. Antibiotics are accessible without prescription and the practice of self-medication with antibiotics is common [293, 310]. In the light of this, it is important to understand how antibiotics are being used for febrile illness and raise awareness about inappropriate use in the community. Forum theatre was used as a tool for our public engagement project. The forum theatre technique allows the audience to express their ideas through actively interacting with actors during the replay part.

Our evaluation of the engagement activities through focus group discussion found that the audience gained knowledge about antibiotics, enjoyed the theatre performance, preferred engagement activities over traditional health talks and they were willing to support future engagement activities. Due to the single time point of the evaluation, we were unable to assess how long the knowledge gained and behaviour changes lasted after the engagement activities.

This finding suggests that forum theatre could be used as a fun and engaging way to do public engagement. We believe that engaging with the community throughout the project until evaluation was the key for successful implementation of engagement activities in our case. In the era of AMR, forum theatre could be an innovative tool to actively engage and disseminate knowledge about inappropriate antibiotic use within the community especially in the context of over-the-counter availability of antibiotics.

7.4 Future direction of work

Although the systematic review identified diseases such as melioidosis, rickettsioses and leptospirosis that are commonly associated with community-acquired sepsis and acute febrile illness in neighbouring countries, they have been out of sight for several decades in Myanmar. Thus, further work is necessary to investigate the true burden of these diseases in different regions of Myanmar. Observational or surveillance studies together with strengthening of laboratory systems might be helpful for this purpose.

The decision tree cost-effectiveness analysis demonstrated the cost-savings of empirical treatment and cost-effectiveness of CRP guided empirical treatment with selected antibiotics compared with the current practice of care in rural Myanmar. These findings warrant further evaluation preferably with clinical trials alongside aetiological investigation of acute fever. For this purpose, novel study designs such as platform trials may be helpful. They are also known as multi-arm, multi-stage design trials and allow investigators to compare multiple treatment options or to add or remove arms during the trial [311]. When evaluating health care interventions such as diagnostics or empirical treatments that affect antibiotic consumption, it is important to take into account the cost of AMR contributed by antibiotic consumption. Otherwise, it could lead to sub-optimal policy recommendations of interventions [185]. There are very few studies that have thoroughly explored economic cost of AMR per antibiotic consumption. Further studies are needed in that area to quantify more precise economic costs of AMR associated with different types of antibiotic consumption.

In our secondary analysis, it was found that variation of antibiotic prescription among primary care doctors remained after accounting for differences in patient's clinical

presentation. Future studies should involve collection of prescriber characteristics to determine which prescriber characteristics could influence antibiotic prescription in order to aid in implementation of antibiotic stewardship programmes. Also, this finding should be further investigated and confirmed in larger public hospital or clinic settings in other low- and middle-income countries.

Finding of a widespread distribution of *B. pseudomallei* in the environmental soil in Myanmar is valuable information for further research. Clinical or surveillance studies should be set up starting from the regions where the organisms were identified. This should be accompanied by awareness campaigns about melioidosis among practising clinicians and provision of necessary training to the laboratory workforce.

Evaluation of our engagement activities showed that forum theatre could be used as a feasible tool for public engagement activities to disseminate antibiotic-related knowledge. Future engagement activities should involve extending AMR related topics to raise awareness about the risk of inappropriate antibiotic use. Additionally, evaluation at multiple time points should be considered to capture long-term retention of knowledge gained and possible behaviour changes after engagement activities.

The systematic review in chapter one summarised all reported NTDs in Myanmar, some of them are pathogens or diseases commonly associated with acute febrile illness in the region. This finding together with literature informed the selection of suitable antibiotics for empirical treatment for management of non-malaria febrile illness in chapter two. Assessing and quantifying variation of antibiotic prescription among primary care doctors for acute fever in chapter four provided another angle that should be considered when designing trials targeting to reduce antibiotic prescription as well as implementation of antibiotic stewardship program. Public engagement activities on

"fever and antibiotic use" explored understanding about antibiotics use for acute fever in the community. Perspectives on antibiotic use from both prescribers and consumers are crucial in informing policy makers in formulating appropriate AMR containment programme. This thesis addresses both perspectives from secondary data analysis and a public engagement project. Last but not least, finding from the soil study confirmed a widespread distribution of *B. pseudomallei* in environmental soil highlighting the need for practising clinicians to consider melioidosis as a possible aetiology for community acquired pneumonia and sepsis in Myanmar.

7.5 Conclusions

This thesis summarised reported neglected tropical infectious diseases in Myanmar. A number of diseases commonly associated with febrile illness were identified. A comprehensive cost-effectiveness analysis of different empirical antibiotic treatments for non-malaria febrile illness was performed through a decision tree modelling approach. Related to this, variability of antibiotic prescription for acute fever among primary care doctors was demonstrated by secondary analysis of a clinical trial dataset. Community understanding of antibiotic use for acute fever was explored through public engagement activities using forum theatre performance. Lastly, widespread distribution of *B. pseudomallei* in environmental soil in Myanmar was confirmed by a large nationwide soil survey and the results were mapped.

Other published works and Conference presentations

Other published works during the DPhil

I have also contributed to the following publications as co-author during the DPhil.

1. Althaus, T., R. C. Greer, **M. M. M. Swe**, J. Cohen, N. N. Tun, J. Heaton, S. Nedsuwan, D. Intralawan, N. Sumpradit, S. Dittrich, Z. Doran, N. Waithira, H. M. Thu, H. Win, J. Thaipadungpanit, P. Srilohasin, M. Mukaka, P. W. Smit, E. N. Charoenboon, M. J. Haenssgen, T. Wangrangsimakul, S. Blacksell, D. Limmathurotsakul, N. Day, F. Smithuis, and Y. Lubell. "Effect of Point-of-Care C-Reactive Protein Testing on Antibiotic Prescription in Febrile Patients Attending Primary Care in Thailand and Myanmar: An Open-Label, Randomised, Controlled Trial." *Lancet Glob Health* 7, no. 1 (Jan 2019): e119-e31. https://dx.doi.org/10.1016/s2214-109x(18)30444-3.

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1. "**Mapping and geographic distribution of *Burkholderia pseudomallei* in Myanmar**". American Society of Tropical Medicine and Hygiene's Annual Meeting, virtual event (November 2020).

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Appendix for chapter 2

Table 1. List of NTDs by WHO, US CDC and PLoS major NTDs

WHO	US CDC	PLoS major NTDs
1. Buruli ulcer	1. Buruli ulcer	**Protozoan infections**
2. Chagas disease	2. Chagas disease	1. Amoebiasis
3. Dengue and Chikungunya	3. Cysticercosis	2. Balantidiasis
4. Dracunculiasis (guinea-worm disease)	4. Dengue fever	3. Chagas Disease
5. Echinococcosis	5. Dracunculiasis (guinea-worm disease)	4. Giardiasis
6. Foodborne trematodiases	6. Echinococcosis	5. Human African Trypanosomiasis
7. Hyman African trypanosomiasis (sleeping sickness)	7. Fascioliasis	6. Leishmaniasis
8. Leishmaniasis	8. Human African Trypanosomiasis (African Sleeping Sickness)	**Helminth infections**
9. Leprosy (Hansen's disease)	9. Leishmaniasis	1. Taeniasis-Cysticercosis
10. Lymphatic filariasis	10. Leprosy (Hansen's disease)	2. Dracunculiasis
11. Mycetoma, chromoblastomycosis and other deep mycoses	11. Lymphatic filariasis	3. Echinococcosis
12. Onchocerciasis (river blindness)	12. Onchocerciasis	4. Food-borne Trematodiases
13. Rabies	13. Rabies	5. Loiasis, Lymphatic filariasis
14. Scabies and other ectoparasites	14. Schistosomiasis	6. Onchocerciasis
15. Schistosomiasis	15. Soil-transmitted Helminths (STH) (*Ascaris*, hookworm, and whipworm)	7. Schistosomiasis
16. Soil-transmitted helminthiases	16. Trachoma	8. Soil-transmitted Helminthiases (Ascariasis, Hookworm Diseases, Trichuriasis, Strongyloidiasis)
17. Snakebite envenoming	17. Yaws	9. Toxocariasis
18. Taeniasis/ Cysticercosis		10. Other Larva Migrans
19. Trachoma		
20. Yaws (Endemic treponematoses)		

		Viral infections 1. Dengue 2. Japanese encephalitis 3. Yellow fever 4. Other arboviral infections 5. Rabies 6. Rift Valley fever 7. Viral hemorrhagic fevers **Bacterial infections** 1. Bartonella 2. Bovine Tuberculosis in humans 3. Buruli ulcer 4. Cholera 5. Enteric pathogens (*Shigella*, *Salmonella*, *E. coli*) 6. Leprosy 7. Leptospirosis 8. Relapsing fever 9. Trachoma 10. Treponematoses (Bejel, Pinta, Syphilis, Yaws) **Fungal infections** 1. Eumycetoma 2. Paracoccidiodomycosis **Ectoparasitic infections**

		1. Scabies 2. Myiasis

Table 2. Search terms used in the systematic review

Database	Search Terms
PubMed	**Search date:** 22 June 2021 **Details:** (((((("Myanmar"[Mesh]) OR ((myanmar[Text Word] OR burma[Text Word] OR rangoon[Text Word] OR yangon[Text Word] OR magway[Text Word] OR mandalay[Text Word] OR naypyidaw[Text Word] OR kayah[Text Word] OR ayeyarwady[Text Word] OR bago[Text Word] OR kachin[Text Word] OR sagaing[Text Word] OR kayin[Text Word] OR tanintharyi[Text Word] OR rakhine[Text Word])))))) AND ((("Buruli Ulcer"[Mesh]) OR "Chagas Disease"[Mesh]) OR "Dengue"[Mesh]) OR "Chikungunya Fever"[Mesh]) OR "Dracunculiasis"[Mesh]) OR "Echinococcosis"[Mesh]) OR "Trematode Infections"[Mesh]) OR "Trypanosomiasis"[Mesh]) OR "Leishmaniasis"[Mesh]) OR "Leprosy"[Mesh]) OR "Elephantiasis, Filarial"[Mesh])) OR "Dermatomycoses"[Mesh]) OR "Onchocerciasis"[Mesh]) OR "Rabies"[Mesh]) OR "Ectoparasitic Infestations"[Mesh]) OR "Trichuriasis"[Mesh]) OR "Strongyloidiasis"[Mesh]) OR "Helminths"[Mesh]) OR "Snake Bites"[Mesh]) OR "Taeniasis"[Mesh]) OR "Trachoma"[Mesh]) OR "Yaws"[Mesh]) OR "Amebiasis"[Mesh]) OR "Balantidiasis"[Mesh]) OR "Giardiasis"[Mesh]) OR "Loiasis"[Mesh]) OR "Toxocariasis"[Mesh]) OR "Larva Migrans"[Mesh]) OR "Encephalitis, Japanese"[Mesh]) OR "Yellow Fever"[Mesh]) OR "Arbovirus Infections"[Mesh]) OR "Hemorrhagic Fevers, Viral"[Mesh]) OR "Bartonella"[Mesh]) OR "Tuberculosis, Bovine"[Mesh]) OR "Cholera"[Mesh]) OR "Shigella"[Mesh]) OR "Enterobacteriaceae"[Mesh]) OR "Leptospirosis"[Mesh]) OR "Borrelia Infections"[Mesh]) OR "Treponemal Infections"[Mesh]) OR "Paracoccidioidomycosis"[Mesh]) OR "Myiasis"[Mesh]) OR "Scrub Typhus"[Mesh]) OR "Typhus, Epidemic Louse-Borne"[Mesh]) OR "Melioidosis"[Mesh])) OR ((buruli ulcer*[Title/Abstract] OR mycobacterium ulcerans[Title/Abstract]))) OR ((chagas[Title/Abstract] OR american trypanosomiasis[Title/Abstract]))) OR dengue[Title/Abstract]) OR chikungunya[Title/Abstract]) OR ((Dracunculiasis[Title/Abstract] OR guinea-worm disease[Title/Abstract] OR guinea-worm infection[Title/Abstract] OR Dracunculosis[Title/Abstract]))) OR ((echinococcosis[Title/Abstract] OR echinococcus infection[Title/Abstract]))) OR ((foodborne trematodiases[Title/Abstract] OR clonorchiasis[Title/Abstract] OR Opisthorchiasis[Title/Abstract] OR Fascioliasis[Title/Abstract] OR Paragonimiasis[Title/Abstract]))) OR ((trypanosomiasis[Title/Abstract] OR sleeping sickness[Title/Abstract]))) OR ((leishmaniasis[Title/Abstract] OR leishmania infection*[Title/Abstract]))) OR ((leprosy[Title/Abstract] OR hansen* disease[Title/Abstract]))) OR ((lymphatic filariasis[Title/Abstract] OR filarial elephantiases[Title/Abstract]))) OR ((mycetoma*[Title/Abstract] OR chromoblastomycosis[Title/Abstract] OR madura foot[Title/Abstract] OR actinomycetoma*[Title/Abstract] OR eumycetoma*[Title/Abstract] OR dermatomycos*[Title/Abstract] OR blastomycos*[Title/Abstract] OR hyalohyphomycos*[Title/Abstract] OR lobomycos*[Title/Abstract] OR sporotrichos*[Title/Abstract] OR tinea[Title/Abstract] OR onychomycos*[Title/Abstract]))) OR ((onchocerciasis[Title/Abstract] OR river blindness[Title/Abstract]))) OR rabies[Title/Abstract]) OR ((scabies[Title/Abstract] OR ectoparasit*[Title/Abstract] OR flea

