Evaluation of C-Reactive Protein Point of Care Testing, and Associated Research Challenges, to Improve the Quality of Antibiotic Prescribing in the Community in Northern Thailand

Thesis

Evaluation of C-Reactive Protein Point of Care Testing, and Associated Research Challenges, to Improve the Quality of Antibiotic Prescribing in the Community in Northern Thailand

By

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ABSTRACT

Background

Antimicrobial resistance (AMR) is a global health challenge, disproportionally affecting low- and middle-income countries (LMICs). Antibiotic use is a key driver of AMR, yet data on their use in LMICs, and in the community where most antibiotics are consumed, are comparatively scarce. C-reactive protein (CRP) is used in some high-income countries to guide antibiotic prescription for community respiratory tract infections (RTIs). Little evaluation has taken place in LMICs.

Methods

A two year retrospective review of antibiotic use in primary care units (PCUs) across a northern Thai district was conducted. A RCT was carried out in ten Thai and Myanmar primary care clinics evaluating CRP testing to optimise antibiotic use in patients with a history of fever. CRP testing was reviewed in a subgroup with sore throats to determine its ability to identify Group A *Streptococcus* (GAS) infection.

Results

Few participants took antibiotics before attending PCUs. RTIs were the commonest infection presentation. Antibiotics appear to be overused in some self-limiting infections. Particularly high proportions were prescribed for sore throats, where the correlations between CRP levels and GAS were poor.

In the trial context, CRP testing significantly reduced the proportion of antibiotics prescribed in Thailand and Myanmar, although a non-significant reduction was seen when Thai participants were considered separately. CRP testing improved antibiotic targeting with respect to high CRP levels. Clinical outcomes and health-seeking behaviour during the study period were unaffected. Most healthcare workers and participants supported CRP testing.

Conclusions

While not uncommon, antibiotic overuse in routine primary care in Thailand was of lower magnitude than anticipated. CRP testing is unlikely to contribute to further large scale reduction in antibiotic prescribing but could better target their use. Identifying who needs antibiotics for sore throats remains challenging. Antimicrobial stewardship interventions in PCUs could have a large impact on prescribing but need to be multi-faceted in nature.

ACKNOWLEDGEMENTS

There have been many people present with me on this PhD journey who have made this thesis possible and the process a lot more enjoyable. Firstly, I would like to thank my supervisors. As my Director of Studies, Associate Professor Yoel Lubell has provided invaluable and constant support. I have learnt many things from him, and appreciate his supervision and kindness throughout our time working together. Secondly, I would like to thank my supervisors Professor Nicholas Day, Professor Christopher Butler and Associate Professor Phaik Yeong Cheah for their guidance, wisdom and support. I'm grateful for the belief Nicholas Day has shown in me from the start and for the opportunities he has given me.

I'm thankful to all those working in the Chiangrai Clinical Research Unit, especially the research nurses who worked tirelessly on the CRP RCT. I'm grateful for the help and friendship I received from Dr Supalert Nedsuwan and Dr Daranee Intralawan, who taught me much about primary care in Thailand. Living in Chiangrai was one of the most enjoyable aspects of the last few years. I am grateful for the welcome we received and the many Thai meals and coffees we shared together.

I'm indebted to the wider team in Mahidol Oxford Tropical Medicine Research Unit (MORU), especially the Clinical Trials Support Group who have ensured that this research could take place. Professor Mavuto Mukaka has taught me much about statistics and patiently answered my many questions. Special thanks go to Professor Stuart Blacksell for his support and advice as my Third Party Mentor and to Dr Leigh Jones for her enthusiastic and dedicated work as the student co-ordinator.

The CRP RCT would not have been possible without the inputs of Dr Thomas Althaus and Associate Professor Marco Haenssgen. I appreciate all the patients who willingly took part and gave their time to the trials, and for the funders who have made this work possible.

Finally, I would like to acknowledge and thank my husband, daughter and family who have supported me throughout this process and, helped me to keep this PhD and life in perspective.

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LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
AMR	Antimicrobial Resistance
AMRCP	Antimicrobial Resistance Containment and Prevention Programme
AOM	Acute Otitis Media
ARF	Acute Rheumatic Fever
ARIs	Acute Respiratory Infections
ASU	Antibiotic Smart Use
AWaRe	'Access', 'Watch', 'Reserve'
BCG	Bacillus Calmette-Guérin
BHS	Beta-Hemolytic Streptococci
CCRU	Chiangrai Clinical Research Unit
CI	Confidence Interval
CRF	Case Record Form
CRP	C-Reactive Protein
DDD	Defined Daily Dose
E. coli	*Escherichia coli*
EML	Essential Medicines List
ESKAPE pathogens	*Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and Enterobacter species
FDA	Food and Drug Administration
GAS	Group A *Streptococcus*
GDP	Gross Domestic Product
GI	Gastrointestinal
GP	General Practitioner

HIC	High-Income Country
HIV	Human Immunodeficiency Virus
IACG	United Nation Interagency Coordination Group on Antimicrobial Resistance
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IMCI	Integrated Management of Childhood Illness
IQR	Interquartile Range
IRR	Incidence Rate Ratio
KAP	Knowledge, Attitudes and Practices
KM	Kilometres
LMIC	Low- and Middle-Income Country
LRTI	Lower Respiratory Tract Infection
MDR	Multidrug Resistant
MOPH	Ministry of Public Health
MORU	Mahidol Oxford Tropical Medicine Research Unit
NCDs	Non-Communicable Diseases
NICE	National Institute for Health and Care Excellence
NPV	Negative Predictive Value
NSP-AMR	National Strategic Plan on Antimicrobial Resistance
OPD	Outpatient Department
(a)OR	(adjusted) Odds Ratio
PCU	Primary Care Unit
PhD	Doctor of Philosophy
POC	Point Of Care
PPV	Positive Predictive Value

RCT	Randomised Controlled Trial
RD	Risk Difference
RDT	Rapid Diagnostic Test
RDU	Rational Drug Use
RR	Relative Risk
RTI	Respiratory Tract Infection
S. aureus	*Staphylococcus aureus*
SAE	Serious Adverse Event
SDGs	Sustainable Development Goals
Spp.	Species
TB	Tuberculosis
UHC	Universal Health Coverage
UHS	Universal Health Scheme
UK	United Kingdom
URTI	Upper Respiratory Tract Infection
US	United States
USD	United States Dollar
UTI	Urinary Tract Infection
WBG	World Bank Group
WHO	World Health Organization

THE CANDIDATE'S CONTRIBUTION AND ASSOCIATED PUBLICATIONS

The work presented in this thesis was primarily carried out by myself with support from my supervisors and colleagues. I am the primary author of all thesis chapters with review from my supervisors. Yoel Lubell (YL) my Director of Studies, was the principal investigator on all studies included in this thesis. I conducted the literature review presented in Chapter 1.

For the antibiotic review, Prapass Wannapinij (PW, data manager) extracted the data from the Provincial and Public Health Office's databases, merged the data sets and carried out the first level of coding for the inclusion criteria. Nipaphan Kanthawang and Pratakpong Wongkiti (research nurses) helped to review the chief complaint field which was recorded in Thai, to confirm the history of fever inclusion criteria. I carried out the rest of the data cleaning, coding, analysis and drafted the manuscript with close supervision from YL and support from the co-authors. The manuscript has been published:

> **Greer RC**, Intralawan D, Mukaka M, et al. Retrospective review of the management of acute infections and the indications for antibiotic prescription in primary care in northern Thailand. BMJ Open. 2018;8(7):e022250-e. doi: 10.1136/bmjopen-2018-022250. PubMed PMID: 30061442.

For the CRP RCT, myself, Thomas Althaus (TA) and YL worked together to design the study, prepare the protocol and study documents. I was responsible for the Thai site-related activities which included recruiting and overseeing the research nurses training, site initiation visits and day to day running of the trial (aside from a period of maternity leave). TA co-ordinated the laboratory based activities in Bangkok and oversaw activities in Myanmar. He carried out the initial analysis and wrote the first draft of the manuscript which included the trial's primary outcome and participants' clinical outcomes:

Althaus T, **Greer RC**, Swe MMM, et al. 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. 2018;7(1):e119-e31. doi: 10.1016/S2214-109X(18)30444-3. PubMed PMID: 30554748.

I was heavily involved in these processes, alongside YL. For the thesis chapter I reviewed, adapted and redid the analysis. New additional analyses for the thesis include the use of the "AWaRe" antibiotic categories, logistic regression analyses for healthcare workers' concordance with the CRP results and their opinions towards the CRP test. I carried out further data cleaning and coding, and led all the analyses for Chapters 4 and the GAS nested study (Chapter 3) with support from YL, my PhD supervisors and the other co-authors. Marco Haenssgen (MH, social scientist) led the creation of the Knowledge, Attitudes and Practices (KAP) questionnaire for healthcare workers and the participants' opinions of CRP testing with input from myself, TA and YL.

The nested GAS study in Chapter 3 is based upon the following publication:

Greer R, Althaus T, Ling C, et al. Prevalence of Group A Streptococcus in primary care patients and the utility of C-reactive protein and clinical scores for its identification in Thailand. Am J Trop Med Hyg. 2020;102(2):377-83. doi: 10.4269/ajtmh.19-0502. PubMed PMID: 31889507.

The urine antibiotic activity and throat swab cultures were carried out in MORU's laboratories in Bangkok and at the Shoklo Malaria Research Unit in Tak Province, Thailand. Laboratory staff in Chiangrai carried out the CRP tests for the control group and processed the other samples for shipment. I'm grateful for all the people who co-ordinated and carried out this work.

Mavuto Mukaka (MM) has provided invaluable statistical support throughout and conducted the time-series analysis included in Chapter 2. YL created the cost-effectiveness figure included in Chapter 5.

Additional publications related to this work but not incorporated in this thesis include a publication which presents data on the causes of fever, using samples from the control group enrolled in the CRP randomised controlled trial (RCT, Chapter 3). It also evaluates the utility of CRP to distinguish between bacterial and viral pathogens:

> Althaus T, Thaipadungpanit J, **Greer RC**, Swe MMM, Dittrich S, Peerawaranun P, et al. Causes of fever in primary care in Southeast Asia and the performance of C-reactive protein in discriminating bacterial from viral pathogens. Int J Infect Dis. 2020;96:334-42. doi: https://doi.org/10.1016/j.ijid.2020.05.016.

The following paper describes the interviews conducted with the healthcare workers involved in the CRP RCT (Chapter 3):

Haenssgen MJ, Charoenboon N, Althaus T, **Greer RC**, Intralawan D, Lubell Y. The social role of C-reactive protein point-of-care testing to guide antibiotic prescription in Northern Thailand. Soc Sci Med. 2018;202:1-12. doi: 10.1016/j.socscimed.2018.02.018. PubMed PMID: PMC5910303.

I was involved in the following survey of antibiotic use in villagers in Chiangrai, Thailand and Salavan, Laos:

> Haenssgen MJ, Charoenboon N, Zanello G, Mayxay M, Reed-Tsochas F, Lubell Y, et al. Antibiotic knowledge, attitudes and practices: new insights from cross-sectional rural health behaviour surveys in low-income and middle-income South-East Asia. BMJ Open. 2019;9(8):e028224. doi: 10.1136/bmjopen-2018-028224.