	infest*[Title/Abstract] OR tungiasis[Title/Abstract] OR lice infest*[Title/Abstract] OR mite infest*[Title/Abstract] OR trombiculiasis[Title/Abstract] OR myiasis[Title/Abstract] OR hypodermyiasis[Title/Abstract] OR screw worm infest*[Title/Abstract] OR tick infest*[Title/Abstract]))) OR Schistosomias*[Title/Abstract]) OR ((soil-transmitted helminth*[Title/Abstract] OR ascaris[Title/Abstract] OR hookworm*[Title/Abstract] OR Ancylostomatoidea[Title/Abstract] OR whipworm[Title/Abstract] OR Trichuriasis[Title/Abstract] OR Trichuriases[Title/Abstract] OR Strongyloidiasis[Title/Abstract])) OR ((snakebite envenoming[Title/Abstract] OR snake bit*[Title/Abstract])) OR ((Taeniasis[Title/Abstract] OR Cysticercosis Taenia[Title/Abstract])) OR ((Trachoma[Title/Abstract] OR Egyptian Ophthalmia[Title/Abstract])) OR ((Yaws[Title/Abstract] OR Endemic treponematoses[Title/Abstract] OR Frambesia[Title/Abstract])) OR ((Amoebiasis[Title/Abstract] OR Amebiases[Title/Abstract] OR Balamuthia Infection*[Title/Abstract])) OR ((Balantidiasis[Title/Abstract] OR Balantidium Infection*[Title/Abstract])) OR ((Giardiasis[Title/Abstract] OR Giardia Infection*[Title/Abstract])) OR ((Loiasis[Title/Abstract] OR Loa Loa infection*[Title/Abstract] OR Loiases[Title/Abstract])) OR Toxocariasis[Title/Abstract]) OR ((Larva Migrans[Title/Abstract] OR Dew Itch[Title/Abstract])) OR Japanese encephalitis[Title/Abstract]) OR Yellow fever[Title/Abstract]) OR ((arbovirus infect*[Title/Abstract] OR arboviral infect*[Title/Abstract] OR african horse sickness[Title/Abstract] OR bluetongue[Title/Abstract] OR encephalitis[Title/Abstract] OR west nile fever[Title/Abstract] OR encephalomyelitis[Title/Abstract] OR phlebotomus fever[Title/Abstract] OR rift valley fever[Title/Abstract] OR tick-borne disease*[Title/Abstract] OR african swine fever[Title/Abstract] OR colorado tick fever[Title/Abstract] OR hemorrhagic fever*[Title/Abstract] OR haemorrhagic fever*[Title/Abstract] OR kyasanur forest disease[Title/Abstract] OR nairobi sheep disease[Title/Abstract] OR zika*[Title/Abstract] OR zikv[Title/Abstract])) OR ((lassa fever[Title/Abstract] OR marburg virus fever[Title/Abstract])) OR bartonella[Title/Abstract]) OR ((bovine tuberculosis[Title/Abstract] OR bovine tb[Title/Abstract])) OR cholera[Title/Abstract]) OR ((enteric pathogen*[Title/Abstract] OR enterobacter*[Title/Abstract] OR shigella*[Title/Abstract] OR salmonella*[Title/Abstract] OR e.coli[Title/Abstract] OR e coli[Title/Abstract] OR escherichia[Title/Abstract])) OR ((leptospiros*[Title/Abstract] OR stuttgart disease[Title/Abstract] OR leptospira infection*[Title/Abstract] OR weil disease[Title/Abstract])) OR ((relapsing fever*[Title/Abstract] OR borrelia infect*[Title/Abstract])) OR ((treponematos*[Title/Abstract] OR bejel[Title/Abstract] OR pinta[Title/Abstract] OR syphili*[Title/Abstract] OR treponemal[Title/Abstract])) OR Paracoccidioidomycos*[Title/Abstract]) OR ((Blastomyces[Title/Abstract] OR brasiliensis Infection[Title/Abstract])) OR ((Myiasis[Title/Abstract] OR Maggot Infest*[Title/Abstract])) OR ((typhus[Title/Abstract] OR brill* disease[Title/Abstract] OR tsutsugamushi[Title/Abstract] OR jail fever[Title/Abstract])) OR ((Melioidos*[Title/Abstract] OR Burkholderia pseudomallei Infection[Title/Abstract]))
Embase	**Search date:** 22 June 2021 **Details:** 1 Myanmar/

	2 (myanmar or burma or rangoon or yangon or magway or mandalay or naypyidaw or kayah or ayeyarwady or bago or kachin or sagaing or kayin or tanintharyi or rakhine).tw. 3 1 or 2 4 Buruli ulcer/ 5 exp dengue/ 6 chikungunya/ or chikungunya virus/ 7 dracunculiasis/ 8 exp echinococcosis/ 9 exp trematodiasis/ 10 exp trypanosomiasis/ 11 exp leishmaniasis/ 12 exp leprosy/ 13 exp lymphatic filariasis/ 14 exp mycetoma/ 15 exp dermatomycosis/ 16 exp onchocerciasis/ 17 rabies/ 18 exp ectoparasitosis/ 19 exp helminth/ 20 exp strongyloidiasis/ 21 snakebite/ 22 exp taeniasis/ 23 trachoma/ 24 exp treponematosis/ 25 exp amebiasis/ 26 balantidiasis/ 27 giardiasis/ 28 loiasis/ 29 toxocariasis/ 30 exp larva migrans/ 31 Arbovirus/ 32 exp RNA virus infection/ 33 virus hemorrhagic fever/ 34 bartonella/ 35 bovine tuberculosis/ 36 cholera/ 37 exp Enterobacteriaceae/ 38 leptospirosis/ 39 exp Borrelia infection/ 40 South American blastomycosis/ 41 exp myiasis/ 42 exp typhus/ 43 melioidosis/ 44 ("buruli ulcer*" or "mycobacterium ulcerans" or chagas or "american trypanosomiasis" or dengue or chikungunya or dracunculiasis or "guinea-worm disease" or "guinea-worm infection*" or dracunculosis or echinococcosis or echinococcus or "foodborne trematodiases" or clonorchiasis or opisthorchiasis).ti,ab. 45 (Fascioliasis or paragonimiasis or trypanosomiasis or "sleeping sickness" or leishmaniasis or "leishmania infection*" or leprosy or "hansen* disease" or "lymphatic filariasis" or "filarial elephantiases" or mycetoma* or

	chromoblastomycosis or "madura foot" or actinomycetoma* or eumycetoma* or dermatomycos* or blastomycos* or hyalohyphomycos* or lobomycos* or sporotrichos* or tinea or onychomycos* or onchocerciasis or "river blindness" or rabies or scabies or ectoparasit* or "flea infest*" or tungiasis or "lice infest*" or "mite infest*" or trombiculiasis).ti,ab. 46 (myiasis or hypodermyiasis or "screw worm infest*" or "tick infest*" or schistosomias* or "soil-transmitted helminth*" or ascaris or hookworm* or Ancylostomatoidea or whipworm or trichuriasis or trichuriases or strongyloidiasis or snakebite* or "snake bit*" or taeniasis or "cysticercosis taenia" or trachoma or "egyptian ophthalmia" or yaws or "endemic treponematoses" or frambesia or amoebias* or amebias* or "balamuthia infection*" or balantidiasis or "balantidium infection*" or giardiasis or "giardia infection*" or loiasis or "loa loa infection*" or loiases or toxocariasis or "larva migrans" or "dew itch" or "japanese encephalitis" or "yellow fever" or "arbovirus infect*" or "arboviral infect*" or "african horse sickness" or bluetongue or encephalitis or "west nile fever" or encephalomyelitis or "phlebotomus fever" or "rift valley fever" or "tick-borne disease*" or "african swine fever" or "colorado tick fever" or "hemorrhagic fever*" or "haemorrhagic fever*" or "kyasanur forest disease" or "nairobi sheep disease" or zika*).ti,ab. (137522) 47 (zikv or "lassa fever" or "marburg virus fever" or bartonella or "bovine tuberculosis" or "bovine tb" or cholera or "enteric pathogen*" or enterobacter* or shigella* or salmonella* or "e.coli" or "e coli" or escherichia or leptospiros* or "stuttgart disease" or "leptospira infection*" or "weil disease" or "relapsing fever*" or "borrelia infect*" or treponematos* or bejel or pinta or syphili* or treponemal or Paracoccidioidomycos* or blastomyces or "brasiliensis infection" or myiasis or "maggot infest*" or typhus or "brill* disease" or tutsugamushi or "jail fever" or melioidos* or burkholderia).ti,ab. 48 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 49 3 and 48
Global Health	1 Myanmar/ 2 (myanmar or burma or rangoon or yangon or magway or mandalay or naypyidaw or kayah or ayeyarwady or bago or kachin or sagaing or kayin or tanintharyi or rakhine).tw. 3 1 or 2 4 Buruli ulcer/ 5 exp dengue/ 6 chikungunya/ or chikungunya virus/ 7 dracunculiasis/ 8 exp echinococcosis/ 9 exp foodborne diseases/ 10 exp trypanosomiasis/ 11 exp leishmaniasis/ 12 exp leprosy/ 13 exp lymphatic filariasis/ 14 exp mycetoma/ 15 exp dermatomycosis/ 16 exp onchocerciasis/ 17 rabies/ 18 exp ectoparasites/

	19 exp helminths/ 20 exp strongyloidiasis/ 21 snake venom/ 22 exp taeniasis/ 23 trachoma/ 24 exp treponematosis/ 25 amoebiasis/ 26 balantidiasis/ 27 giardiasis/ 28 loiasis/ 29 toxocariasis/ 30 exp larva migrans/ 31 arboviruses/ 32 exp viral haemorrhagic fevers/ 33 bartonella/ 34 exp mycobacterium bovis/ 35 cholera/ 36 exp Enterobacteriaceae/ 37 leptospirosis/ 38 exp borrelia/ 39 South American blastomycosis/ 40 exp myiasis/ 41 exp typhus/ 42 melioidosis/ 43 ("buruli ulcer*" or "mycobacterium ulcerans" or chagas or "american trypanosomiasis" or dengue or chikungunya or dracunculiasis or "guinea-worm disease" or "guinea-worm infection*" or dracunculosis or echinococcosis or echinococcus or "foodborne trematodiases" or clonorchiasis or opisthorchiasis).ti,ab. 44 (Fascioliasis or paragonimiasis or trypanosomiasis or "sleeping sickness" or leishmaniasis or "leishmania infection*" or leprosy or "hansen* disease" or "lymphatic filariasis" or "filarial elephantiases" or mycetoma* or chromoblastomycosis or "madura foot" or actinomycetoma* or eumycetoma* or dermatomycos* or blastomycos* or hyalohyphomycos* or lobomycos* or sporotrichos* or tinea or onychomycos* or onchocerciasis or "river blindness" or rabies or scabies or ectoparasit* or "flea infest*" or tungiasis or "lice infest*" or "mite infest*" or trombiculiasis).ti,ab. 45 (myiasis or hypodermyiasis or "screw worm infest*" or "tick infest*" or schistosomias* or "soil-transmitted helminth*" or ascaris or hookworm* or Ancylostomatoidea or whipworm or trichuriasis or trichuriases or strongyloidiasis or snakebite* or "snake bit*" or taeniasis or "cysticercosis taenia" or trachoma or "egyptian ophthalmia" or yaws or "endemic treponematoses" or frambesia or amoebias* or amebias* or "balamuthia infection*" or balantidiasis or "balantidium infection*" or giardiasis or "giardia infection*" or loiasis or "loa loa infection*" or loiases or toxocariasis or "larva migrans" or "dew itch" or "japanese encephalitis" or "yellow fever" or "arbovirus infect*" or "arboviral infect*" or "african horse sickness" or bluetongue or encephalitis or "west nile fever" or encephalomyelitis or "phlebotomus fever" or "rift valley fever" or "tick-borne disease*" or "african swine fever" or "colorado tick fever" or "hemorrhagic fever*" or "haemorrhagic fever*" or "kyasanur forest disease" or "nairobi sheep disease" or zika*).ti,ab.

	46 (zikv or "lassa fever" or "marburg virus fever" or bartonella or "bovine tuberculosis" or "bovine tb" or cholera or "enteric pathogen*" or enterobacter* or shigella* or salmonella* or "e.coli" or "e coli" or escherichia or leptospiros* or "stuttgart disease" or "leptospira infection*" or "weil disease" or "relapsing fever*" or "borrelia infect*" or treponematos* or bejel or pinta or syphili* or treponemal or Paracoccidioidomycos* or blastomyces or "brasiliensis infection" or myiasis or "maggot infest*" or typhus or "brill* disease" or tutsugamushi or "jail fever" or melioidos* or burkholderia).ti,ab. 47 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 48 3 and 47
Web of science	# 1 10,377 TOPIC: (myanmar or burma or rangoon or yangon or magway or mandalay or naypyidaw or kayah or ayeyarwady or bago or kachin or sagaing or kayin or tanintharyi or rakhine) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years # 2 54,446 TOPIC: ("buruli ulcer*" or "mycobacterium ulcerans" or chagas or "american trypanosomiasis" or dengue or chikungunya or dracunculiasis or "guinea-worm disease" or "guinea-worm infection*" or dracunculosis or echinococcosis or echinococcus or "foodborne trematodiases" or clonorchiasis or opisthorchiasis) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years # 3 102,873 TOPIC: (Fascioliasis or paragonimiasis or trypanosomiasis or "sleeping sickness" or leishmaniasis or "leishmania infection*" or leprosy or "hansen* disease" or "lymphatic filariasis" or "filarial elephantiases" or mycetoma* or chromoblastomycosis or "madura foot" or actinomycetoma* or eumycetoma* or dermatomycos* or blastomycos* or hyalohyphomycos* or lobomycos* or sporotrichos* or tinea or onychomycos* or onchocerciasis or "river blindness" or rabies or scabies or ectoparasit* or "flea infest*" or tungiasis or "lice infest*" or "mite infest*" or trombiculiasis) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years # 4 168,137 TOPIC: (myiasis or hypodermyiasis or "screw worm infest*" or "tick infest*" or schistosomias* or "soil-transmitted helminth*" or ascaris or hookworm* or Ancylostomatoidea or whipworm or trichuriasis or trichuriases or strongyloidiasis or snakebite* or "snake bit*" or taeniasis or "cysticercosis taenia" or trachoma or "egyptian ophthalmia" or yaws or "endemic treponematoses" or frambesia or amoebias* or amebias* or "balamuthia infection*" or balantidiasis or "balantidium infection*" or giardiasis or "giardia infection*" or loiasis or "loa loa infection*" or loiases or toxocariasis or "larva migrans" or "dew itch" or "japanese encephalitis" or "yellow fever" or "arbovirus infect*" or "arboviral infect*" or "african horse sickness" or bluetongue or encephalitis or "west nile fever" or encephalomyelitis or "phlebotomus fever" or "rift valley fever" or "tick-borne disease*" or "african swine fever" or "colorado tick fever" or "hemorrhagic fever*" or "haemorrhagic fever*" or "kyasanur forest disease" or "nairobi sheep disease" or zika*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years # 5 654,594 TOPIC: (zikv or "lassa fever" or "marburg virus fever" or bartonella or "bovine tuberculosis" or "bovine tb" or cholera or "enteric pathogen*" or

	enterobacter* or shigella* or salmonella* or "e.coli" or "e coli" or escherichia or leptospiros* or "stuttgart disease" or "leptospira infection*" or "weil disease" or "relapsing fever*" or "borrelia infect*" or treponematos* or bejel or pinta or syphili* or treponemal or Paracoccidioidomycos* or blastomyces or "brasiliensis infection" or myiasis or "maggot infest*" or typhus or "brill* disease" or tutsugamushi or "jail fever" or melioidos* or burkholderia) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years # 6 949,413 #5 OR #4 OR #3 OR #2 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years # 7 382 #6 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
Central Biomed Library (Myanmar database)	1. Buruli ulcer 2. Mycobact 3. Chagas disease 4. Trypnosomiasis 4. Dengue 5. Chikungunya 6. Arbovir 7. Dracunculiasis 8. guinea-worm disease 9. Echinococcosis 10. Trematodiases 11. Clonorchiasis 12. Opisthorchiasis 13. Fascioliasis 14. Paragonimiasis 15. Paragonimus 15. Trematode 16. Trematode worms 17. Worms 18. Flukes 19. Parasit 20. Trypanosomiasis 21. Sleeping sickness 22. Leishmaniasis 24. Leprae 25. Lepr 26. Filaria 27. Wuchereria 28. Mycetoma 29. Chromoblastomycosis 30. Mycoses 31. Onchocerciasis 32. River blindness 33. Rabies 34. Scabies 35. Sarcoptes scabiei 36. Ectoparasites

	37. Schistosomiasis 38. Helminth 39. Ascaris 40. Hookworm 41. Whipworm 42. Trichuriasis 43. Strongyloid 44. Snake bite 45. Taenia 46. Cysticercosis 47. Trachoma 48. Chlamydia 49. Yaws 50. Treponema 51. Treponematoses 52. Amoebiasis 53. Entamoeba 54. Dysentery 55. Balantidiasis 56. Balantidium 57. Giardia 58. Diarrhoea 59. Loiasis 60. Toxocariasis 61. Larva Migrans 62. Encephalitis 63. Fever 64. Rift Valley fever 65. Zoonoses 66. Haemorrhagic fever 67. Bartonella 68. Tuberculosis 69. Cholera 70. Vibrio 71. Shigella 72. Salmonella 73. Escherichia 74. Enterobacteriaceae 75. Lepto 76. Borrelia 77. Treponematoses 78. Eumycetoma 79. Paracoccidioidomycosis 80. Myiasis 81. Typhus 82. Typhoid 83. Rickettsia 84. Melioid 85. Burkholderia

Table 3. Criteria for assessment of risk of bias assessment

Bacteria	Low risk	High risk	Reference
Escherichia coli enteritis	Isolation of the pathogen by culture of clinical specimen (or) detection of nucleic acid by molecular method (PCR)	microscopy	https://www.cdc.gov/ecoli/clinicians.html
Cholera	Identification of the pathogen by direct microscopy (dark field microscopy) (or) culture of stools (or) detection of genetic material by PCR	Rapid Antigen test	https://www.cdc.gov/cholera/diagnosis.html
Salmonellosis	Isolation of the pathogen by culture of clinical specimens (or) PCR	Serology (e.g., Widal test)	https://www.cdc.gov/typhoid-fever/health-professional.html
Shigellosis	Isolation of shigella from faeces/ rectal swabs (or) detection of genetic material/ virulent gene by PCR	routine microscopy (*not specific for shigella species)	https://emedicine.medscape.com/article/968773-workup
Leprosy	clinical examination with or without detection of acid-fast bacilli in slit skin smear/ skin or nerve biopsy (or) Isolation of the pathogen by culture (or) PCR	stand-alone serology (anti-PGL-I and anti-LID-1 antibody titres by ELISA and by the NDO-LID rapid test)	https://apps.who.int/iris/bitstream/handle/10665/274127/9789290226383-eng.pdf
Melioidosis	Isolation and identification of the pathogen by culture of clinical specimens (or) detection of genetic material by PCR (or) Rapid detection of the organism in the specimen by IFA	Serology (Indirect Haemagglutination test/ ELISA)	https://wwwnc.cdc.gov/eid/article/21/2/14-1045_article
Rickettsiosis	Isolation by culture (or) detection of genetic material by PCR/ loop amplification (or) **paired serology** by IFA/ ELISA (≥ 4-fold increase in antibody titer between two consecutive samples)	Weil-Felix test, rapid Antigen test	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2829893/

Leptospirosis	Paired serology (≥ 4-fold increase in antibody titre) by microscopic agglutination test (MAT) / a single high MAT titer > 400 (or) PCR	positive MAT titre < 1/400 (or) ELISA (or) dark field microscopy (or) IgM-specific serologic screening test	
Trachoma	Clinical diagnosis in endemic region		
Syphilis	Direct detection methods (i.e. dark-field microscopy, direct fluorescent antibody test and nucleic acid amplification test) (or) positive serological tests for both non-treponemal (VDRL/ PRP) and treponemal (TPHA/ TPPA) tests	either non-treponemal test or treponemal test performed	https://www.who.int/reproductivehealth/publications/rtis/syphilis-ANC-screenandtreat-guidelines/en/
Yaws	Dual Path Platform Syphilis Screen and Confirm assay, detection of DNA in skin lesion by PCR	Treponema pallidum particle agglutination (TPPA) and rapid plasma reagin (RPR) (* these tests cannot differentiate yaws from syphilis)	https://www.who.int/news-room/fact-sheets/detail/yaws
Virus	**Low risk (Standard Laboratory case definition)**	**High risk**	
Dengue infection	Viral isolation (or) Detection of DENV nucleic acid (or) NS1 Ag in clinical specimens (or) IgM/ IgG Anti-DENV seroconversion in acute and convalescent serums (or) > 4-fold rise in titres in serum specimens collected 2 weeks apart.	IgM/ IgG anti-DENV detection in a single serum sample	https://www.cdc.gov/dengue/healthcare-providers/diagnosis.html
Chikungunya infection	Detection of the viral nucleic acid by PCR (or) detection of chikungunya IgM antibody confirmed with neutralizing antibodies	detection of chikungunya IgM antibody	https://www.cdc.gov/chikungunya/hc/diagnostic.html

Japanese encephalitis virus infection	Detection of viral nucleic acid by PCR (or) detection of JE virus IgM antibody in CSF and serum confirmed with neutralizing antibody testing	JE virus IgM antibody in a single CSF/ serum specimen (due to cross reactivity with other flavivirus)	https://www.cdc.gov/japaneseencephalitis/healthcareproviders/healthcareproviders-diagnostic.html#:~:text=Laboratory%20diagnosis%20of%20JE%20is,longer%20persistence%20has%20been%20documented.
Rabies infection	Viral isolation (or) detection of viral nucleic acid by PCR (or) rabies antigen in clinical specimens (human) (or) Detection of viral antigen in the tissues of animals. (or) Clinical pictures that are compatible with rabies with preceding history of dog bite.		https://www.cdc.gov/rabies/diagnosis/animals-humans.html#:~:text=Diagnosis%20in%20humans&text=Saliva%20can%20be%20tested%20by,the%20base%20of%20hair%20follicles.
Zika virus infection	Detection of virus nucleic acid by PCR in the clinical specimens (or) Plaque reduction neutralization test (quantitative assays that measure virus-specific neutralizing antibody titres)	Detection of Zika virus IgM antibody (due to cross-reactivity with other flavivirus).	https://www.cdc.gov/zika/laboratories/types-of-tests.html
Protozoa	**Low risk**	**High risk**	
Amoebiasis	Conventional/ real-time PCR (or) Antigen (or) Antibody detection (ELISA/ IHA/ IFA)	Identification of the parasites (cysts/ trophozoites) in clinical specimens by microscopy	https://www.cdc.gov/dpdx/amebiasis/index.html
Giardiasis	Microscopy with direct fluorescent antibody testing (DFA) (or) PCR test (or) Ag detection by ELISA		https://www.cdc.gov/parasites/giardia/medical-professionals.html