Chapter 1 General Introduction to the Thesis, Thailand, Antimicrobial Resistance and Optimising Antibiotic Use

The overall aim of this thesis is to understand whether C-reactive protein (CRP) testing can be used to optimise antibiotic use in Thai primary care. In order to do this, current antibiotic use in primary care units (PCUs) was reviewed and a RCT conducted to evaluate the impact of CRP testing to guide antibiotic use in primary care patients with an acute febrile illness. A particular focus is on patients presenting with a sore throat and history of fever in whom antibiotic use is especially high. In this subset of patients the correlation between CRP results and clinical scores for tonsillitis was assessed, as was their utility in the identification of patients with group A *streptococcus* (GAS) positive throat swabs.

1.1 Introduction

Infections are amongst the commonest reasons for seeking healthcare, especially in LMICs where the burden of infectious diseases is high. Antibiotics are often prescribed to treat these infections and at times to prevent complications. However, as a general practitioner (GP) I know how challenging it can be to determine whether patients truly need antibiotics. Without access to diagnostics and knowledge of local epidemiology, clinicians can be left uncertain as to whether antibiotics should be prescribed. The desire to help patients recover quickly and to prevent illnesses from worsening needs to be balanced against the dangers of unnecessary antibiotic use. Antibiotics can cause side effects, increase treatment costs, medicalise self-limiting illnesses, encourage further attendances, as well as distracting from other treatment options. All this takes place against the background of antimicrobial resistance (AMR). Concerns about AMR are growing globally with the ultimate fear that resistant bacterial infections will become untreatable. As I sit writing this introduction, we are facing the start of the COVID-19 pandemic; this is a stark and all too real example of how our lives could change if we are unable to cure infections (bacterial or viral). If we are to preserve our precious supply of

antibiotics then support is needed for clinicians to enable them to optimise their antibiotic use; this will be the focus of my thesis.

In 2015 I found myself in northern Thailand with my husband, who was overseeing a new clinical research site: Chiangrai Clinical Research Unit (CCRU). We were the first investigators based there and set about building relationships with local collaborators and recruiting additional research staff. Thailand has been investing heavily in its primary care system and is trying to promote family medicine as a speciality, and therefore is an interesting place to conduct primary care research.

There are obvious differences between Thailand and the United Kingdom (UK) that shape both the disease burden and primary care services; Thailand is a tropical LMIC whereas the UK has a temperate climate and is a high-income country (HIC). Thailand has a higher burden of some infectious diseases such as human immunodeficiency virus (HIV), tuberculosis (TB) and dengue, along with less well known infections like scrub typhus and leptospirosis. Thailand has a complex healthcare system with substantial contribution from the private sector, unlike the UK where healthcare is predominantly delivered by the National Health Service. Antibiotics are available over the counter in Thailand whereas a prescription is required in the UK.

Despite these differences there are similarities between the countries; both have democratic governments and a constitutional monarch. Both recognise the importance of universal health coverage (UHC) and primary healthcare, and have the infrastructure in place to deliver this. Both have ageing populations and increasing levels of non-communicable diseases (NCDs).

As part of my Doctor of Philosophy (PhD) I was keen to learn more about how infections are normally managed, what determines antibiotic use and whether it was accurate that almost everyone gets an antibiotic when unwell in Thailand. I wanted to see if simple interventions could be introduced to reduce unnecessary antibiotic use at the same time as identifying those who need antibiotics. This is

especially important in settings with more vulnerable populations who struggle to access healthcare and follow-up appointments.

In this introductory chapter I will provide some background context for Thailand and its healthcare system. A brief overview of AMR will be given, including Thailand's response to date. I will then move on to consider antibiotics, the reasons for overusing antibiotics, their prescription in Thai primary care, what optimal use looks like and how it may be achieved. Finally the gaps in knowledge and research questions I hope to answer in this thesis will be summarised.

1.2 Country Context: Thailand

Thailand is a country in Southeast Asia affectionately known as the Land of Smiles. It shares borders with Myanmar, Laos, Cambodia and Malaysia. Thailand has a population of almost 70 million people and is the third largest country in Southeast Asia [1]. According to the national census in 2010, 95% of the population were Thai and over 90% were Buddhist. The majority of the population live in rural areas [2].

Thailand became an upper middle-income country in 2010 [3]; its key development indicators are summarised in Table 1-1. The main focus of the economy has shifted from agriculture to services and manufacturing; although many of the poor continue to work in agriculture [3-5]. Regional inequalities exist with the northern and northeastern regions being poorer than the central and southern regions of Thailand [3, 5]. In comparison to many of its neighbours, Thailand is relatively stable and forward thinking; it has taken up international leadership positions in the development of programmes such as the sustainable development goals (SDGs) [3, 6].

Great progress has been made in education with over 99% of those eligible now enrolled in primary school education, although this does not guarantee attendance and the quality of education in some areas is viewed as needing improvement [1, 3]. Nationally, 5.2% of the population have never studied and 57.6% have completed only some level of primary school education [5].

Indicator	Number	Year	Reference
Population (millions)	69.4	2018	WBG, 2019 [1]
GDP (billion USDs)	505.0	2018	WBG, 2019 [1]
GDP growth rate (annual %)	4.1	2018	WBG, 2019 [1]
Gross national income per capita (USDs)	6,610	2018	WBG, 2019 [1]
Poverty headcount ratio (% below the national poverty line)	8.6	2016	WBG, 2019 [1]
Primary school enrolment (%)	99.63	2017	WBG, 2019 [1]
Educational attainment (years)	9.1	2017	IHME, 2018 [7]

Table 1-1: Key development indicators for Thailand

GDP: Gross Domestic Product, IHME: Institute for Health Metrics and Evaluation, USDs: United States Dollars, WBG: World Bank Group.

1.2.1 The Thai Healthcare System

The Thai healthcare system is made up of public, private and a small number of charitable providers; almost 80% of hospital beds are provided by the public healthcare system [8]. The public healthcare system has benefitted from continued political and financial investment in recent years leading to the introduction of UHC in 2002, when 18 million uninsured people received cover and additional coverage was given to 29 million people [8-10]. Out of pocket health expenses have reduced as have some health inequalities, although more needs to be done to help at risk populations, particularly migrant workers and the poor [4, 9-12].

Alongside the Universal Health Scheme (UHS), there are insurance schemes for civil servants and private sector employees. Those living in more affluent areas and cities have higher levels of private health insurance and care tends to be provided by private clinics and hospitals. In poorer, rural areas there is more reliance on the UHS and public primary care providers [5, 8].

The public healthcare system provides provincial and district level hospitals as well as PCUs, which are present in each sub-district with a population over 5,000 people [8]. Patients are able to access hospital (inpatient and outpatient) care directly and provincial hospitals provide all levels of care

(tertiary, secondary and primary) to those in their catchment area which seems to encourage acute rather than chronic care and preventative medicine [8].

Thailand meets the World Health Organization's (WHO's) recommended ratio of healthcare workers to population, however not all of them work in the public sector and the vast majority work in hospital specialities [8, 13]. PCUs are typically staffed by public health officers and nurses. Only 5% have a doctor on site due to low doctor numbers and the traditional set up; the majority of primary care trained doctors are based in the hospitals which oversee the PCUs in their catchment areas [14]. Incentives have been introduced to increase the numbers of medical graduates going into primary care with limited success.

1.2.2 The Burden of Diseases in Thailand

The leading causes of death in Thailand are NCDs. Communicable, maternal, perinatal and nutritional conditions represent 16% of the deaths, and 10% are caused by injuries [15]. In 2017, the highest ranking infectious diseases were lower respiratory tract infections (LRTIs) and HIV/AIDS (acquired immune deficiency syndrome) [7].

The WHO Thailand Country Cooperation Strategy (2017-2021) identified five priority areas which are AMR, global health diplomacy (international trade and health), migrant health, NCDs and road safety [9]. Key health indicators for Thailand are summarised in Table 1-2.

Thailand has an extensive childhood vaccination programme with good coverage; it includes the following routine vaccinations for 2020: Bacillus Calmette-Guérin (BCG), hepatitis B, diphtheria, pertussis, tetanus, polio, *Haemophilus influenzae* type B, rotavirus, Japanese B Encephalitis, measles, mumps, rubella, and human papillomavirus vaccinations [16, 17]. Hepatitis A and pneumococcal vaccinations are available but not yet part of the routine schedule [16].

Indicator	Number	Year	Reference
Life expectancy at birth (years):		2016	WHO, 2019 [18]
All	75.5		
Female	79.3		
Male	71.8		
Fertility rate (births/woman)	1.5	2017	WBG, 2019 [1]
Maternal mortality rate (per 100,000 live births, [uncertainty interval])	38 (34 - 42)	2015	WHO, 2019 [19]
Under 5 mortality rate (per 1,000 live births)	8.7	2017	IHME, 2018 [7]
Prevalence of HIV (% of those aged 15 - 49)	1.1	2018	WBG, 2019 [1]
Estimated vaccination coverage (%):		2018	WHO, 2019 [17]
Measles 2nd dose	87		
BCG	99		
Diphtheria, tetanus & pertussis	97		
Hepatitis B	97		
Polio	97		
Healthcare access and quality index (based on amendable mortality)	69.5	2016	WHO, 2019 [19]
Healthcare workers (per 10,000 population):		2017	WHO, 2019 [18]
Doctors	8.1		
Nurses and midwives	29.6		
Dentists	1.7		
Pharmacists	4.2		
Proportion of GDP spent on healthcare (%)	6.5	2014	SEARO, 2017 [9]

Table 1-2: Health indicators and vaccine coverage in Thailand

GDP: gross domestic product, SEARO: WHO's regional office for South-East Asia

1.3 Antimicrobial Resistance

1.3.1 Introduction to Antimicrobial Resistance

Antimicrobial resistance (AMR) occurs when microorganisms (e.g. bacteria, viruses, fungi, parasites) are able to tolerate exposure to antimicrobials (e.g. antibiotics, anti-virals, anti-fungals, anti-malarials) at levels which would normally be fatal or inhibit their growth. This resistance means that

some infections become untreatable and fatalities can occur from previously manageable infections. AMR can lead to increased morbidity through longer illnesses and hospital stays, and treatment costs and adverse reactions can be increased through the need to use 2nd and 3rd line antibiotics. Widespread AMR, and antibiotic resistance in particular, can have wider detrimental effects on health and healthcare services[1]. Antibiotics are commonly used prophylactically for surgical procedures or to prevent infections in immunosuppressed patients. AMR threatens our ability to conduct these lifesaving and life improving treatments. Unless AMR is tackled now it is thought that WHO's SDGs for 2030 may be unattainable and recent advances could be over turned [20, 21].

1.3.2 The Development and Transmission of Antimicrobial Resistance

AMR is a naturally occurring event, which is thought to lead to a survival advantage for those bacteria. Bacteria develop resistance through two main mechanisms: preventing the antibiotic from reaching its target, and modifying the antibiotic or its target stopping the antibiotic from entering the bacteria [22, 23]. Acquired resistance can occur through random mutations or be received from another resistant microorganism through horizontal gene transfer, commonly through plasmids [22, 24-26].

Use, overuse or misuse of antibiotics is thought to be one of the main drivers of AMR [22, 25, 27-29]. A meta-analysis of studies evaluating antibiotic use in the community for respiratory tract infections (RTIs) and urinary tract infections (UTIs) found that individuals (both adults and children) prescribed antibiotics (amoxicillin and trimethoprim) were more likely to develop antibiotic resistance to that antibiotic than those not prescribed antibiotics and that this effect could persist for 12 months [30]. Several limitations do apply because most of the studies were observational, did not collect antibiotic adherence data and were conducted in HICs [30]. At the population level, in Europe, AMR in *Streptococcus pneumoniae, Streptococcus pyogenes* (or GAS) and *Escherichia coli* (*E. coli)* is more

[1] For the remainder of my thesis I will use 'AMR' to refer to resistance to antibiotics, rather than all antimicrobials.

prevalent with increased antibiotic use in the community [31]. The link between human antibiotic use and AMR is, however, complex and can be affected by many factors including those related to the healthcare system such as availability of diagnostics, antibiotics and infection control, as well as by public health factors such as vaccine coverage, sanitation, living conditions and lifestyle factors such as travel and migration [22, 32].

1.3.3 The Burden of Antimicrobial Resistance

1.3.3.1 The Global Burden of Antimicrobial Resistance

Understanding the burden of AMR is important in order to motivate action and to target interventions to tackle AMR. However, reliable estimates are challenging to produce because of the paucity of surveillance data on AMR infections and their clinical outcomes [32-36].

O'Neill and colleagues estimated that 700,000 deaths a year were attributable to AMR globally in 2014 but this could rise to 10 million per year by 2050 [33]. The reliability of these estimates has been discussed; the main limitations are the lack of global data and the need to extrapolate estimates for the United States (US) and Europe to the rest of the world leading to high levels of uncertainty [34, 37]. They estimated that the high level economic costs of AMR could reduce gross domestic product (GDP) globally by 2% to 3.5%, this is consistent with estimates from the World Bank Group (WBG) [20, 33]. Both groups felt poorer regions would be more affected and argue that tackling AMR now, although costly will actually save money in the future [20, 33].

1.3.3.2 The Burden of Antimicrobial Resistance in Thailand

On a national level there have been two key studies estimating the mortality burden of AMR in Thailand [38, 39]. Lim et al. used retrospective data from nine public hospitals to calculate excess 30 day mortality for those admitted with a multidrug resistant (MDR) bacteraemia compared to a non-MDR bacteraemia. They estimate that in 2010, in Thailand, 19,122 out of 45,209 (43%) deaths of patients with hospital-acquired infections were attributable to MDR infections [38]. Pumart et al.

estimated that at least 3.24 million extra days in hospital and 38,481 deaths were due to AMR infections in 2010. Using a societal perspective, the indirect costs of morbidity and premature mortality were estimated to be at least 40,000 million Thai Baht [39].

Phodha et al. estimated the additional treatment costs of having a resistant HAI compared to a susceptible one, from the hospital's perspective. After adjusting for potential confounders including the infection site and bacteria, they estimated resistant infections cost 42% more than susceptible infections. Nationally, this would equate to an additional 2.3 billion United States Dollars (USDs) being spent on treating AMR infections a year. Taking a societal perspective, they estimate that 4.2 billion USDs could be saved a year when taking into account premature deaths and reduced quality of life in people who have had AMR infections [40].

Shrestha et al. estimated the economic cost of AMR per antibiotic dose consumed in Thailand and the US, using data from the Lim et al. [38] and Pumart et al. [39] studies mentioned above [41]. They tried to capture the direct treatment costs for resistant rather than susceptible infections and the indirect societal productivity losses due to premature deaths from five resistant infections. The total estimated annual economic costs of AMR were 0.5 billion USDs in Thailand. The cost per standard unit (smallest deliverable dose) of co-amoxiclav was 0.7 (0.2 to 2.1) USDs. These estimates are likely to be conservative due to the captured costs and productivity losses. The estimates are limited by the quality of data used, the number of organisms included, the lack of community data and reliance on expert opinion [41]. However, these estimates do provide a starting point to compare the costs of AMR interventions against the likely economic benefits.

1.3.4 The Response to Antimicrobial Resistance

1.3.4.1 The Global Response to Antimicrobial Resistance

A one health approach is increasingly recognised as vital to the fight against AMR, recognising that multiple players and sectors are involved in antimicrobial use and health [21, 32, 42, 43]. In 2015, the

World Health Assembly endorsed WHO's global action plan on AMR [32]. A year later it received political backing from the United Nations General Assembly [21]. This global action plan identified five strategic objectives:

- *'To improve awareness and understanding of antimicrobial resistance through effective communication, education and training.*
- *To strengthen the knowledge and evidence base through surveillance and research.*
- *To reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures*
- *To optimize the use of antimicrobial medicines in human and animal health.*
- *To develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions*' [32].

1.3.4.2 The Thai Response to Antimicrobial Resistance

Thailand's first national strategic plan on antimicrobial resistance (NSP-AMR) was endorsed by the cabinet in 2016 [44]. It advocates for a one health approach, engagement with society, and use of local evidence. Thailand's NSP-AMR has five goals (reduce AMR morbidity by 50%, reduce antimicrobial consumption in humans by 20% and in animals by 30%, increase knowledge of AMR and appropriate use of antimicrobials amongst the public by 20%, and increase the capacity of the national AMR management system). To achieve this it has six strategies (surveillance, regulation, infection prevention and control in humans, AMR prevention and control in agriculture and animals, and public knowledge) [44]. Progress towards the NSP-AMR objectives include the expansion of Thailand's national AMR surveillance centre to cover 85 hospitals [45]. In comparison with other countries in the WHO South-East Asia region Thailand's AMR response has been quite advanced [46].

Much work still needs to be done in order to understand the burden and effects of AMR in Thailand. The quality of laboratory surveillance data needs to be improved and linked to clinical outcome data.

The paucity of community based data needs addressing and progress towards the Thai NSP-AMR needs formal evaluation.

1.4 Antibiotics

1.4.1 Introduction to Antibiotics

Antibiotics are medications used to treat and prevent bacterial infections. Early discoveries date back to the early 1900s but it wasn't until World War II that many new discoveries were made [47, 48]. The development of new antibiotics has since slowed and a limited number of those under development may be effective against the Gram-negative ESKAPE pathogens (*Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and Enterobacter species), which cause particular concern when resistance develops [49].

Global total human antibiotic consumption increased by 65% between 2000 and 2015. By 2015, the total antibiotic consumption in LMICs was almost 2.5 times higher than in HICs and two thirds of the countries with the highest consumption rates were LMICs. The increased consumption of antibiotics in LMICs was positively associated with growth in GDP per capita [50]. The differences in antibiotic consumption between countries and regions are not fully understood. Variation may be affected by the quality of antibiotic use (e.g. having an appropriate indication for antibiotics) or could be explained by socio-economic factors, the availability of UHC and the burden of infectious diseases and AMR amongst other things [50-52].

WHO introduced the 'Access', 'Watch', 'Reserve' ("AWaRe") antibiotic classifications into their Essential Medicines List (EML) in 2017 in order to try to balance the need to access antibiotics whilst reducing the risk of AMR (Table 1-3) [53].

'Access'		'Watch'	'Reserve'
Amikacin	Cloxacillin	Azithromycin	Ceftazidime &
Amoxicillin	Doxycycline	Cefixime	avibactam
Amoxicillin/clavulanic	Gentamicin	Cefotaxime	Colistin
acid (co-amoxiclav)	Metronidazole	Ceftazidime	Fosfomycin
Ampicillin	Nitrofurantoin	Ceftriaxone	(intravenous)
Benzathine	Phenoxymethylpenicillin	Cefuroxime	Linezolid
benzylpenicillin	Procaine	Ciprofloxacin	Meropenem &
Benzylpenicillin	benzylpenicillin	Clarithromycin	vaborbactam
Cefalexin	Spectinomycin	Meropenem	Plazomicin
Cefazolin	Sulfamethoxazole/	Piperacillin &	Polymyxin B
Chloramphenicol	trimethoprim (Septrin)	tazobactam	
Clindamycin			

Table 1-3: 'Access', 'Watch' and 'Reserve' ("AWaRe") classification of antibiotics

Created from WHO, the Selection and Use of Essential Medicines 2019, executive summary [53]

WHO have set a target that more than 60% of antibiotic consumption should come from the 'Access' group; this group is effective against common pathogens, including most of those causing RTIs and has a lower risk of resistance developing [54]. The 'Watch' group has a higher risk of resistance and includes most of the Critically Important Antimicrobials; their use should be limited to the treatment of specific infections. The 'Reserve' group should be used as a 'last resort' to treat MDR infections [53].

1.4.2 The Value of Antibiotic Prescriptions for Common Community Infections

Antibiotics are commonly used for RTIs in the community [31, 55]. Cochrane reviews have found no evidence to support the use of antibiotics for the treatment of common colds and that antibiotics are unlikely to offer significant benefit for acute bronchitis [56, 57]. The situation is more complex for sore throats. A 2013 Cochrane review of antibiotics for sore throats found that symptoms resolved

16 hours earlier with antibiotics, only giving a modest benefit especially when you consider that over 80% of patients in the placebo group were better by one week. Antibiotics reduced suppurative complications including acute otitis media (AOM), sinusitis and quinsy and non-suppurative complications such as acute rheumatic fever (ARF), although data was drawn from studies conducted before 1961. The absolute benefit of antibiotics for individual patients will be less now given the low incidence rates of these complications, especially in HICs, where the authors estimate a number needed to benefit of almost 200 to prevent one case of AOM. The authors therefore conclude that antibiotics for sore throats should be discretionary rather than mandatory. Clinicians need to take into account the local incidence rates of complications and balance the benefits of antibiotics against the risks of antibiotic side effects and AMR [58]. In all these reviews data are lacking for children, the elderly, those with co-morbidities and those living in LMICs [56-58].

1.4.3 Reasons for Overuse or Sub-optimal Use of Antibiotics

The overuse of antibiotics is multifactorial. At the healthcare system level there can be concerns about access to healthcare and antibiotics; in lower income settings these challenges can be substantial and antibiotic prescribing can be seen as a necessity where following patients up or repeat visits are not possible [51, 59, 60]. If data on the incidence of common infections and resistance patterns are not available then clinicians may compensate for this by overly relying on broad spectrum antibiotics [32, 35, 42, 59, 61]. Poor drug quality or falsified medications can cause inadequate treatment, leading to further antibiotic use [32, 62-64]. Financial incentives and competition within systems can affect prescribing behaviours for example healthcare workers may be more likely to prescribe incentivised medicines [59, 65, 66].

At the healthcare worker level, antibiotics can be overprescribed due to concerns about illness severity and to prevent complications [66-69]. There can be genuine diagnostic uncertainty, especially in general practice where diagnostic tests are not always available [35, 59, 70]. Some doctors will prescribe antibiotics in order to preserve their doctor-patient relationship and meet the

patients' expectations for antibiotics, even though studies have found that patient expectations are often overestimated or misjudged [59, 66, 67, 69-73]. Other reasons for overprescribing antibiotics include high workloads, time pressure, poor communication and concerns about prolonged illnesses [66, 68, 70].

At the patient level, a lack of awareness of AMR and the role of antibiotics can increase antibiotic demands [59]. Concerns about the current illness and the risks of complications can lead to requests for antibiotics, as well as difficulties related to taking time off work or education due to illness [74, 75]. Factors at all these levels can result in a culture of sub-optimal antibiotic use. The interplay between these factors will be dependent on the local context and individuals involved.

1.4.4 Antibiotic Use in Thailand

For the most part, antibiotics are widely available and accessible through multiple sources in Thailand [76, 77]. The Thai Drug Act classes the majority of antibiotics as dangerous drugs which need to be dispensed by a pharmacist but do not require a prescription. However, antibiotic dispensing is not currently regulated and antibiotics can often be found in village stores and other shops without a pharmacist [76, 78]. Simulated client studies have shown that high proportions of patients attending pharmacies are given antibiotics for conditions for which they are unlikely to be beneficial: pharyngitis (74% to 87.5%) [79, 80], coughs and colds (75% to 76%) [81], watery diarrhoea (52.2% to 76%) [80, 82, 83] and skin abrasions (64%) [80].