Leishmaniasis	Detection of Leishmania parasites (DNA) by microscopy/culture of tissue specimens or detection of parasite DNA by PCR	Serology (IFA/ ELISA) *most serology assays do not reliably distinguish active and quiescent infections	https://www.cdc.gov/parasites/leishmaniasis/health_professionals/index.html
Helminth	**Low risk**	**High risk**	
Ascariasis	Detection of eggs/ lava by microscopy-based methods or identification of adult worm (or) molecular methods (including PCR)		https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5652060/
Hookworm infection	Detection of eggs/ lava by microscopy-based methods or identification of adult worm (or) molecular methods (including PCR)		https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5652060/
Strongyloidiasis	Detection of eggs/ lava by microscopy-based methods or identification of adult worm (or) molecular methods (including PCR)		https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5652060/
Microfilariasis	blood smear examination by microscopy (or) Antigen/ Antibody detection by immunoassays (or) Antigen detection by rapid test		https://www.cdc.gov/dpdx/lymphaticFilariasis/index.html
Trichuriasis	Detection of eggs/ lava by microscopy-based methods		https://www.cdc.gov/dpdx/trichuriasis/
Taeniasis	Detection of eggs/ lava by microscopy-based methods or identification of adult worm (or) molecular methods (including PCR), serology test (Ag/ Ab) detection) , Imaging (CT/ MRI) for cysticercosis		https://www.cdc.gov/parasites/taeniasis/health_professionals/index.html

Trematodes infection	detection of ova in stool/ urine samples by microscopy (or) PCR	Serological testing (Antibody to adult worm)	https://www.cdc.gov/parasites/schistosomiasis/health_professionals/index.html#dx
soil transmitted helminths	detection of helminth/ eggs in stool samples by microscopy (or) PCR		
Schistosomiasis	Identification of parasite eggs (stool for *S. mansoni* or S. japonicum eggs and urine for *S. haematobium* eggs). Antibodies and/or antigens detection in blood		https://www.who.int/news-room/fact-sheets/detail/schistosomiasis
Mycetoma	The diagnosis of mycetoma is based on clinical presentation and identification of the causative organisms which can be detected by directly examining the grains that are discharged by the sinuses. The samples can be obtained by Fine Needle Aspiration (FNA) or surgical biopsy. Imaging (Ultrasound/ MRI) can also be used.		https://www.cdc.gov/fungal/diseases/mycetoma/health-professionals.html
Note: If the article does not mention detail method of diagnosis, it is regarded as "Not Clear"			

Table 4. Geographic location of reported NTDs in included articles

States/ Regions	No of reported NTDs				No of articles
	Bacterial NTDs	Viral NTDs	Protozoal NTDs	Helminth NTDs	
Yangon	171	121	32	111	295
Mandalay	20	42	3	18	65
Magway	5	2	2	14	14
Ayeyarwaddy	2	3	0	7	8
Sagaing	3	0	0	0	3
Bago	8	1	0	14	13
Tanintharyi	1	1	1	0	2
Naypyidaw	2	1	0	7	7
Mon	1	2	0	2	4
Kayin	0	1	0	0	1
Kayar	0	0	0	3	1
Kachin	4	0	0	3	5
Shan	0	2	1	3	6
Rakhine	0	3	2	0	7
Multiple regions	23	11	0	27	48
Nationwide	4	8	0	2	13
Thailand-Myanmar border	15	4	6	28	29
China-Myanmar border	2	7	1	0	10
Other countries	7	0	8	35	33
Not specified	42	25	8	30	87
Total	310	234	64	304	651

Table 5. Reported NTDs stratified by aetiology and age groups

	Child (< 12 years)	Adult (≥ 12 years)	Both age groups	Age not specified	Total
Bacterial NTDs (n=310)					
E. coli enteritis	36	3	7	3	49
Cholera	13	8	8	12	41
Salmonellosis	12	20	4	8	44
Shigellosis	18	5	5	4	32
Leprosy	2	14	14	28	58
Melioidosis	0	25	0	6	31
Rickettsioses	0	12	3	3	18
Leptospirosis	1	10	3	6	20
Trachoma	0	1	3	7	11
Syphilis	0	3	0	1	4
Yaws	0	0	1	1	2
Sub-total	82	101	48	79	310
Viral NTDs (n=234)					
Dengue	106	35	14	25	180
Chikungunya	12	6	3	6	27
JEV infection	13	2	3	2	20
Rabies	1	1	1	2	5
Zika virus disease	0	1	1	0	2
Sub-total	132	45	22	35	234
Protozoal NTDs (n=65)					
Amoebiasis	12	10	5	10	37
Giardiasis	12	6	3	2	23
Leishmaniasis	0	3	0	1	4
Sub-total	24	19	8	13	64
Helminth (n=304)					
Ascariasis	46	18	15	9	88
Hookworm disease	18	11	13	5	47
Strongyloidiasis	6	19	4	2	31
Microfilariasis	0	21	13	3	37
Trichuriasis	33	12	12	6	63
Taeniasis/ Cysticercosis	2	6	2	0	10
Trematodes	1	3	1	0	5
Soil transmitted helminths	16	2	5	0	23
Sub-total	122	92	65	25	304

Fungus (n=4)					
Mycetoma	0	4	0	0	4
Sub-total					4
Total	360	261	143	152	916

Appendix for chapter 3

Table 1. Probability parameters for viral and bacterial aetiologies in different febrile syndromes

Parameter	Base case value	Range for sensitivity analysis		Probability distribution	Reference
		Low value	High value		
Children (1 - 12 years)					
URTI					
Bacteria	0.041	0.03	0.20	Beta(15,326)	Base case value [312]; assumption for the range is based on plausibility and expert opinion. The base case value was informed by a study that investigated aetiologies of URTI among children in Mwanza, Tanzania where 4.1% (14 out of 339) had bacterial infection [312].
Viruses	0.959	0.80	0.97	1 - Beta(15, 326)	For base case value, the remaining URTI cases were assumed to be caused by viruses (1- probability of bacterial URTI); assumption for the range was based on plausibility and expert opinion.
LRTI					
Bacteria	0.11	0.05	0.30	expert elicitation	Base case value [313]; assumption for the range was based on plausibility and expert opinion; probability distribution was derived from a pooled probability elicited from the experts.
Viruses	0.89	0.70	0.95	1 - expert elicitation	For base case value, we assumed all the remaining cases were caused by viruses (1- probability of bacteria LRTI); assumption for the range was based on plausibility and expert opinion.
Undifferentiated fever					

Viruses	0.212	0.15	0.30	dirichlet (384,142,110,44,1140)	Base case value [28]; assumption for the range was based on plausibility and expert opinion; for probability distribution, the prior chosen corresponds to the posterior that would be obtained from dirichlet-multinomial conjugacy if 383, 141, 109, 43 and 1139 undifferentiated fever cases were caused by viruses, rickettsioses, leptospirosis, bacteraemia and others respectively. This was informed by a fever study that investigated aetiologies of febrile patients in rural Laos [28].
Rickettsioses	0.079	0.01	0.12		
Leptospirosis	0.061	0.01	0.10		
Bacteraemia	0.024	0.005	0.05		
Others	0.624	0.40	0.70		
Adolescents and adults (> 12 years)					
URTI					
Bacteria	0.079	0.02	0.28	Beta (24, 270)	Base case value [314]; assumption for the range was based on plausibility and expert opinion; The base case value was informed by a study that investigated aetiologies of URTI among adults in Thailand where 7.9% (23 out of 292) of adults with URTI had bacterial infection [314].
Viruses	0.921	0.70	0.98	1- Beta (24, 270)	For base case value, all the remaining URTI cases were assumed to be caused by viruses (1- probability of bacterial URTI); assumption for the range was based on plausibility and expert opinion.
LRTI					
Bacteria	0.21	0.10	0.30	expert elicitation	Base case value was informed by a study that investigated aetiologies of LRTI in adults in primary care in 11 European countries. In the study 21% (654 out of 3104) of patients had a potential bacterial pathogen [315]. Assumption for the range was based on plausibility and expert opinion. Probability distribution was derived from a pooled probability elicited from the experts.
Viruses	0.79	0.60	0.90	1 - expert elicitation	For base case values, all the remaining cases were assumed to be caused by viruses (1- probability of bacterial LRTI); assumption for the range was based on plausibility and expert opinion.

Undifferentiated fever					
Viruses	0.145	0.10	0.50	Dirichlet* (15.5,13,18.5,2.2,55.8)	Base case value [316]; assumption for the range was based on plausibility and expert opinion.
Rickettsioses	0.120	0.05	0.28		Base case value [26]; high value of the range [317]; assumption for the low value was based on plausibility and expert opinion.
Leptospirosis	0.175	0.01	0.37		Base case value [26]; high value of the range [27]; assumption for low value was based on plausibility and expert opinion.
Bacteraemia	0.012	0.01	0.09		Base case value [27]; high value of the range [149]; assumption for low value was based on plausibility and expert opinion.
Others	0.548	0.40	0.60		Base case value was assumed to be the probability remaining after viral and bacterial aetiologies; high value [28]; assumption for low value was based on plausibility and expert opinion.
* For probability distribution, the prior chosen corresponds to the posterior that would be obtained from dirichlet-multinomial conjugacy if 14.5, 12, 17.5, 1.2 and 54.8 undifferentiated fever cases were caused by viruses, rickettsioses, leptospirosis, bacteraemia and others respectively starting with a vague prior (1,1,1,1,1)					

Table 2. Probability parameters for untreated mortalities for children

Parameter	Base case value	Range for sensitivity analysis		Probability distribution	Reference
		Low value	High value		
URTI					
Viruses	0.001	0.0005	0.009	Beta(26, 24950)	Base case value [190]; assumption for the range was based on plausibility and expert opinion. To derive parameters for the beta distribution, the standard error was assumed to be 20% of the base case value.
Bacteria	0.002	0.0009	0.01	Beta(25, 12450)	Base case value and the range was based on plausibility and expert opinion. To derive parameters for the beta distribution, the standard error was assumed to be 20% of the base case value.
LRTI					
Viruses	0.01	0.005	0.05	Beta(26, 2450)	Base case value and the range was based on plausibility and expert opinion. To derive parameters for the beta distribution, the standard error was assumed to be 20% of the base case value.
Bacteria	0.05	0.03	0.12	Expert elicitation	Base case [318]. Assumption for the range was based on plausibility and expert opinion. Probability distribution was derived from a pooled probability elicited from the experts.
Undifferentiated fever					
Viruses	0.001	0.0005	0.009	Beta(26, 24950)	Base case value [190]; assumption for the range was based on plausibility and expert opinion. To derive parameters for the beta distribution, the standard error was assumed to be 20% of the base case value.

Rickettsioses	0.07	0.00	0.25	Expert elicitation	Base case value [141]; assumption for the range was based on plausibility and expert opinion. Probability distribution was derived from a pooled probability elicited from the experts.
Leptospirosis	0.03	0.00	0.20	Expert elicitation	Base case value [142]; assumption for the range was based on plausibility and expert opinion. Probability distribution was derived from a pooled probability elicited from the experts.
Bacteraemia	0.35	0.10	0.75	Beta(17, 31)	Base case value and the range was based on plausibility and expert opinion. To derive parameters for the beta distribution, the standard error was assumed to be 20% of the base case value.
Others	0.001	0.0005	0.009	Beta(26, 24950)	Base case value [190]; assumption for the range was based on plausibility and expert opinion. To derive parameters for the beta distribution, the standard error was assumed to be 20% of the base case value.
Dysentery	0.06	0.02	0.15	Beta(24, 368)	Base case value and the range was based on plausibility and expert opinion. To derive parameters for the beta distribution, the standard error was assumed to be 20% of the base case value.
Diarrhoea	0.01	0.002	0.03	Expert elicitation	Base case value and the range was based on plausibility and expert opinion. Probability distribution was derived from a pooled probability elicited from the experts.
UTI	0.03	0.01	0.10	Beta(25, 784)	Base case value and the range was based on plausibility and expert opinion. To derive parameters for the beta distribution, the standard error was assumed to be 20% of the base case value.