There are several ways to refer to antibiotics in Thai; the majority of people in northern Thailand refer to antibiotics as 'anti-inflammatories', a minority use the formal word for antibiotic, and others refer to them as 'germ-killers' or use the specific names of antibiotics [75, 84]. This seems to lead to a misunderstanding that antibiotics can treat muscle pain and inflammation [75, 85]. '*Yaa chud*' are packets of unlabelled medications which usually contain a few antibiotics and are sold in some stores and pharmacies for certain symptoms or illnesses such as pain or common colds [86-88]. These

packets carry a high risk of antibiotic misuse and despite the government's attempts to prevent their sale their use is ongoing.

In 2015, the antibiotic consumption rate was 18.3 defined daily doses (DDDs) per 1,000 inhabitants per day, which is 16.6% higher than the average global rate based on the IQVIA database [50, 89]. In 2017, the Thai national household survey found that 7.9% of the 27,762 people questioned reported having taken antibiotics within the last month; a further 12.3% were unsure whether they had taken antibiotics or not [90]. People reported sourcing 50.3% of antibiotics from public facilities, 26.7% from pharmacies, 20.0% from private facilities and 3.0% from local stores [90]. Sourcing antibiotics from informal places such as local stores and social contacts is reported infrequently by the public (1.6% to 9%) [75, 90, 91], but may be more common in some groups, such as those from ethnic minorities who may struggle to access more formal care [75] (these groups might also be poorly represented in surveys such as the one mentioned above, which included only adults that could speak Thai).

Reported antibiotic use prior to presenting to a health facility varies from 7.8% of adults with a UTI [92], 13.1% of adults with a sore throat [93], to 54.8% of children admitted to hospital with diarrhoea [94]. Reported medication use, however, is often inaccurate due to uncertainty about the medications taken, patient recall and the time frames used.

1.4.5 Antibiotic Prescription in Thai Primary Care

1.4.5.1 Upper Respiratory Tract Infections

Levels of antibiotics prescribed for upper respiratory tract infections (URTIs) in the community in Thailand range from 6.2% to 89% (Table 1-4) [95-104]. Only national numbers reported by the Ministry of Public Health (MOPH) for PCUs in 2019 meet the 20% target set by the Antibiotic Smart Use (ASU) programme for common colds and sore throats [104, 105]. The MOPH's figures show that antibiotic prescription for URTI and acute bronchitis have fallen from 39.9% in 2013 to 6.2% in 2019

in PCUs, and from 54.4% to 23.9% in outpatient departments (OPDs), in the same time period [104]. The methodology is not detailed, however, electronic summary data is available for each PCU and OPD department at the individual patient level, which includes diagnoses by International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) code and prescription data.

Pharyngitis and tonsillitis are associated with the highest rates of antibiotic use (75.5% to 92%) [96, 97, 102]. This is likely to represent overtreatment; estimates of the prevalence of GAS from Siriraj Hospital in Bangkok range from 3.3% to 7.9% and the prevalence of other BHS range from 3.8% to 9.2% [93, 97, 99]. Treebupachatsakul et al. reported that 17% of the pharyngitis or tonsillitis cases had a Centor score of three or more indicating the need for antibiotics; however three quarters of the patients were prescribed antibiotics [97]. The authors of two of these studies noted high levels of amoxicillin/clavulanic acid use which is an unnecessarily broad choice of antibiotic when GAS remains fully sensitive to penicillin [96, 101, 106, 107].

The use of antibiotics for bronchitis varied more widely with 22% to 74% of patients receiving antibiotics; however patient numbers were low in most studies [97, 101-103]. All the study authors considered antibiotics to be inappropriate for bronchitis which is usually a viral infection [97, 101-103]. When common colds were differentiated from other URTIs, antibiotic prescribing was lower (3.7% to 16%) but given the large numbers of patients involved this still remains an important source of inappropriate antibiotic use [97, 101].

Setting	Condition	Antibiotic prescribed	Type of antibiotic	Appropriateness of antibiotics
>18 years 2 health centres Bangkok slum Retrospective record review 2001 **[96]**	All URTIs	62.9% of 4,608 patients	-	Based on Thai guidelines Antibiotics appropriate if likely bacterial pathogen or high fever, severe cough or abscess. Considered type & duration. More antibiotics if self-paying, male, younger (< 40 vs > 60 years)
	All likely viral	60.3% of 4,107 patients	For colds: Amoxicillin +/- clavulanic acid 70.4%, Dicloxacillin 9.7% Roxithromycin 6.3%	36.4% had appropriate antibiotics
	All likely bacterial:	89.4% of 405 patients	-	1.7% appropriate antibiotics Type: 85.1% of antibiotics used were not in guidelines
	Pharyngitis/ tonsillitis	91.6% of 309 patients	Amoxicillin +/- clavulanic acid 71.3%, Roxithromycin 13.5% Dicloxacillin/ Cloxacillin 5.1%	Type: as above
	Otitis media	83.1% of 89 patients	Amoxicillin +/- clavulanic acid 44.3% Chloramphenicol ear drop 35.7% Dicloxacillin/ Cloxacillin 35.7%	Type: as above
	Sinusitis	71.4% of 7 patients	-	Type: as above

Adults without chronic disease OPD Siriraj tertiary hospital Bangkok Retrospective note review 2001 **[102]**	All URTIs	74% of 837 episodes	Amoxicillin 34.5%, Co-trimoxazole 22.3%, Roxithromycin 9.4%	Overuse of antibiotics, say should be less than 10% overall. Especially high for tonsillitis and pharyngitis. Type: co-trimoxazole not recommended in their guideline (mostly 1 doctor prescribing)
	Non-specific URTIs	73% of 720 episodes	-	
	Pharyngitis	81% of 49 episodes	-	
	Bronchitis	74% of 38 episodes	-	
	Tonsillitis	92% of 24 episodes	-	
Normally healthy adults OPD Siriraj tertiary hospital, Bangkok Prospective, CRF used 2004 **[97]**	All URTIs	30.1% to 292 patients	-	Overuse. 6.9% should have received antibiotics according to their guideline: 17% with pharyngitis/ tonsillitis with Centor ≥ 3 and 100% with sinusitis. 7.9% GAS overall
	Common cold	3.7% of 162 patients		
	Pharyngitis/ tonsillitis	75.5% of 94 patients		
	Bronchitis	25% of 32 patients		
	Sinusitis	75% of 4 patients		
>15 years OPD King Chulalongkorn tertiary hospital, Bangkok Retrospective record review 2010 **[98]**	URTI & acute bronchitis	81.3% of 379 patients	Amoxicillin 41.2%, Amoxicillin/ clavulanic acid 27.9%, Roxithromycin 19.5%	'Very high' antibiotic use Multivariate analysis: sore throat, abnormal lung signs and non-medical resident review increased antibiotic use

>2 years OPD Siriraj tertiary hospital, Bangkok Prospective CRF used 2011 **[99]**	URTI (sore throat, rhinorrhoea, cough)	75% of 23,637 patients	Amoxicillin Amoxicillin/ clavulanic acid % not given	High use
Unclear if adults or children Medical OPDs Siriraj tertiary hospital, Bangkok Retrospective chart review 2014 **[100]**	URTI	34.7% of 314 diagnoses	-	-
Public primary care centres, Thailand 2014-2015 **[95]**	All patients	12% (11-14%) of 14,420 patients	-	NB referenced from another article but reference not found
	URTI	43% (20-52%) of 13,485 patients		
3 months to 15 years Normally well, no pneumonia Paediatric OPD Ramathibodi tertiary hospital (2.8% ED), Bangkok	Acute RTIs	28.6% of 2,553 visits	-	10% needed antibiotics. 77.5% (75.8% -79.1%) appropriate overall, mostly due to over-prescription. Appropriate: indication, type & duration. Generally assumed pharyngitis, otitis media & rhinosinusitis needed antibiotics

Note review 2016 **[101]**				Levels of appropriateness varied in different OPDs, type of doctor (faculty staff less appropriate), more appropriate in younger children
	Common cold	16% of 1,869 visits		84.1% appropriate
	Acute bronchitis	22% of 296 visits		78% appropriate
	Pharyngitis/ tonsillitis	-% of 245 visits		27.3% appropriate- overuse of amoxicillin/ clavulanic acid and azithromycin.
	AOM	-% of 80 visits		71.3%
	Rhinosinusitis	-% of 46 visits		78.3%
Adults & children OPD Samchuk Hospital, Central Thailand Retrospective note review 2017 **[103]**	URTI & acute bronchitis	38.4% of 9,286 patients	Penicillins 70.5% Lincomycin 16.9% Macrolides 9.3% Cephalosporins 1%	
	Nasopharyngitis	4.3% of 3,238 patients		
	Pharyngitis	77.3% of 2,360 patients		
	URTI unspecified	12.3% of 1,501 patients		
	Acute bronchitis	45.9% of 1,073 patients		
	AOM	83.8% of 240 patients		

	Tonsillitis	87.3% of 725 patients		
Age unclear PCUs in Thailand excluding Bangkok Electronic reporting 2018-9 (1 full year) **[104]**	URTIs and acute bronchitis	6.2% of 9,922,274 patients	-	Meets the target of <20% antibiotics
Age unclear Hospital OPDs in Thailand excluding Bangkok Electronic reporting 2018-9 (1 full year) **[104]**	URTIs and acute bronchitis	23.9% of 1,632,453 patients	-	Exceeds the target of <20% antibiotics

Table 1-4: A summary of studies reviewing antibiotic prescriptions for URTI in Thai primary care

ED: emergency department, CRF: case record form

1.4.5.2 Acute Diarrhoea

Table 1-5 shows studies detailing antibiotic prescriptions for acute diarrhoea, which were almost exclusively conducted in children. Antibiotic prescription ranged from 8.1% to 82.2% [99, 104, 108-110]. Invasive disease, when reported, was usually classed as bloody diarrhoea or diarrhoea with a fever and was present in 6.9% to 23.3% of cases [108-110]. Antibiotic use for invasive disease was considered appropriate, whereas antibiotics should have been withheld from cases of watery diarrhoea. The authors concluded that antibiotics were being overused for acute diarrhoea [99, 108-110]. When specified, levels of appropriate use ranged from 27.4% to 51.1%. Almost all of the inappropriate use was due to over-prescription of antibiotics for watery diarrhoea. The type of antibiotic or its dose and duration do not seem to have been considered [108-110]. Norfloxacin and co-trimoxazole were the most commonly used antibiotics, with some use of ciprofloxacin and Colistin [99, 108-110].

Setting	Condition	Antibiotic prescribed	Type of antibiotic	Appropriateness of antibiotics
<5 years OPD 2 general and 8 community hospitals, central Thailand Prospective audit 1995 **[108]**	Diarrhoea 12.5% invasive (includes some IPD cases)	82.2% of 275 patients	Co-trimoxazole 67.3%, Colistin 19.9%, Norfloxacin 9.7%	27.4% appropriate (rest were over-prescribed). Dose & duration not considered Type: Colistin 2nd most commonly prescribed ORS use 14%
2 months to 5 years OPD 10 hospitals, southern Thailand Retrospective record review 2004 **[109]**	Acute diarrhoea 6.9% invasive	61.4% of 2,882 patients	Co-trimoxazole 66.1% Norfloxacin 27.1% Colistin 4.9%	Appropriate 44.1% Inappropriate 55.9% (98.8% overused) Appropriate: no antibiotics if non-invasive, antibiotics if invasive. Dose & duration not considered Type: high use co-trimoxazole despite Shigella resistance More appropriate in general hospitals than community ones
>15 years old OPD King Chulalongkorn tertiary hospital, Bangkok Retrospective record review 2009-2010 **[110]**	Acute diarrhoea 23.3% invasive	45.1% of 390 patients	Norfloxacin 72.7%, Ciprofloxacin 19.3%, Ceftriaxone & Ciprofloxacin 3.4%,	Inappropriate in 48.9%; all overuse (their guideline: use if blood, fever or moderate dehydration) More likely to get antibiotics if self-paying, tenesmus or non-medical staff treated Cost of inappropriate antibiotics 17.4THB, 31.4% of total treatment cost

>2 years OPD Siriraj tertiary hospital, Bangkok Prospective CRF used 2011 **[99]**	Diarrhoea	78% of 4,876 patients	Norfloxacin Ciprofloxacin	High use
Age unclear PCUs in Thailand excluding Bangkok Electronic reporting 2018-9 (1 full year) **[104]**	Acute diarrhoea	8.1% of 692,800 patients	-	Meets the target of < 20% antibiotics
Age unclear Hospital OPDs in Thailand excluding Bangkok Electronic reporting 2018-9 (1 full year) **[104]**	Acute diarrhoea	18.9% of 1,672,252 patients	-	Meets the target of < 20% antibiotics

Table 1-5: A summary of studies reviewing antibiotic prescriptions for acute diarrhoea in Thai primary care

ORS: oral rehydration solution, IPD: inpatient department, THB: Thai Baht, CRF: case record form

1.4.5.3 Other Infections

Studies of antibiotic prescription for other infections presenting in primary care are shown in Table 1-6. A study from Siriraj Hospital in Bangkok found inappropriately high use of broad spectrum antibiotics for bacterial cellulitis; they suggest 80% of patients could have a narrower antibiotic based on the positive cultures (21 blood cultures, and 40 pus or swab cultures) [111]. UTIs were considered in two studies which found that the type of antibiotics being recommended empirically may not be suitable for the local resistance pattern [92, 112].

Setting	**Condition**	**Antibiotic prescribed**	**Type of antibiotic**	**Appropriateness of antibiotics**
Adults & children Secondary analysis of QuickVue influenza RDT field test (unclear if guidance given re interpretation of RDT results) 5 hospital OPDs East Thailand 2003-2004 **[113]**	Influenza-like-illness	82% of 300 patients	Amoxicillin 89%	Inappropriate use was common
	With positive influenza RDT	73% of 106 patients		
	With negative influenza RDT	87% of 194 patients		
≤15 years OPD MOPH hospital Central Thailand Retrospective note review 2011-2012 **[114]**	Influenza B	6.7% of 119 patients	-	-
Adults >18 years Excluded pregnant women OPD Tak Province Prospective chart review 2013-2014 **[92]**	Symptoms of UTI (dysuria, frequency, flank pain)	63.2% of 247 patients	Their guideline: nitrofurantoin 3/7 for women and ciprofloxacin 7/7 for men.	All given antibiotics if urine dip and microscopy positive in line with guidelines. Not clear if guidelines recommend use with discordant results Type: treated in line with guidelines but antibiotics did not
	Urine dip & microscopy positive	100% of 85 patients		
	Discordant dip & microscopy	56% of 100 patients		

	Dip & microscopy negative	21.4% of 56 patients		cover the pathogen in 10.6% of the positive samples
15-60 years Women OPD Thammasat tertiary hospital, Bangkok Prospective observational 2014-2016 **[112]**	UTI (symptoms and pyuria)	100% of 80 patients	Ciprofloxacin 71.3%, Norfloxacin/ Ofloxacin 17.5%, Amoxicillin/ clavulanic acid 6.3%	91.3% inappropriate: 90.4% duration, 38.4% type, 21.9% dose Local resistance patterns need to be incorporated into guidelines
>18 years OPD Siriraj tertiary hospital, Bangkok Retrospective record 2016 **[111]**	Bacterial cellulitis	100% of 770 patients	Amoxicillin/ clavulanic acid 29.9%, Dicloxacillin 26.2%, Ceftriaxone 10.1%, Ceftriaxone & clindamycin 6.8%	Inappropriately high usage of broad spectrum antibiotics (80% could have been narrow. BHS and methicillin susceptible *S. aureus* most common pathogens).

Table 1-6: A summary of studies reviewing antibiotic prescriptions for other infections in Thai primary care

RDT: rapid diagnostic test

The generalisability of the antibiotic prescription data may be limited as data mostly came from hospital OPDs, frequently from one tertiary hospital in Bangkok. This data may not be generalizable to other parts of the country and to PCUs which could have a different patient population presenting to them. Those with co-morbidities, and the very old and young were excluded in some studies. Data were often only collected for a few months rather than a full calendar year so may not be sensitive to temporal or seasonal changes in antibiotic use.

The studies and MOPH figures were usually dependant on ICD-10 coding of illnesses so proportions of antibiotic use would depend on how illnesses are coded and it is possible that inappropriate antibiotic use would be missed in undiagnosed cases and in those with a different diagnosis. Concerns have been raised that antibiotic use may be misreported in order to meet antibiotic prescribing targets.

1.5 Optimising Antibiotic Use in the Community

Optimising antibiotic use has been identified as one of the key tools for tackling AMR by WHO and the IACG [32, 35]. The optimal use of antibiotics should include access to antibiotics and ensuring good quality antibiotics when needed [35, 51, 62, 63]. For antibiotic use to be considered optimal the appropriate antibiotic needs to be given at the right dose and taken for the right duration. Antibiotics should not be given for inappropriate indications such as viral illnesses. Optimal antibiotic use will also take into account the individual patient and their co-morbidities.

Knowing whether antibiotics are indicated requires knowledge of the incidence of local infectious diseases; however there is little data available from the community where most patients will be seen. Even in hospital settings, well-resourced research studies often only identify a cause of fever in a minority of patients [115-118]. Fewer data are available for lower income settings.

Diagnosing infections can be done microbiologically, clinically or with some combination of the two. Microbiological diagnoses can be made through diagnostic tests but their role can be limited by test availability, accuracy, cost and the time requirements. Making the correct diagnosis can be a challenge in primary care especially if patients present early with non-specific symptoms; in such cases multiple (rapid diagnostic tests) RDTs would be required to rule out the need for antibiotics. Laboratory tests such as biomarkers for infection, clinical scores and guidelines can aid clinical diagnosis.

Once the infection has been diagnosed knowledge of local antibiotic resistance patterns is required to inform evidence based antibiotic guidelines; in some settings this will require increasing laboratory capacity and even writing these guidelines [35, 119]. Antibiotic guidelines should take into account the EML/"AWaRe" antibiotic classifications and detail the dose and treatment durations required for frequent infections [35, 53].

Finally, the treatment plan needs to be accepted and communicated to patients. Shared decision making has been shown to reduce antibiotic use in primary care for RTIs [120]. Treatment adherence can be limited with 10% to 25% of patients not completing their antibiotic course [74, 121, 122]. Given all these requirements and challenges it is perhaps unsurprising that optimal antibiotic use can be hard to define and achieve [42].

1.5.1 Interventions to Optimise Antibiotic Use in the Community in Thailand

A literature review searching for interventions to optimise antibiotic use was conducted using the MEDLINE, Embase, Cochrane Central Register of Controlled Trials and Web of Science databases. The search ran from January 2000 until the 15th of April 2020. The grey literature was also explored. It revealed two main Thai programmes relating to AMR and optimal antibiotic use; the ASU programme and Thailand's Antimicrobial Resistance Containment and Prevention Programme (AMRCP) [105, 123].

The ASU programme started in 2007. Guidelines were produced for three conditions which do not normally need antibiotics - common colds with sore throats, acute diarrhoea and simple wounds [105, 124]. After implementing ASU policies in one hospital in central Thailand, antibiotic prescribing for almost 10,000 outpatients with URTIs and acute bronchitis fall from 73.1% in 2010 to 38.4% in 2017 [103]. In 2011, a study of outpatients older than 2 years old with URTIs and acute diarrhoea found a BHS prevalence of 7.9% (14/183 swabs) and non-typhoidal *Salmonella spp.* present in 14.7% of 41 stool samples. In a larger group with the same presenting symptoms, they reduced antibiotic use to under 20% without affecting clinical recovery, using multi-faceted interventions [99]. This evidence was used to underpin a target of < 20% antibiotic use for URTIs and acute diarrhoea introduced into the pay-for-performance system for hospitals and PCUs between 2012 and 2014 [99, 125]. In August 2016, it was also used to inform key performance indicators in the Food and Drugs Association's (FDA's) rational drug use (RDU) plan. National figures reported by the MOPH suggest that this target is having a large impact with antibiotic prescriptions for URTIs and acute bronchitis,

and diarrhoea [104]. However, this literature review did not identify any additional safety data or effect on outcomes such as sourcing antibiotics or healthcare from elsewhere. Offering alternatives to antibiotic prescriptions such as herbal medicine is seen as one of the ASU's triumphs and can help to replace the economic loss of not prescribing antibiotics [84, 105, 125-127]. The ASU programme is seen as a success story and is used as an example for other countries hoping to rationalise their antibiotic use [125, 127].

The AMRCP (2012 to 2016) led to attempts to reclassify some antibiotics as prescription only medication and the banning of antibiotics as growth promoters in animals. Responsible use of antibiotics became part of the hospitals' accreditation system and campaigns on stopping AMR were produced [123].

The literature search revealed five interventional studies targeting antibiotic prescriptions in the community (Table 1-7) [99-102, 128]. There were four before-and-after studies, and one cluster RCT. All but one study were conducted in OPDs in Bangkok limiting the generalisability of their results. All of the interventions involved some degree of education. Antibiotic prescription rates were fed back to healthcare workers in four studies and this was the main intervention in one [99-101, 128]. URTIs were the infections of interest in three studies [100-102] while two studies addressed URTIs and diarrhoea [99, 128]. In addition to reporting antibiotic prescribing for the targeted conditions, one study considered the appropriateness of the antibiotics used [101].

The impact of the interventions varied with two studies having a positive effect on their primary outcome, both audited antibiotic use and in addition one study provided education and management guidelines [99, 100], whereas other studies had a mixed impact. In one study, an educational meeting about current antibiotic use and new antibiotic guidelines resulted in a significant reduction in antibiotic prescriptions for all URTIs and common colds, but non-significant reductions for nonspecific URTIs, pharyngitis and bronchitis, and a small increase in tonsillitis [102]. Providing training and guidelines to nurses in PCUs and an audit of prescribing resulted in a significant

reduction in antibiotic prescriptions for children under five with ARIs but not diarrhoea [128]. Distributing antibiotic guidelines by email, displaying posters in examination rooms and auditing antibiotic prescribing every 2 months significantly improved appropriate antibiotic use in acute RTIs overall but not when broken down into individual conditions [101]. None of the studies followed up patients to see if they sourced antibiotics from elsewhere or sought additional healthcare. Patient and healthcare worker satisfaction with the interventions were not reported, and no cost-effectiveness analyses were done. The two studies which assessed clinical recovery found that participants recovered despite not receiving antibiotics [99, 102].