Table 3. Probability parameters for untreated mortalities in adolescents and adults

Parameter	Base case value	Range for sensitivity analysis		Probability distribution	Reference
		Low value	High value		
URTI					
Viruses	0.001	0.0005	0.009	Beta(26, 24950)	Base case value [190]; assumption for the range was based on plausibility and expert opinion. To calculate parameters for the beta distribution, the standard error was assumed to be 20% of the base case value.
Bacteria	0.002	0.0009	0.01	Expert elicitation	Base case value and the range was based on plausibility and expert opinion. Probability distribution was derived from a pooled probability elicited from the experts.
LRTI					
Viruses	0.01	0.005	0.05	Beta(26, 2450)	Base case value [190]; Assumption for the range was based on plausibility and expert opinion. To derive parameters for the beta distribution, the standard error was assumed to be 20% the base case value.
Bacteria	0.05	0.03	0.12	Expert elicitation	Base case [318]; Assumption for the range was based on plausibility and expert opinion. Probability distribution was derived from a pooled probability elicited from the experts.
Undifferentiated fever					
Viruses	0.001	0.0005	0.009	Beta(26, 24950)	Base case value [190]; assumption for the range was based on plausibility and expert opinion. To derive parameters for the beta distribution, the standard error was assumed to be 20% the base case value.

Rickettsioses	0.07	0.00	0.25	Expert elicitation	Base case value [141]; assumption for the range was based on plausibility and expert opinion. Probability distribution was derived from a pooled probability elicited from the experts.
Leptospirosis	0.03	0.00	0.20	Expert elicitation	Base case value [142]; assumption for the range was based on plausibility and expert opinion. Probability distribution was derived from a pooled probability elicited from the experts.
Bacteraemia	0.35	0.10	0.75	Beta(17, 31)	Base case value and the range was based on plausibility and expert opinion. To derive parameters for the beta distribution, the standard error was assumed to be 20% of the base case value.
Others	0.001	0.0005	0.009	Beta(26, 24950)	Base case value [190]; assumption for the range was based on plausibility and expert opinion. To derive parameters for the beta distribution, the standard error was assumed to be 20% of the base case value.
Dysentery	0.06	0.02	0.15	Beta(24, 368)	Base case value and the range was based on plausibility and expert opinion. To derive parameters for the beta distribution, the standard error was assumed to be 20% of the base case value.
Diarrhoea	0.01	0.002	0.03	Beta(26, 2450)	Base case value and the range was based on plausibility and expert opinion. To derive parameters for the beta distribution, the standard error was assumed to be 20% of the base case value.
UTI	0.03	0.01	0.10	Beta(25, 784)	Base case value and the range was based on plausibility and expert opinion. To derive parameters for the beta distribution, the standard error was assumed to be 20% of the base case value.

Table 4. Probability parameters for current practice of care

Parameter	Base case value	Range for sensitivity analysis*		Probability distribution	References/ Notes
		Low value	High value		
Children (1-12 years)					
Probability of health workers prescribing antibiotics for febrile children with					
Acute respiratory infection (URTI and LRTI)	0.67	0.40	0.85	Beta(23, 12)	67% (22 out of 33) of HCWs gave antibiotics to children with ARI.
Undifferentiated fever	0.27	0.13	0.45	Beta(10, 25)	27% (9 out of 33) of HCWs gave antibiotics to children with undifferentiated fever
Type of antibiotics used for acute respiratory infection					
Beta-lactam antibiotics[1]	0.95	0.77	0.99	Beta(22, 2)	Among 22 HCWs who gave antibiotics for ARI, 21(95%) used beta-lactam antibiotics and one used azithromycin.
Azithromycin	0.05	0.01	0.23	1- Beta(22, 2)	
Type of antibiotics used for undifferentiated fever					
Beta-lactam antibiotics[2]	0.89	0.52	0.99	Beta(9, 2)	Among 9 HCWs who gave antibiotics for undifferentiated fever, 8 used beta-lactam antibiotics and one used ciprofloxacin.
Ciprofloxacin	0.11	0.02	0.48	1- Beta(9, 2)	
Adolescents and adults (> 12 years)					
Probability of health workers prescribing antibiotics for febrile patients with					

Acuter respiratory infection (URTI and LRTI)	0.67	0.40	0.85	Beta(23, 12)	67% (22 out of 33) of HCWs gave antibiotics to patients with ARI.
Undifferentiated fever	0.42	0.25	0.61	Beta(15,20)	42% (14 out of 33) of HCWs gave antibiotics to patients with undifferentiated fever.
Type of antibiotic used for ARI					
Beta-lactam antibiotics[3]	0.86	0.65	0.97	Beta(20,4)	Among 22 HCWs who gave antibiotics for ARI, 19 (86%) used beta-lactam antibiotics and 3 (14%) used azithromycin.
Azithromycin	0.14	0.03	0.35	1-Beta(20,4)	
Type of antibiotic used for undifferentiated fever					
Beta-lactam antibiotics[4]	0.86	0.57	0.98	Dirichlet(12,2,2)	Among 14 HCWs who gave antibiotics for patients with undifferentiated fever, 11 (86%) used beta-lactam antibiotics, one (7%) used ciprofloxacin and one (7%) used chloramphenicol.
Ciprofloxacin	0.07	0.002	0.33		
Chloramphenicol	0.07	0.002	0.33		
Both age groups					
Probability of prescribing antibiotics[5] in febrile patients with					
Dysentery	0.80	0.60	0.90	Beta(5,2)	To derive parameters for the beta distribution, the standard error was assumed to be 20% of the base case value.
UTI	0.80	0.40	0.90	Beta(5,2)	To derive parameters for the beta distribution, the standard error was

					assumed to be 20% of the base case value.
Probability of getting oral rehydration therapy					
Watery diarrhoea	0.54	0.49	0.60	Beta(191, 161)	Base case value [91]; 54% (190 out of 350) of under five children in rural Myanmar received oral rehydration therapy (ORT) or increased fluids in Demographic and Health Survey.

* The ranges are 95% binomial confidence intervals
[1] 90% amoxicillin, 5% cloxacillin, 5% cephalexin
[2] 75% amoxicillin, 12.5% flucloxacillin-amoxicillin, 12.5% ampicillin-cloxacillin
[3] 95% amoxicillin, 5% cefixime
[4] 92% amoxicillin, 8% cefalexin
[5] Assumed parameters based on plausibility and expert opinion

Table 5. Efficacy of empirical antibiotics for children

Parameter	Base case value	Range for sensitivity analysis		Probability parameters	Reference
		Low value	High value		
Amoxicillin					
Bacterial URTI	0.91	0.82	0.99	Beta(72,8)	Base case value [319]; assumption for the range +/- 10% of the base case value. In the reference study, clinical success was observed in 91% (71 out of 78) children with tonsillitis treated with amoxicillin.
Bacterial LRTI	0.89	0.80	0.98	Beta(1276,155)	Base case value [320]; assumption for the range +/- 10% of base case value. Of 1429 children with LRTI treated with oral amoxicillin, 1275 (89%) had treatment success.
Rickettsial infection	0	0	0	0	Penicillin is not effective against rickettsial infection [321].
Leptospirosis	0.99	0.90	1	Beta(11,1)	Base case value [322]; assumption for the range +/- 10%. All ten patients treated with amoxicillin had treatment success.
Bacteraemia	0.60	0.42	0.78	Beta(10,7)	A 60% efficacy was assumed for base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to

					be 20% of the base case value to derive parameters for beta distribution.
Dysentery	0.60	0.42	0.78	Beta(10,7)	Amoxicillin was not recommended for treatment of dysentery in 2005 WHO guideline due to poor mucosal penetration [323]. A 60% efficacy was assumed for base case value, assumption for the range +/-30% of base case value.
UTI	0.50	0.35	0.65	Beta(10,7)	A 50% efficacy was assumed for base case value due to high level of antibiotic resistance in *Enterobacteriaceae* isolated from UTI in Myanmar (52% of isolates are ESBL producers) [324], assumption for the range +/-30% of base case value.
Azithromycin					
Bacterial URTI	0.95	0.86	0.99	Beta(135, 8)	Base case value [325]; assumption for the range +/- 10% of the base case value . In the reference study, clinical success was observed in 95% (134 out of 141) of children with group A streptococcus tonsilitis.
Bacterial LRTI	0.91	0.82	0.99	Beta(233,25)	Base case value [326]; assumption for the range +/- 10% of base case value. Of 256 treated children, 232 (91%) had clinical cure at 4-6 weeks.
Rickettsial infection	0.97	0.87	0.99	Beta(148,5)	Base case value [162]; assumption for the range +/- 10% of base case

					value. Of 151 treated patients, 147 (97%) had treatment success within 5 days.
Leptospirosis	0.97	0.87	0.99	Beta(148,5)	Base case value[162]; assumption for the range +/- 10% of base case value. Of 151 treated patients, 147 (97%) had treatment success within 5 days.
Bacteraemia	0.60	0.42	0.78	Beta(10,7)	A 60% efficacy was assumed for base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution.
Dysentery	0.94	0.84	0.99	Beta(29,3)	Base case value[327]; assumption for the range +/-10%. In the reference study, clinical success was observed in 28 out of 30 patients at day 3. Azithromycin is a second line antibiotic recommended for dysentery in WHO guidelines.
UTI	0.40	0.28	0.52	Beta(16,23)	A 40% efficacy was assumed for base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution. Azithromycin is generally not recommended to treat

					UTI due to low concentration in urine[328].
Amoxicillin + Azithromycin					
Bacterial URTI	0.95	0.86	0.99	Beta(135, 8)	Base case value [325]; assumption for the range +/- 10% of the base case value . In the reference study, clinical success was observed in 95% (134 out of 141) of children with group A streptococcus tonsilitis.
Bacterial LRTI	0.91	0.82	0.99	Beta(233,25)	There is conflicting evidence regarding the benefit of combined beta lactam and azithromycin for treatment of community acquired pneumonia [329, 330]. Thus, efficacy was assumed the same as azithromycin. Base case value [326]; assumption for the range +/- 10%. Of 256 treated children, 232 (91%) had clinical cure at 4-6 weeks.
Rickettsial infection	0.97	0.87	0.99	Beta(148,5)	As amoxicillin is not effective against rickettsial infection, efficacy was assumed the same as azithromycin. Base case value [162]; assumption for the range +/- 10%. Of 151 treated patients, 147 (97%) had treatment success within 5 days.
Leptospirosis	0.97	0.87	0.99	Beta(148,5)	No empirical data for efficacy of combined amoxicillin and azithromycin for leptospirosis. Thus, efficacy was assumed the same as azithromycin [162].

Bacteraemia	0.70	0.50	0.91	Beta(8,4)	A 70% efficacy was assumed for base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution.
Dysentery	0.93	0.84	0.99	Beta(29,3)	Base case value[327]; assumption for the range +/-10%. In the reference study, clinical success was observed in 28 out of 30 patients at day 3. Azithromycin is a second line antibiotic recommended for dysentery in WHO guideline.
UTI	0.60	0.35	0.65	Beta(10,7)	A 60% efficacy was assumed for base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution.
Oral Rehydration Salt plus Zinc tablets					
Diarrhoea	0.93	0.83	0.99	Beat (950, 67)	Base case value[331]; assumption for the range +/- 10%. In the reference study (meta-analysis), of 1015 children with watery diarrhoea treated with ORT, failure to rehydrate occurred in 66 (7%).

Table 6. Efficacy of current prescribing antibiotics in children

Parameter	Base case value	Range for sensitivity analysis		Probability distribution	Reference
		Low value	High value		
Beta-lactam antibiotics					
Bacterial URTI	0.91	0.82	0.99	Beta(72,8)	Base case value [319]; assumption for the range +/- 10% of the base case value. In the reference study, clinical success was observed in 91% (71 out of 78) children with tonsillitis treated with amoxicillin.
Azithromycin					
Bacterial URTI	0.95	0.86	0.99	Beta(135, 8)	Base case value [325]; assumption for the range +/- 10% of the base case value . In the reference study, clinical success was observed in 95% (134 out of 141) of children with group A streptococcus tonsilitis.
Ciprofloxacin					
Rickettsial infection	0.20	0.14	0.26	Beta(21, 80)	Ciprofloxacin has not been widely studied for treatment of rickettsioses. A few case reports and small studies showed rickettsial infection successfully treated with ciprofloxacin [332-334]. A 20% efficacy is assumed for based case value and +/- 30% for the range. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution.