Study design	Intervention	Outcome	Pre-intervention	Post-intervention	Relative effect	Number of participants	Comments
Adult patients Before-and-after Siriraj hospital OPD Bangkok 2001 **[102]**	Educational meeting: current use & new guidelines Target: doctors	ABU URTIs	74%	44.1%	RR 0.6 (0.55-0.65), RD -29.9, p<0.001	837 episodes pre, 774 post	Significant reduction in ABU Type of antibiotic improved (less amoxicillin, co-trimoxazole, roxithromycin & doxycycline. More penicillin V) More specific diagnoses given
		Nonspecific URTIs	73%	49%	RD -24	720 pre, 242 post	
		Pharyngitis	81%	78%	RD -3	49 pre, 192 post	
		Tonsillitis	92%	94%	RD 2	24 pre, 17 post	
		Bronchitis	74%	40%	RD -34	38 pre, 99 post	
		Common cold	20%	10%	RD -10, p<0.01	5 pre, 223 post	
		Recovery without antibiotics				All better or improving by day 7	
<5 years Cluster RCT 18 PCUs, Northeast Thailand Published 2005 **[128]**	Educational training: 3 days, 4 clinical guidelines. Support visit and audit of prescribing at 3-4/12 Target: nurses	ABU ARI	Intervention: 41.6%	Intervention: 27%	RD -14.6 (95% CI -22.5 to -6.7). P=0.022	Unclear, average 35 patients per cluster, 9 in each arm. Roughly 315/ arm	Significant reduction in ABU for ARIs in children but not in diarrhoea
			Control: 26.7%	Control: 29.5%	RD 2.8 (95% CI -6.0 to 11.7)		
		ABU diarrhoea	Intervention: 84.8%	Intervention: 83%	RD -1.8 (95% CI -16.6 to 12.9) P=0.308		

			Control: 96.8%	Control: 94.7%	RD -2.1 (95% CI -8.4 to 4.2)		
>2 years old Before-and-after Siriraj hospital OPDs 2011-2012 **[99]**	Educational meeting: current use, guidelines. Standardised medical record forms Throat & stool cultures Patient leaflets Monthly audit ABU & patient recovery Target: healthcare workers	ABU URTI	75%	13%	RD -62	23,637 pre 1,241 post	Large reduction in ABU without affecting clinical recovery. Part of ASU. Used to introduce 20% antibiotic target into pay for performance 2013 183 throat swabs: 7.9% BHS 41 stool samples: 14.7% non-typhoidal *Salmonella spp*.
		ABU diarrhoea	78%	19.1%	RD -58.9	4,876 pre 210 post	
		Patient recovery at day 3			No difference whether antibiotics used or not (> 95% improving or cured)		
Patients unclear Before-and-after Siriraj Hospital OPD Bangkok 2014-2015 **[100]**	Feedback on their ABU in last 4/12. Note saying antibiotics not needed for most URTIs Target: doctors	ABU URTI	34.7%	26.1%	RD -8.6 OR 0.37 (95% CI 0.16-0.85), p=0.02	314 diagnoses pre-intervention, 346 diagnoses post-intervention	
3 months to 15 year old patients	Guidelines emailed Posters in examination rooms	Overall ABU acute RTI	28.6%	20.4%	RD -8.2, p<0.001	2,553 pre, 5,584 post	Improved the type of antibiotic being used for pharyngitis/

Before-and-after Ramathibodi hospital OPDs Bangkok 2016-2017 **[101]**	ABU audit every 2/12 Target: doctors	Appropriate ABU acute RTIs	77.5% (75.8-79.1%)	83.4% (82-84.8%)	RD 5.9, p<0.001 RR 1.11 (95% CI 1.09-1.12)	tonsillitis (more amoxicillin and less amoxicillin/ clavulanic acid and azithromycin). Heterogeneity between departments. More effect if more inappropriate initially
		Pharyngitis/ tonsillitis	27.3%	30.4%	RD 3.1 NS	
		AOM	71.3%	70.5%	RD -0.8 NS	
		Rhinosinusitis	78.3%	70.5%	RD -7.8 NS	
		Common cold	84.1%	91.3%	RD 7.2 P<0.05	
		Bronchitis	78%	71.3%	RD -6.7 NS	

Table 1-7: A summary of interventional studies targeting antibiotic use in the community in Thailand

ABU: antibiotic use, RD: risk difference – percentage points unless specified, NS: non-significant

The literature search revealed several other interventions that may help to optimise antibiotic use. Pharyngitis and tonsillitis are frequently highlighted as conditions in which antibiotics are overused in Thailand [96, 97, 102]. A study of 360 adults presenting to a hospital OPD with a sore throat evaluated the use of two GAS rapid antigen tests and the Centor clinical score. GAS was found on 3.3% of the throat swabs. The QuickVue Dipstick Strep A test had a positive predictive value (PPV) of 31.8% and a negative predictive value (NPV) of 98.5% compared against throat swabs. While the Sofia Strep A+ Fluorescent Immunoassay had a PPV of 36.4% and NPV of 97.9%. The Centor score was raised (≥ 3) in 4.2% of the patients, with a PPV of 53.3% and NPV of 98.8%. The higher sensitivity of the Centor score and lower costs make its use more favourable [93].

The Centor score was evaluated in an older study from the same hospital OPD. A Centor score of ≥ 3 had a PPV of 43.8% and NPV of 94.2% in normally healthy adults presenting with an URTI. The throat swabs found GAS in 7.9% and other BHS in 9.2% of the 292 patients. Pharyngitis or tonsillitis was diagnosed clinically in 32.2% of the patients, for whom 75.5% were prescribed antibiotics; despite the antibiotic guidelines recommending antibiotics only to those with a Centor score of ≥ 3 (17% of the pharyngitis or tonsillitis diagnoses) [97].

A field test of the QuickVue influenza RDT in five hospital OPDs resulted in a reduction of antibiotic use by doctors treating adults and children with influenza-like-illnesses. Patients with a positive influenza test had a 0.42 likelihood of antibiotic prescription compared to those with a negative test of the same age, gender and OPD. There was heterogeneity between the effect sizes amongst the different OPDs [113].

Diagnosing UTIs with the help of point of care (POC) tests could improve antibiotic use in those with symptoms of UTIs. A study of 247 patients presenting with UTI symptoms to clinics on the Thai-Myanmar border found that using a urine dipstick test (leucocyte +/- nitrates positive) alongside microscopy (raised white blood cells, presence of bacteria and low epithelial cells) was more accurate than clinical symptoms or either test alone in detecting culture proven UTIs (sensitivity 98% and

specificity 81%). Antibiotics were prescribed to 63.2% of all patients (healthcare workers were aware of the POC test results). Urine cultures were positive in 71.1% of those clinically diagnosed with a UTI. Using urine dipstick tests alone would have resulted in 57.1% being over-treated and using microscopy alone would have resulted in 25.6% being undertreated [92].

In summary most interventions to optimise antibiotic prescribing in Thailand to date have focused on education and prescribing targets. The use of POC tests and clinical scores have been evaluated in a few studies on sore throats, influenza and UTIs. Biomarkers of infection including CRP testing have not been evaluated in the Thai context.

1.5.2 Biomarkers of Infection

Biomarkers of infection can help to optimise antibiotic use by estimating disease severity, differentiating bacterial and non-bacterial infections, and guiding management decisions such as the requirements for antibiotics. When deciding if antibiotics are required, biomarkers may be more generalizable than disease specific tests which need adapting according to factors such as the local epidemiology, population and season.

Biomarkers of infection do however have disadvantages; alone they cannot diagnose the cause of infection or test for antibiotic susceptibility, therefore clinical knowledge and skills are still required to determine patient management. Depending on the test used, additional costs, infrastructure, training and time will be required compared to clinical judgement alone.

A comprehensive review of biomarkers to differentiate bacterial from non-bacterial acute febrile illnesses found 59 studies reviewing 112 host biomarkers between 2010 and 2015. CRP, procalcitonin and white blood cells were the most commonly studied biomarkers. CRP, the most frequently studied, could differentiate between bacterial and non-bacterial infections in 92% of 36 studies (sensitivity 61.2% to 100%, specificity 26% to 100%) [129].

Many of the studies evaluating biomarkers of infection have been conducted in hospitals in HICs, predominantly recruiting adults and those without immunosuppression or complex co-morbidities. It is therefore important that larger, high-quality evaluations are conducted in the community, in LMICs, in children and in those with more complex medical histories [129-132].

1.6 Current Challenges Related to Community Antibiotic Use and Antimicrobial Resistance

AMR may be one of the biggest public health challenges we face. There are many gaps in our knowledge of AMR not least the paucity of data to estimate its true burden, particularly in the community. We need to understand more about the links between antibiotic use and AMR. Any interventions aiming to reduce antibiotic use should ideally be measured against ongoing effects on AMR levels.

Antibiotics are widely available in the community in Thailand without a prescription but are most commonly received from healthcare professionals. There is a paucity of detailed data on antibiotic prescriptions in the community in Thailand. The majority of studies have focused on URTIs and diarrhoea, drawing on data from OPDs in Bangkok. Data is lacking for PCUs, particularly those in more remote areas. We lack data on the appropriateness of antibiotic use, although it seems that prescribing is particularly high for tonsillitis and pharyngitis. We need to investigate interventions to optimise antibiotic use while still maintaining access to antibiotics and ensuring that clinical outcomes are not affected. The acceptability of the intervention for healthcare workers and patients should be evaluated. Multi-centre, randomised study designs are required to generate higher quality evidence. Biomarkers of infection are a promising intervention but studies have thus far focused on hospital and HIC settings. There is good evidence to support the use of CRP testing in adults with RTIs in HICs but there is a paucity of data from LMICs, in children and in those with non-RTIs.

1.7 Aims and Objectives of this Thesis

It is not possible to address all of the challenges and gaps identified in this introductory chapter. The overall aim of this thesis is to evaluate the use of CRP POC testing to optimise the use of antibiotics in Thai primary care. In order to do this I have identified the following objectives:

- **To explore the indicators for antibiotic use in primary care in Thailand.**

  Chapter 2 is a retrospective review of antibiotic use over two years in public PCUs in a district in northern Thailand. This chapter gives detailed patient level data describing conditions and situations where antibiotics are used.

- **To study the impact of CRP guided antibiotic management of febrile illnesses on antibiotic use and patient recovery.**

  Chapter 3 details a RCT conducted in primary care in northern Thailand and Myanmar. Patients with a fever or history of fever were randomised to one of two CRP intervention arms (using different CRP cut offs) or to the routine care arm. This RCT explores the role of CRP POC testing to guide antibiotic use in two LMICs, in children (half of the participants) and in those with RTIs and other febrile illnesses. Healthcare workers' concordance with the CRP results and guidance are explored, alongside their opinions and views towards the CRP POC test.

- **To assess patients' compliance and opinions towards CRP guided antibiotic management.**

  Chapter 4 describes patients' concordance with the management guidelines provided within the RCT. Patients' health-seeking behaviour is explored before and during the study. Their adherence to antibiotic treatment or no treatment within the two week follow-up period is reviewed. Urine antimicrobial activity is assessed in a subgroup at day 0 and day 5 and compared with patient-reported antibiotic use. Patients' and care givers' opinions on CRP testing are evaluated using close-ended questions.

- **To evaluate if CRP testing can be used to differentiate pharyngitis caused by GAS.**

Nested within the RCT a subgroup of participants are studied to explore whether CRP levels can be used to identify GAS infection in patients presenting to primary care with a sore throat and fever (Chapter 3). CRP levels are compared against clinical scores (Centor and FeverPAIN) and microbiology findings. The prevalence of GAS and other beta-hemolytic streptococci (BHS) infections are described alongside their antibiotic susceptibility profiles.