Leptospirosis	0.20	0.14	0.26	Beta(21, 80)	There are few studies that investigated quinolones for treatment of leptospirosis in humans. Animal and in-vitro studies showed some susceptibility of Leptospira to quinolones [335-337]. A 20% efficacy is assumed for based case value and +/- 30% for the range. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution.
Bacteraemia	0.20	0.14	0.26	Beta(21, 80)	A prospective study showed that 9.5% of febrile adolescents and adults in Myanmar had blood stream infection. Half of them were caused by enteric fever (*S.* Typhi and Paratyphi isolates were 100% resistant to ciprofloxacin) [149]. A 20% efficacy is assumed for based case value and +/- 30% for the range. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution.
Antibiotics					
Dysentery	0.60	0.40	0.80	Beta(10,7)	A 60% efficacy was assumed for base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to be 20% of the base case value to derive parameters for beta distribution.
Antibiotics					
UTI	0.60	0.40	0.80	Beta(10,7)	A 60% efficacy was assumed for the base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution.

Oral Rehydration therapy					
Diarrhoea	0.93	0.83	0.99	Beat (950, 67)	Base case value[331]; assumption for the range +/- 10%. In the reference study (meta-analysis), of 1015 patients with watery diarrhoea treated with ORT, failure to rehydrate occurred in 66 (7%).

[1] Efficacy of beta-lactam antibiotics (in the current practice) for other aetiologies or diseases (bacterial LRTI, rickettsioses, leptospirosis, and bacteraemia) is assumed to be the same as amoxicillin efficacy in empirical treatment.

[2] Efficacy of azithromycin (in the current practice) for other aetiologies or diseases (bacterial LRTI, rickettsioses, leptospirosis, and bacteraemia) is assumed to be the same as azithromycin efficacy in empirical treatment.

Table 7. Efficacy of empirical antibiotic treatment for adolescents and adults

Parameter	Base case value	Range for sensitivity analysis		Probability distribution	Reference
		Low value	High value		
Amoxicillin					
Bacterial URTI	0.96	0.86	0.99	Beta(73, 4)	Base case value [338]; assumption for the range +/- 10% of base case value. In the reference study, bacterial eradication was observed in 96% (72 out of 75) of patients with throat swab positive for *streptococcus* day-2 onwards.
Bacterial LRTI	0.84	0.76	0.92	Beta(160,31)	Base case value[339]; assumption for the range +/- 10% of the base case value. Of 189 patients with confirmed bacterial LRTI treated with amoxicillin in primary care, illness deterioration occurred in 30 (16%).
Rickettsial infection	0	0	0	0	Penicillin is not effective against rickettsial infection [321]
Leptospirosis	0.99	0.90	1	Beta(11,1)	Base case value [322]; assumption for the range +/- 10%. All ten patients treated with amoxicillin had treatment success.
Bacteraemia	0.60	0.42	0.78	beta(10,7)	A 60% efficacy was assumed for base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution.

Dysentery	0.60	0.42	0.78	beta(10,7)	A 60% efficacy was assumed for base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution. Amoxicillin is not recommended for treatment of dysentery in 2005 WHO guideline due to poor mucosal penetration [323].
UTI	0.50	0.35	0.65	beta(10,7)	A 50% efficacy was assumed for the base case value due to high level of antibiotic resistance in *Enterobacteriaceae* isolated from UTI in Myanmar (52% of isolates are ESBL producer) [324], assumption for the range +/-30% of the base case value.
Azithromycin					
Bacterial URTI	0.81	0.73	0.89	Beta(176, 41)	Base case value [340]; assumption for the range +/- 10% of the base case value. In the reference study, bacterial eradication was observed in 81% (175 out of 215) of adolescents and adults with group A β haemolytic streptococcal pharyngitis/ tonsillitis treated with 3-day azithromycin.
Bacterial LRTI	0.90	0.81	0.99	beta(157,19)	Base case value [341]; assumption for the range +/- 10%. In the reference study, clinical cure rate occurred in 89.7% (156 out of 174) of patients treated with azithromycin.
Rickettsial infection	0.97	0.87	0.99	beta(148,5)	Base case value [162]; assumption for the range +/- 10%. Of 151 treated patients, 147 (97%) had treatment success within 5 days.
Leptospirosis	0.97	0.87	0.99	beta(148,5)	Base case value[162]; assumption for the range +/- 10%. Of 151 treated patients, 147 (97%) had treatment success within 5 days.

Bacteraemia	0.60	0.42	0.78	beta(10,7)	A 60% efficacy was assumed for the base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution.
Dysentery	0.94	0.85	0.99	beta(33, 3)	Base case value[342]; assumption for the range +/-10%. In the reference study, treatment success was observed in 94% (32 out of 34) of patients treated with azithromycin at day 3.
UTI	0.40	0.28	0.52	beta(13, 13)	A 40% efficacy was assumed for base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to be 20% of the base case value to derive parameters for beta distribution. Azithromycin is generally not recommended to treat UTI due to low concentration in urine[328].
Amoxicillin + Azithromycin					
Bacterial URTI	0.96	0.86	0.99	Beta(73, 4)	Base case value [338]; assumption for the range +/- 10% of the base case value. In the reference study, bacterial eradication was observed in 96% (72 out of 75) of patients with throat swab positive for *streptococcus* day-2 onwards.
Bacterial LRTI	0.95	0.85	0.99	Beta(888,46)	Base case value [164]; assumption for the range +/- 10% of base case value. In the reference study, 30-day mortality was 5% (45 out of 932) patients on beta lactam plus macrolide treatment.
Rickettsial infection	0.97	0.87	0.99	Beta(148,5)	Base case value [162]; assumption for the range +/- 10% of base case value. Of 151 treated

					patients, 147 (97%) had treatment success within 5 days.
Leptospirosis	0.97	0.87	0.99	Beta(148,5)	Base case value[162]; assumption for the range +/- 10%. Of 151 treated patients, 147 (97%) had treatment success within 5 days.
Bacteraemia	0.70	0.49	0.91	Beta(8, 4)	A 70% efficacy was assumed for base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to be 20% of the base case value to derive parameters for beta distribution.
Dysentery	0.94	0.85	0.99	Beta(33, 3)	Base case value[342]; assumption for the range +/-10%. In the reference study, treatment success was observed in 94% (32 out of 34) of patients treated with azithromycin at day 3.
UTI	0.70	0.49	0.91	Beta(8, 4)	A 70% efficacy was assumed for base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to be 20% of the base case value to derive parameters for beta distribution.
Doxycycline					
Bacterial URTI	0.85	0.77	0.94	Beta(163, 29)	Base case value [343]; assumption for the range +/- 10%. Clinical success was observed in 85% (162 out of 190) pneumonia patients treated with doxycycline at 3-5 weeks. Assumed the same efficacy as LRTI.
Bacterial LRTI	0.85	0.77	0.94	Beta(163, 29)	Base case value [343]; assumption for the range +/- 10%. Clinical success was observed in 85% (162 out of 190) pneumonia patients treated with doxycycline at 3-5 weeks.

Rickettsial infection	0.97	0.87	0.99	Beta(141, 6)	Base case value [162]; assumption for the range +/- 10%. Clinical cure was observed in 97% (140 out of 145) of patients treated with doxycycline.
Leptospirosis	0.97	0.87	0.99	Beta(141, 6)	base case value [162]; assumption for the range +/- 10%. Clinical cure was observed in 97% (140 out of 145) of patients treated with doxycycline.
Bacteraemia	0.50	0.35	0.65	Beta(13, 13)	A 50% efficacy was assumed for base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution.
Dysentery	0.60	0.42	0.78	Beta(10,7)	A 60% efficacy was assumed for the base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution. Tetracycline is not recommended for treatment of dysentery in 2005 WHO guidelines due to antimicrobial resistance [323].
UTI	0.60	0.42	0.78	Beta(10,7)	A 60% efficacy was assumed for the base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution.
Oral Rehydration Salt plus Zinc tablets					
Diarrhoea	0.93	0.83	0.99	Beat (950, 67)	Base case value[331]; assumption for the range +/- 10%. In the reference study (meta-analysis), of 1015 patients with watery diarrhoea treated

					with ORT, failure to rehydrate occurred in 66 (7%).

Table 8. Efficacy of current prescribing antibiotics for adolescents and adults

Parameter	Base case value	Range for sensitivity analysis		Probability distribution	Reference
		Low value	High value		
Beta-lactam antibiotics[1]					
Bacterial URTI	0.96	0.86	0.99	Beta(73, 4)	Base case value [338]; assumption for the range +/- 10% of the base case value. In the reference study, bacterial eradication was observed in 96% (72 out of 75) of patients with throat swab positive for *streptococcus* day-2 onwards.
Azithromycin[2]					
Bacterial URTI	0.81	0.73	0.89	Beta(176, 41)	Base case value [340]; assumption for the range +/- 10% of the base case value. In the reference study, bacterial eradication was observed in 81% (175 out of 215) of adolescents and adults with group A β haemolytic streptococcal pharyngitis/ tonsillitis treated with 3-day azithromycin.
Ciprofloxacin					
Rickettsioses	0.20	0.14	0.26	Beta(21, 80)	Ciprofloxacin has not been widely studied for treatment of rickettsioses. A few case reports and small studies showed rickettsial infection successfully treated with ciprofloxacin [332-334]. A 40% efficacy is assumed for the based case value

					and +/- 30% for the range. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution.
Leptospirosis	0.20	0.14	0.26	Beta(21, 80)	There are few studies that investigated quinolones for treatment of leptospirosis in humans. Animal and in-vitro studies showed susceptibility of Leptospira to quinolones [335-337]. A 20% efficacy is assumed for based case value and +/- 30% for the range. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution.
Bacteraemia	0.20	0.14	0.26	Beta(21, 80)	A prospective study showed that 9.5% of febrile adolescents and adults in Myanmar had blood stream infection. Half of them were caused by enteric fever (*S.* Typhi and Paratyphi isolates were 100% resistant to ciprofloxacin) [149]. A 20% efficacy is assumed for the based case value and +/- 30% for the range. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution.
Chloramphenicol					
Rickettsioses	0.86	0.78	0.96	Beta(25, 5)	Base case value [344]; assumption for the range +/- 10% of the base case value. In the reference study, the cure rate was 86% (24 out of 28) in patients treated with chloramphenicol.
Leptospirosis	0	0	0	0	Leptospira are not susceptible to vancomycin, rifampicin, metronidazole, and chloramphenicol [321].
Bacteraemia	0.50	0.35	0.65	Beta(13, 13)	A recent prospective study in Myanmar showed that 9.5% of hospitalized febrile adolescents and adults had blood stream infection. Half of them were

					caused by enteric fever (all *S.* Typhi and Paratyphi isolates were 100% sensitive to chloramphenicol) [149]. A 50% efficacy is assumed for based case value and +/- 30% for the range. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution.
Antibiotics					
Dysentery	0.60	0.40	0.80	Beta(10,7)	A 60% efficacy was assumed for the base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution.
Antibiotics					
UTI	0.60	0.40	0.80	Beta(10,7)	A 60% efficacy was assumed for base case value due to lack of empirical data. Assumption for the range +/-30% of the base case value. The standard error was assumed to be 20% of the base case value to derive parameters for the beta distribution.
Oral Rehydration therapy					
Diarrhoea	0.93	0.83	0.99	Beat (950, 67)	Base case value[331]; assumption for the range +/-10%. In the reference study (meta-analysis), of 1015 patients with watery diarrhoea treated with ORT, failure to rehydrate occurred in 66 (7%).
[1] Efficacy of beta-lactam antibiotics (in the current practice) for other aetiologies or diseases (Bacterial LRTI, rickettsioses, leptospirosis, and bacteraemia) is assumed to be the same as amoxicillin efficacy in the empirical treatment. [2] Efficacy of azithromycin (in the current practice) for other aetiologies or diseases (Bacterial LRTI, rickettsioses, leptospirosis, and bacteraemia) is assumed to be the same as azithromycin efficacy in the empirical treatment.					