Chapter 2 Retrospective Review of Antibiotic Prescriptions and the Indications for their Use in Primary Care Units in Northern Thailand

2.1 Introduction

The overuse of antibiotics is a key driver of AMR. Antibiotic use data is lacking for LMICs and the community. As discussed in Chapter 1, the majority of antibiotics in Thailand are accessed from healthcare professionals. Community antibiotic prescription data has tended to focus on URTIs and diarrhoea, and the majority of studies in the community have been conducted in Bangkok, hospital OPDs, in single centres and over short periods of time. This chapter presents a review of antibiotic prescribing in PCUs in northern Thailand, which seeks to address some of the paucity in community antibiotic data. A wide range of infections were considered in this 2 year multi-centre review. Current antibiotic guidelines are reviewed alongside healthcare workers' concordance with them. The results are then discussed to see where antibiotic use can be optimised.

2.1.1 Causes of Fever in Northern Thailand

One of the key focus areas of this thesis is the optimization of the use of antibiotics in febrile illness - one of the commonest presentations in primary care, and a challenge for healthcare workers in identifying when antibiotics are indicated. Knowledge of local infectious diseases is required in order to know which antibiotics should be used and for what conditions, therefore before reviewing the antibiotics currently used in primary care, I briefly describe the evidence on causes of fever in the region.

The causes of acute undifferentiated febrile illnesses in Thailand have been evaluated in several studies. The majority have focused on adult patients [117, 133-135], while some studies have also included children [136, 137]. The definitions used for acute undifferentiated febrile illness are similar but the conditions excluded vary; some studies excluded those with malaria or dengue while others include them [117, 133-137]. The studies represent a mixed patient group; two studies enrolled

admitted patients [117, 135], one study enrolled outpatients [136] and others included a mixture of inpatients and outpatients [133, 134, 137]. The panel of diagnostic tests used varies, although the majority collected acute and convalescent samples for serology. The proportion of patients with a microbiological diagnosis ranged from 29.4% to 68.3% [117, 133-137]. Frequent diagnoses include dengue (1.5% to 39.6%) [117, 133-137], leptospirosis (1.1% to 36.9%) [117, 133-137], scrub typhus (1.1% to 22.5%) [117, 134, 137] and Influenza A (6% to 11%) [135-137]. The incidence of malaria in one study which did not exclude it was 25.3% on the Thai-Myanmar border, between 1999 and 2002 [134], but transmission of malaria across the region has been shown to have fallen dramatically in recent years [138, 139].

Heterogeneity was seen temporally in a study which recruited from three regions of Thailand. Cases of leptospirosis were statistically significantly higher in northeastern Thailand (31.1% to 47.7%) compared to southern (20.5%) or central Thailand (6.5%) [135]. Seasonality was reported by some; scrub typhus and leptospirosis were more common in the wet and early cool seasons [117, 135, 137]. These infections also seem to be more prevalent in rural areas or where agricultural work dominates [117, 134, 135]. The study with the highest incidence of dengue coincided with a dengue outbreak, which demonstrates how results can be influenced by time [133].

One notable study of hospitalised patients was based in the provincial hospital in Chiangrai which serves the PCUs in this antibiotic review [117]. Between 2006 and 2008, 231 adult patients with an undifferentiated fever or history of fever were recruited. The cause of fever was identified in half of the patients. The most common cause was scrub typhus (22.5%), followed by dengue (11.5%), leptospirosis (7.5%), murine typhus (3.5%) and Japanese encephalitis (0.5%). There were also 12 patients with positive blood, sputum, urine or fungal cultures, from those tested as part of routine care. The common bacterial infections found (scrub typhus, leptospirosis and murine typhus) can usually be treated with doxycycline [140]. Limitations of the study include the small number of

infections tested for (the five mentioned above) and that the cultures were not collected systematically for all study participants, only when indicated as part of routine care [117].

2.1.2 Community Antibiotic Guidelines in Chiangrai

No specific local antibiotic guidelines are available for the PCUs in Chiangrai. National treatment guidelines exist for some infections such as dengue. RDU guidelines for common colds with sore throats, simple diarrhoea and simple wounds exist [124]. These guidelines are summarised in Table 2-1. There are no local guidelines currently available relating to UTIs.

Condition	**Are antibiotics indicated?**	**Type of antibiotic**
Common cold, viral rhinosinusitis and acute bronchitis	No	NA
Pharyngitis or tonsillitis due to GAS	At least 3 of: -fever > 39°C & severe sore throat -exudates on tonsils, red uvula, white plaques on tongue -painful cervical lymphadenopathy -do not have cold symptoms	Penicillin V 500mg, BD-TDS, 10/7 OR amoxicillin 500mg, BD-TDS, 10/7. Penicillin allergy: roxithromycin 10-14/7 OR erythromycin 10-14/7
Simple diarrhoea	Only if temperature > 38°C AND bloody diarrhoea	Norfloxacin 400mg BD, 3-5/7 OR trimethoprim/ sulfamethoxazole 10mg/kg/day and 50mg/kg/day. Not amoxicillin
Skin wounds	Only if one of the following is present: -wound > 6 hours old -wound > 5cm long -difficult to clean e.g. puncture wound -ragged edges so hard to close	Dicloxacillin 250mg QDS 2/7

Condition	Are antibiotics indicated?	Type of antibiotic
	-on the foot -pressure/ crush injury -patient with diabetes, >65 years old, alcoholic, peripheral vascular disease, immunosuppressed	
	Contaminated wounds (e.g. soil, saliva, pus, stool, manure, dirty water)	Amoxicillin/ clavulanic acid 375mg TDS 2/7 OR 625mg BD for 2/7 OR cephalexin, OR clindamycin, OR erythromycin /roxithromycin with metronidazole

Table 2-1: A summary of Thailand's Rational Drug Use guidelines for common colds, rhinosinusitis, acute bronchitis, sore throats, diarrhoea and skin wounds

NA: not applicable, BD: twice a day, TDS: three times a day, QDS: four times a day

Created and translated from the Thai MOPH's Rational Drug Use initiative and implementation [124]

2.2 Aims and Objectives

In order to address the paucity in local antibiotic prescription data, we conducted a 2 year review of antibiotic prescribing in all PCUs in the central district of Chiangrai Province. We aimed to answer the following questions:

- What proportion of patients attending publicly funded PCUs receive antibiotic prescriptions?
- What are the indications for antibiotic use in the community in northern Thailand?
- Which antibiotics are prescribed, by type and "AWaRe" category?
- What are the common infection related presentations?
    - What proportion of infection illnesses receive antibiotic prescriptions?
    - How concordant are the prescriptions with antibiotic guidelines?
- Where are antibiotics used without a clear indication?

2.3 Methods

We conducted a retrospective review of antibiotic prescriptions in PCUs in the central district of Chiangrai Province between January 2015 and December 2016.

2.3.1 Study Sites

Mueang Chiangrai District is the central district in Chiangrai Province, the northernmost province in Thailand. The district includes the province's capital city and is the most populous district in the province with 241,436 inhabitants in 2017 [141]. The district's 1,284 square kilometres (km) includes some urban areas but is mostly rural [141].

Thailand has an extensive system of PCUs which are found in each sub-district. On average, PCUs provide care for 5,000 people (Chapter 1) [8]. There are 32 PCUs in Mueang Chiangrai District, 26 of which are within a 30 km or approximately 40 minute drive of the provincial hospital. The furthest PCU is two hours' drive from the provincial hospital (Figure 2-1). The PCUs are typically staffed by two to five registered nurses and public health officers, although four of the remote PCUs are staffed only by public health officers. Public health officers are able to review patients and prescribe antibiotics but have less training than registered nurses, which may affect their antibiotic prescribing practices. Annual chronic disease visits are provided by the primary care doctors who are normally based at the provincial hospital. They also provide support and advice as needed. PCUs provide care for acute and chronic medical conditions, as well as offering dental and traditional medicine services, such as massages for musculoskeletal pain [142].

2.3.2 Inclusion and Exclusion Criteria

Patients were included if they had at least one of the following:

- Systemic antibiotic prescription
- ICD-10 code for infection
- Fever as the chief complaint

- Temperature > 37.5°C recorded at the PCU.

Patients were excluded if they attended a PCU which was actively recruiting into the RCT evaluating CRP POC testing (Chapter 3) [142].

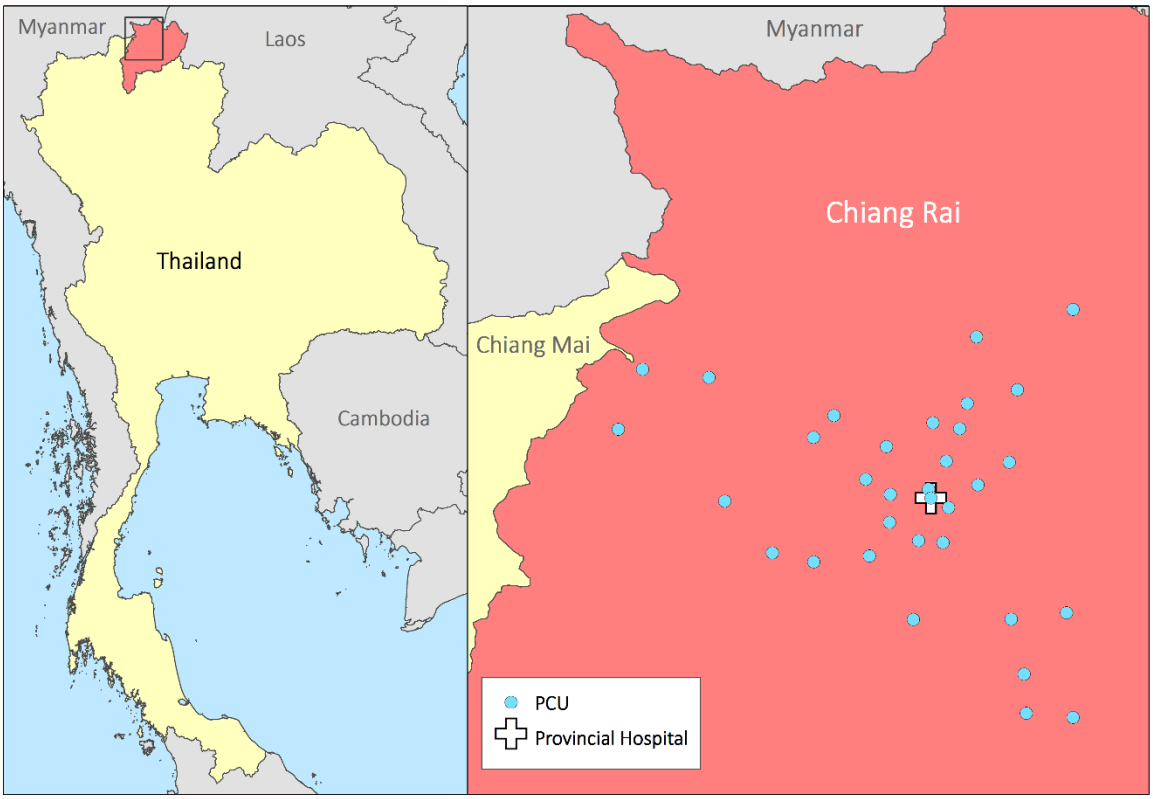

Figure 2-1: Map of Thailand and the location of primary care units in Mueang Chiangrai District.

*Reprinted from Greer, R.C., et al., Retrospective review of the management of acute infections and the indications for antibiotic prescription in primary care in northern Thailand. BMJ Open, 2018. **8**(7): p. e022250-e022250. License CC BY [142].*

2.3.3 Study Outcomes

The primary outcome was the proportion of illness episodes prescribed an antibiotic. Secondary outcomes include the indicators for antibiotic use, the type of antibiotics prescribed, and the frequency and type of infection presentations. Additional, new analyses included in this thesis chapter include a breakdown of antibiotics prescribed by "AWaRe" category and concordance with antibiotic guidelines.