Table 9. Parameters for calculation of disability adjusted life years (DALYs)

Parameter	Alive	Dead	Reference/ Source
Children			
Age (years) at the onset of febrile illness (a)	5	5	Median age of children with febrile illness in the MAM VHW data.
Years of life lost due to premature dead at age (a)	-	64	Expectancy of life at 5-9 years age group (WHO life table for Myanmar) [345]
Disability weight (acute infectious episode, moderate illness)	0.051	0.051	WHO 2019 global health estimate [346]
Duration of moderate illness (year)	7/365	7/365	Assumed parameter
Disability weight (acute infectious episode, severe illness)	-	0.133	WHO 2019 global health estimate[346]
Duration of severe illness (year)	-	7/365	Assumed parameter
Adolescents and adults			
Age (years) at onset of febrile illness (b)	35	35	Median age of adolescents and adults with febrile illness in the MAM VHW data.
Years of life lost due to premature dead at age (b)	-	36	Expectancy of life at 35 - 39 years age group (WHO life table for Myanmar) [345]
Disability weight (acute infectious episode, moderate illness)	0.051	0.051	WHO 2019 global health estimate [346]
Duration of moderate illness (year)	7/365	7/365	Assumed parameter
Disability weight (acute infectious episode, severe illness)	-	0.133	WHO 2019 global health estimate [346]
Duration of severe illness (year)	-	7/365	Assumed parameter
DALY = YLL (years of life lost) + YLD (years lost due to disability) YLL = no. of deaths × years of life lost due to premature death at age of death			

YLD = no. of illness × disability weight × duration of disability before remission or death

Table 10. Parameters for the cost

Parameters	Base case value (US$)	Range for sensitivity analysis		Probability distribution	Reference
		Lower (US$)	Upper(US$)		
Cost per consultation	5.9	4.1	10.3	Gamma(25, 0.236)	The cost was estimated by dividing annual support cost for malaria community health worker (CHW) program in Myanmar by annual median number of consultations per CHW (MAM data). The base case value (2215 US$/ 378), lower value (1511 US$/378) and upper value (3878 US$/378) [184]. A standard error of 20% was assumed to calculate parameters for the gamma distribution.
Cost for a full course of antibiotics					
Amoxicillin	1.5	1.2	1.8	Gamma(25, 0.06)	Base case value was estimated based on the price available on UNICEF supply catalogue (2022), https://supply.unicef.org/ , assumption for the range +/- 20% of the base case value.
Azithromycin	1.1	0.9	1.3	Gamma(25, 0.044)	
Amoxicillin + azithromycin	2.6	2.1	3.1	Gamma(25, 0.104)	

Doxycycline	0.4	0.3	0.5	Gamma(25, 0.016)	A standard error of 20% was assumed to calculate parameters for the gamma distribution.
Ciprofloxacin	0.5	0.4	0.54	Gamma(25, 0.02)	
Chloramphenicol	0.6	0.4	0.7	Gamma(25, 0.024)	
Other cost					
ORS + Zinc tab	0.8	0.64	0.96	Gamma(25, 0.032)	Ref: UNICEF supply catalogue (2022)
Cost of CRP rapid test	2.0	1.6	2.4	Gamma(25, 0.08)	Base case value [190]; assumption for the range +/- 20% of the base case value. A standard error of 20% was assumed to calculate parameters for the gamma distribution.
Health care cost	188.9	135.1	242.7	Gamma(25, 7.56)	This represents extra health care costs for deteriorating patients before they die. We assumed 5 days inpatient treatment cost in a medical ward at a 200-bed public hospital in Myanmar [347].
Loss of work	11.4	9.1	13.7	Gamma(25, 0.46)	Base case value: the cost was calculated by minimum daily wage multiplied with 5 assuming 5 days loss of work due to febrile illness (minimum daily wage = 4800 MMK [348]). Assumption for the range +/- 20% of base case value.
AMR cost contributed by a full course of antibiotics					
Amoxicillin	0.36	0.10	1.13	Gamma(25, 0.014)	Base case value [185]; assumption for the range +/- 20% of the base case value. A standard error of 20% was assumed to calculate parameters for the gamma distribution.
Azithromycin	0.01	0	0.03	Gamma(25, 0.0004)	
Amoxicillin + Azithromycin	0.37	0.10	1.16	Gamma(25, 0.015)	

Doxycycline*	0.10	0.05	0.15	Gamma(25, 0.004)	
Ciprofloxacin	0.68	0.19	2.1	Gamma(25, 0.027)	
Chloramphenicol*	0.10	0.05	0.15	Gamma(25, 0.004)	
* Assumed the same AMR cost as narrow spectrum penicillin due to lack of empirical data.					

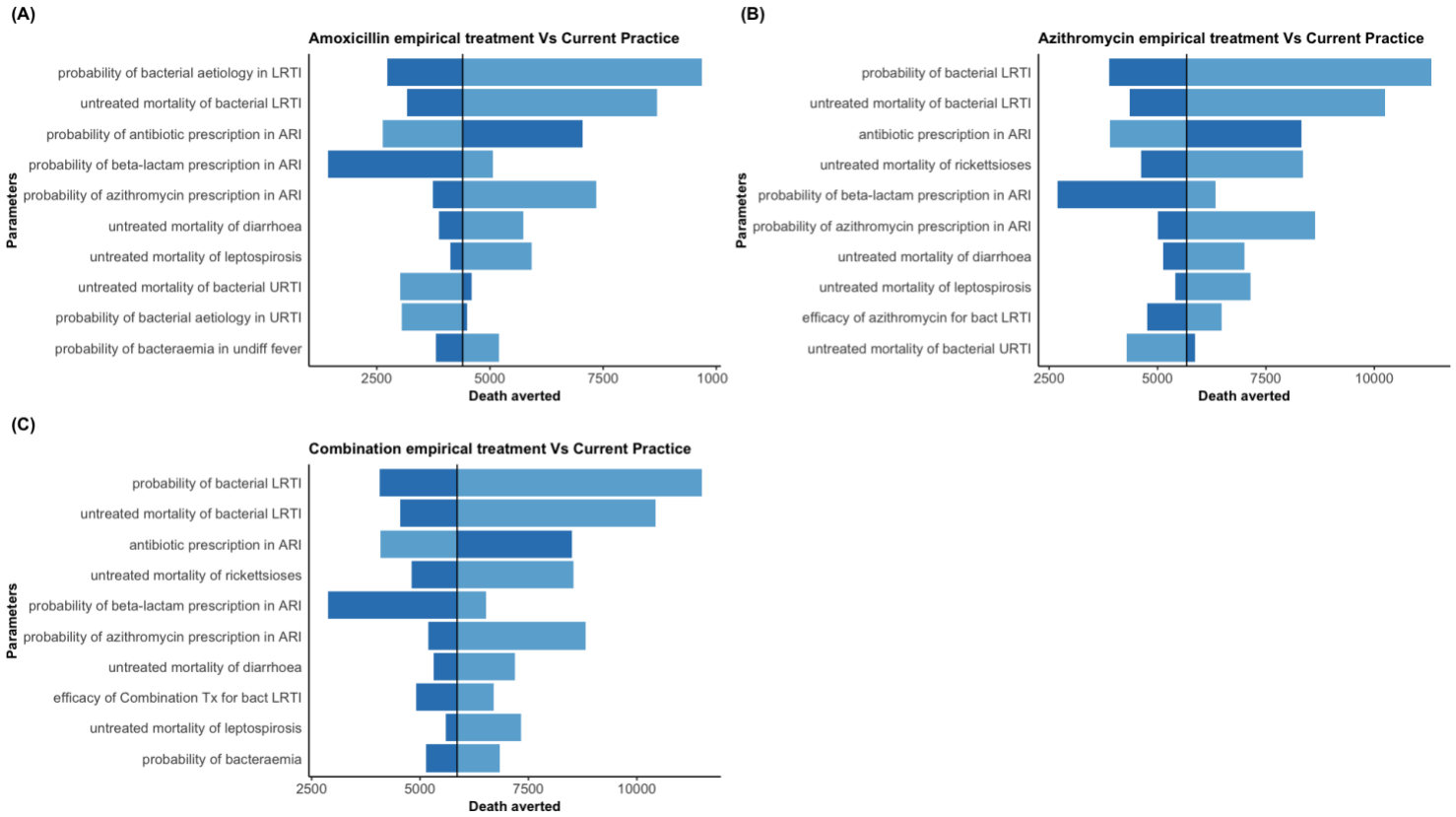


Figure 1. Deterministic one-way sensitivity analysis comparing empirical treatment against the current practice for children. The vertical lines represent the base case number of deaths averted.

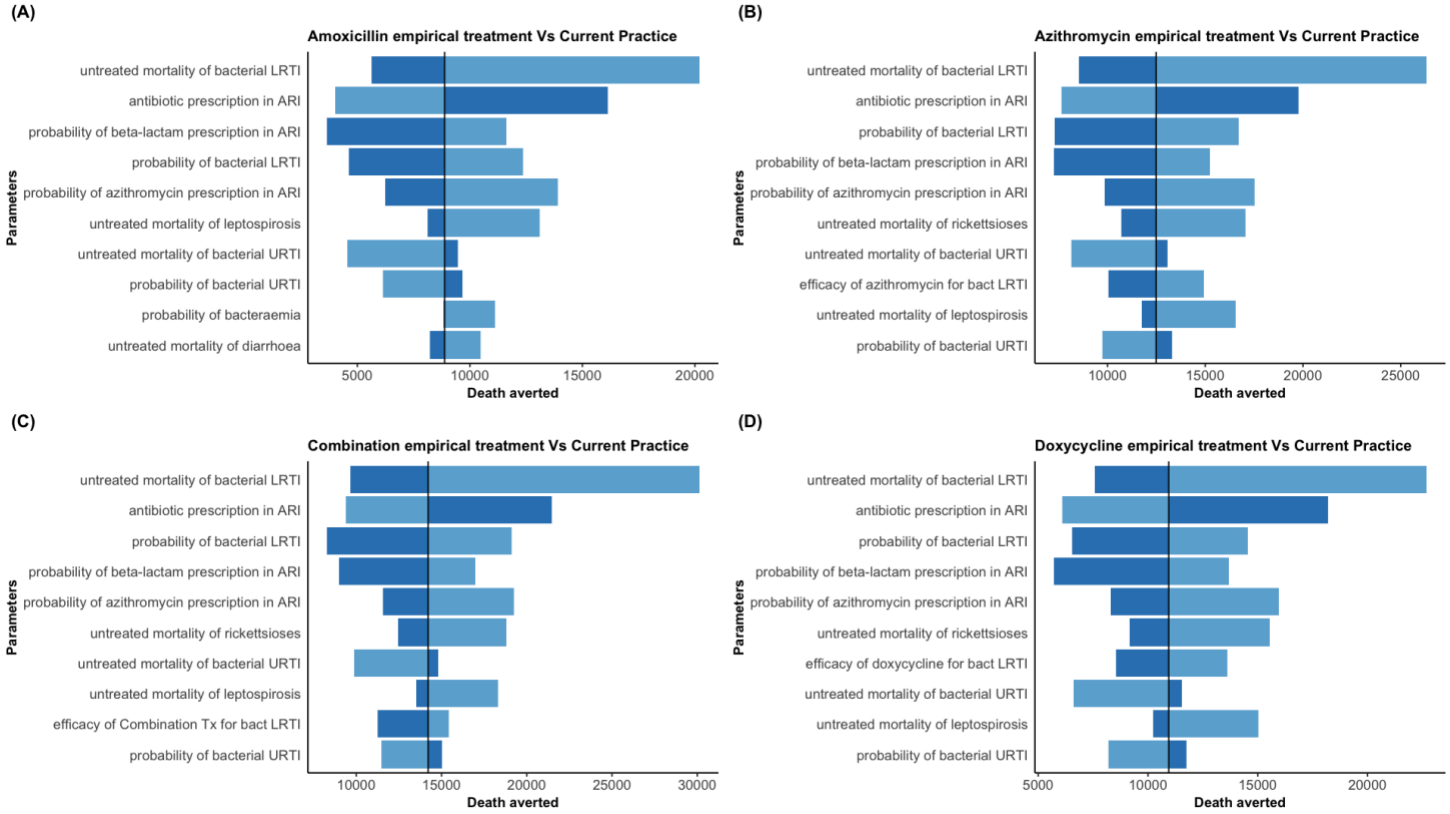


Figure 2. Deterministic one-way sensitivity analysis empirical treatment against the current practice for children. The vertical lines represent the base case number of deaths averted.

Appendix for chapter 4

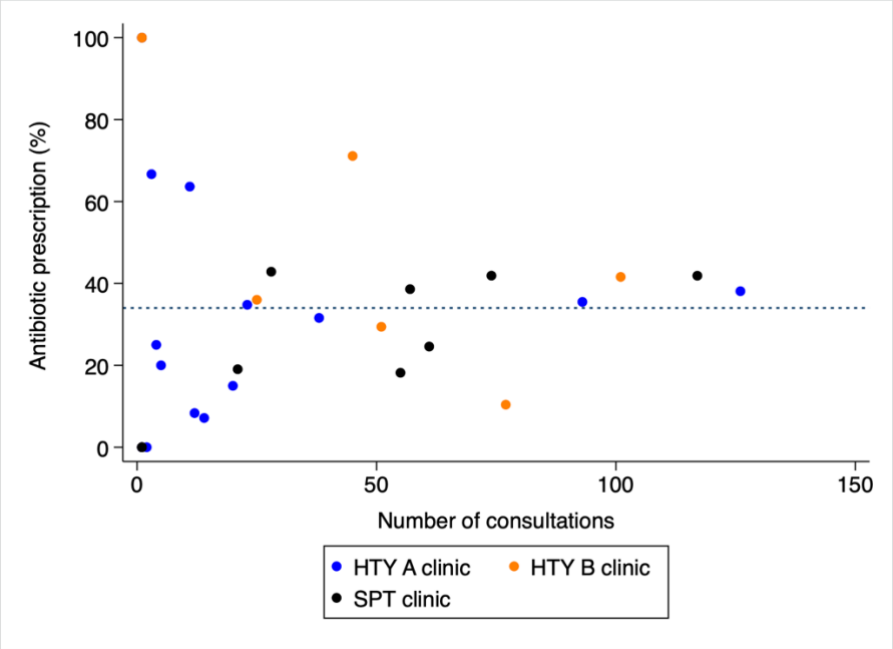


Figure 1. Scatter plot showing observed prescription rate of prescribing doctors in three clinics. Each dot represents a prescribing doctor with corresponding prescription rate in y-axis and number of consultations in x-axis. A horizontal dashed line represents overall prescription rate. Prescribing doctors with at least two consultations are shown in the figure for clarity.

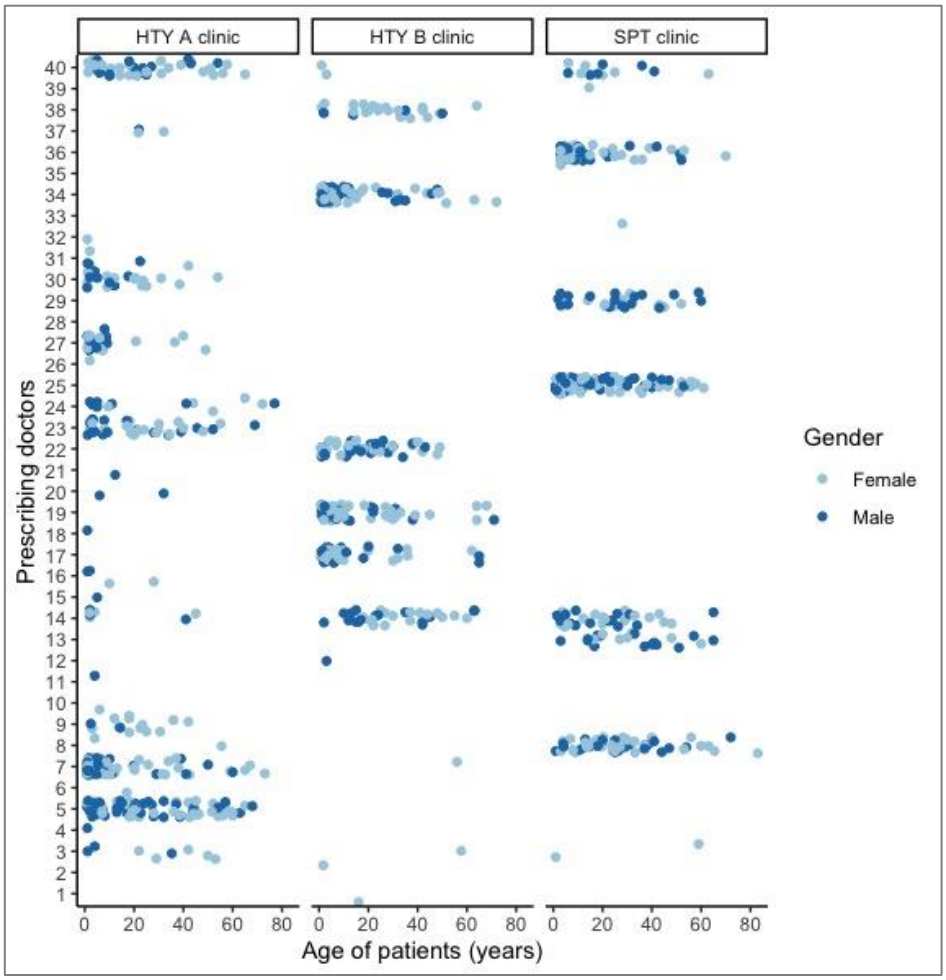


Figure 2. Dot plot showing distribution of age and gender of patients consulted by each prescribing doctor in three clinics. Each dot represents a single (light blue dot represents female patient and purple dot represents male patient). y-axis shows each prescribing doctor and x-axis shows distribution of age of patients (years) within each prescriber in three clinics.

Appendix for chapter 5

Table 1. *B. pseudomallei* positive and negative townships in 15 states and regions of Myanmar

States and regions	*B. pseudomallei* positive townships, n=21	*B. pseudomallei* negative townships, n=140
Ayeyawady	Bogale, Hinthada, Kangyidaunt, Maubin, Pyapon, Thabaung	Danubyu, Ingapu, Kyaunggon, Labutta, Myanaung, Myaungmya, Ngapudaw, Pantanaw, Yegyi
Kayin	Hpa-An, Kawkareik, Myawaddy	Kyainseikgyi, Thandaunggyi
Bago	Paukkhaung, Paungde, Shwedaung, Zigon	Daik-U, Kawa, Kyaukkyi, Letpadan, Nyaunglebin, Okpho, Penwegon, Phyu, Swar, Taungoo, Thanatpin, Waw, Yedashe
Rakhine	Gwa, Kyaukphyu	Ramree, Thandwe, Toungup
Mon	Kyaikmaraw, Thanbyuzayat	Bilin, Chaungzon, Kyaikto, Mawlamyine, Paung, Thaton, Ye
Yangon	Hmawbi, Kyauktan, Twantay	Dala, Hlaingtharya, Hlegu, Htantabin, Kawhmu, Kayan, Kungyangon, Shwepyithar, Taikkyi, Thanlyin, Thongwa
Magway	Magway	Aunglan, Chauk, Myaing, Myothit, Natmauk, Pakokku, Pauk, Pwintbyu, Salin, Sinbaungwe, Taungdwingyi, Yenangyaung, Yesagyo
Kachin		Bhamo, Hpakant, Kamine, Machanbaw, Mogaung, Mohnyin, Momauk, Myitkyina, Nanmati, Putao, Waingmaw
Sagaing		Ayadaw, Chaung-U, Depayin, Kale, Kalewa, Kawlin, Khin-U, Mawlaik, Monywa, Myinmu, Pale, Sagaing, Salingyi, Shwebo, Taze, Wetlet, Wuntho, Ye-U, Yinmabin
Mandalay		Kyaukse, Madaya, Mahlaing, Meiktila, Myingyan, Natogyi, Pyawbwe, Pyinoolwin, Singu, Taungtha, Thazi, Wundwin
Kayar		Bawlakhe, Demoso, Hpasawng, Loikaw

Tanintharyi		Bokpyin, Dawei, Kawthoung, Launglon, Myeik, Palaw, Tanintharyi, Thayetchaung, Yebyu
Shan		Hopong, Hsihseng, Hsipaw, Kalaw, Kyaukme, Lashio, Loilem, Nansang, Naungkhio, Nyaungshwe, Phekon, Pindaya, Pinlaung, Pinlon, Shwenyaung, Taunggyi, Yatsuk
Naypyitaw		Lewe, Poke Ba Thi Ri, Pyinmana, Tatkon, Zay Yar Thi Ri
Chin		Falam, Hakha, Paletwa, Tedim, Thantlang

Table 2. Site and sample positivity of *B. thailandensis* in 15 states and regions of Myanmar

State and regions	Site Positivity	Sample Positivity
Ayeyawady	10/36 (28%)	20/360 (6%)
Kayin	7/24 (29%)	11/240 (5%)
Bago	6/37 (16%)	10/370 (3%)
Rakhine	2/13 (15%)	8/130 (6%)
Mon	13/26 (50%)	29/260 (11%)
Yangon	7/36 (19%)	10/360 (3%)
Magway	4/29 (14%)	6/290 (2%)
Kachin	8/28 (29%)	11/280 (4%)
Sagaing	5/42 (12%)	5/420 (1%)
Mandalay	4/24 (17%)	10/240 (4%)
Kayar	2/9 (22%)	2/90 (2%)
Tanintharyi	2/20 (10%)	11/200 (6%)
Shan	2/36 (6%)	2/360 (1%)
Nay Pyi Taw	0/9	0/90
Chin	0/18	0/180
Total	72/387 (19%)	135/3870 (3%)

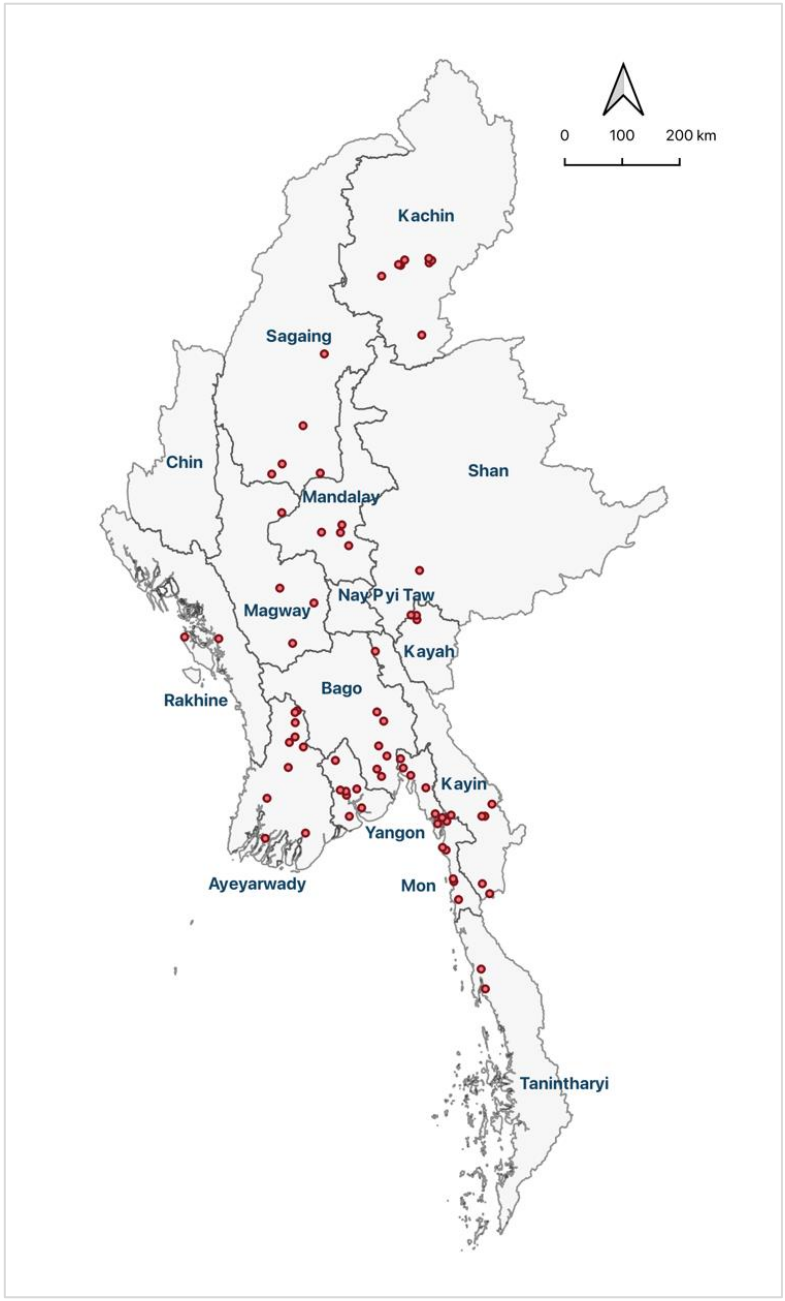


Figure 1. Distribution of *Burkholderia thailandensis* in 14 states and regions of Myanmar. Each dot represents a positive site (defined by at least one soil sample positive for *B. thailandensis*).