2.3.4 Ethical Approval

Ethical approval was granted from the Chiangrai Provincial and Public Health Office Ethics Committee (number 56/2560). Exemption was given by the Oxford Tropical Research Ethics Committee (OxTREC).

2.3.5 Data Collection

Routine, electronic data from each clinical encounter is submitted to the Provincial and Public Health Office by each PCU. With permission from the Provincial and Public Health Office, a data manager from MORU extracted data from the main databases. Data were extracted for the PCU attended, patients' number, age, sex, date of visit, chief complaint, temperature, ICD-10 code and drug prescriptions [142]. The required data were stored in several databases which had to be merged using the patient's identification number in order to create a complete dataset.

2.3.6 Data Cleaning and Coding

2.3.6.1 Inclusion Criteria

The inclusion criteria were classed as being present, absent or missing by the data manager. Antibiotic prescriptions were recorded as free text in the drug prescription field. I used the drug formulary to create a list of possible antibiotics which were then searched for using string functions (Appendix 1). Common brand names were included. All medications prescribed in the dataset were reviewed to make sure no antibiotics were missing from the original list or had been overlooked due to spelling errors. If no prescriptions were recorded we assumed this was accurate rather than representing missing data.

I created a predefined list of ICD-10 codes for infections which could benefit from antibiotic prescriptions or for which antibiotics may be prescribed but are not always indicated by reviewing the full list of ICD-10 codes (Appendix 2) [143]. The diagnoses were recorded as ICD-10 codes in a

free text field. The data manager coded these as present, absent or missing. I then reviewed the appropriateness of the coding using information in the chief complaint and prescription fields.

The word 'fever' was searched for in the chief complaint field which was also a free text field. Correct coding of this variable needed to be manually checked because at times 'no fever' was recorded or the word 'fever' was present in Thai but was part of another word such as 'patient' (literal translation – 'person with a fever'). Therefore this field was checked by two native Thai speaking nurses for accuracy. A fever over 37.5°C was noted as being present if it was documented in the temperature examination field [142].

2.3.6.2 Exclusion Criteria

The RCT overlapped with this antibiotic review in four of the 32 PCUs, which started recruitment into the RCT between June and August 2016. Any participants attending one of these four PCUs were excluded from this review from the first day the PCU started enrolment into the RCT.

2.3.6.3 Other Cleaning and Coding

Repeat attendances within one month of the initial visit were classed as one illness episode regardless of the diagnoses or presenting symptoms; this was done in order to review antibiotic use throughout each illness. Antibiotic prescriptions were reviewed for each presentation during the illness episode. All other variables were taken from the initial visit.

Duplicate entries were searched for and removed, combining the information for completeness where necessary. Children were defined as being aged less than 12 years old, and adolescents and adults were aged 12 or above. The diagnoses were grouped into body systems (respiratory, gastrointestinal [GI], skin, urogenital, eyes, ears and others). Each system was broken down into common diagnoses such as respiratory system - acute sinusitis. The respiratory system was then grouped into URTIs and LRTIs [142].

2.3.7 Statistical Analyses

2.3.7.1 Descriptive Statistics

Descriptive statistics were used to summarise the data; categorical variables were summarised using counts and percentages, while non-normally distributed data used medians and IQRs. Comparisons were made using the rank sum test for non-normally distributed data and the χ^2 test was used for categorical data.

2.3.7.2 Logistic and Poisson Regression Models

The indications for antibiotic prescription were reviewed using a logistic regression model (sex, age category, documented temperature, PCUs staffed only by public health officers, and positioned ≥ 30 km from the provincial hospital). Adjusted and unadjusted models were fitted and stratified by PCU to allow for clustering of patients. Variables with a p value of < 0.05 in the univariate model were considered in the multivariate model. We also included documented temperature as we felt this was a natural confounder of antibiotic prescription. We chose to use this variable for fever rather than the more subjective history of a fever. ICD-10 codes were not included because the selection of the ICD-10 code was likely to be linked to the clinician's intention to prescribe antibiotics. For example, a sore throat which was likely to be prescribed an antibiotic would be coded as 'tonsillitis' rather than 'common cold' or 'non-specific URTI'. Incidence rate ratios (IRRs) for monthly antibiotic prescriptions over the 2 year period were created using a Poisson regression model [142].

2.3.7.3 Time-series Analysis

The trends in antibiotic prescription were described over the 2 year period using a time-series analysis. This allowed for seasonal variations to be separated from longer term trends. Monthly antibiotic prescriptions were weighted by the number of contributing PCUs. The approach is described by the study statistician in the corresponding publication as follows: *'Symmetric locally weighted moving averages were used. In this procedure, less weight was applied to time points (in*

months) farthest away from the present time point. The data were available on a monthly basis; however, a quarterly window was used to identify seasonality as follows:

$$\hat{X}_t = \frac{1}{9}(X_{t-2} + 2X_{t-1} + 3X_t + 2X_{t+1} + X_{t+2})$$

Similarly, a 12-month time-series window was used to obtain a trend line that would be sensitive to monthly changes but with reduced noise from seasonal variation:

$$\hat{X}_t = \frac{1}{24}(X_{t-6} + X_{t+6}) + \frac{1}{12}(X_t + X_{t-1} + X_{t+1} + X_{t-2} + X_{t+2} + X_{t-3} + X_{t+3} + X_{t-4} + X_{t+4} + X_{t-5} + X_{t+5})$$

Where $\hat{X}_t$ *is the time-series modelled monthly prevalence of antibiotic prescription'* [142].

2.3.7.4 Other Statistical Considerations

An alpha of 0.05 was considered to be statistically significant. Missing data was not imputed. Data analyses were performed using STATA V.14, Texas USA.

2.4 Results

In total, there were 762,868 visits to the 32 PCUs during the study period (1st of January 2015 - 31st December 2016). The majority were for chronic disease management or screening, such as diabetes, hypertension, mental health and dental disorders (145,410 visits), essential hypertension reviews (98,822) and routine child health examinations (75,701). The four most remote PCUs were staffed by public health officers and did not have any registered nurses working there during the study period.

2.4.1 Data Coding and Cleaning of the Inclusion Criteria

Reviewing the medications prescribed identified 741 occasions where the antibiotic name was misspelt or the English spelling of amoxicillin was used rather than the standard American spelling.

During the review of ICD-10 codes several codes were removed (Appendix 2). Frequent examples include:

- A15-18: TB, B18: chronic viral hepatitis, and B24: HIV; these codes were removed because patients were attending for routine reviews and repeat prescriptions rather than acute diagnoses.
- B85: pediculosis and phthiriasis; PCUs carried out screening visits at local schools.
- H01.1: non-infectious dermatoses of the eyelid, and J30: vasomotor and allergic rhinitis; these were included in the original search for simplicity but were not felt to be reasons to prescribe systemic antibiotics.
- K05: gingivitis and periodontal diseases, K12: recurrent oral aphthae, K12.1: Other forms of stomatitis; dental diagnoses were removed as it transpired that they were seen in large numbers by dental staff not the regular PCU staff.
- M60: myositis; this code was being used for myalgia and muscle pain rather than myositis [142].

Identifying those with a history of fever was challenging because there were 1,888 visits incorrectly coded as having a fever using a string search for 'fever'. This identified visits where the patient was recorded as 'no fever', as a 'patient' (literally translated from Thai as a 'person with a fever'), received an influenza vaccine (the Thai word for influenza contains the word fever) and requests for medications to lower fevers.

Any temperatures over 40°C were converted to missing data. After this cleaning process was complete 103,196 visits met our inclusion criteria; of these 5,966 were excluded because they attended a PCU which was taking part in the CRP RCT. In total, 13,569 repeat attendances were identified, resulting in 83,661 illness episodes (Figure 2-2) [142].

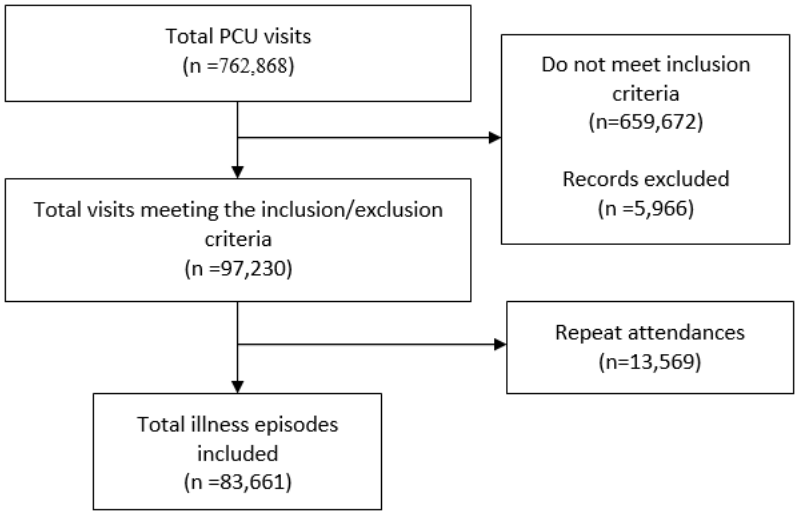

Figure 2-2: Flowchart showing the screening and inclusion of illness episodes in the antibiotic review

2.4.2 Patient Characteristics

The majority (54.7%) of the patients were female. The median age was 24 years (IQR 6 – 51 years).

The proportion of patients meeting the individual inclusion criteria is shown in Figure 2-3.

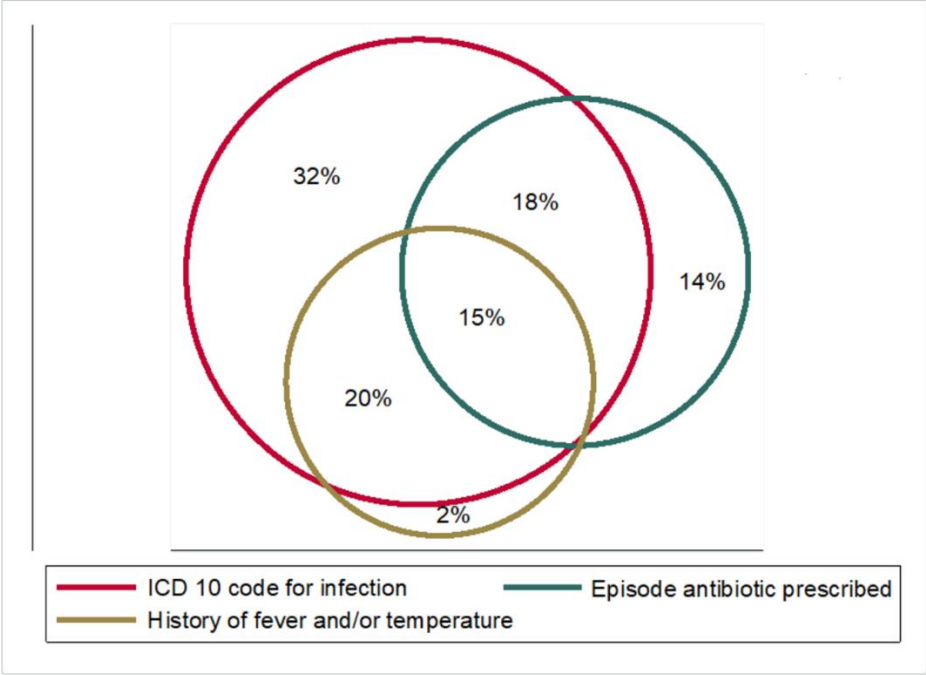

Figure 2-3: A Venn diagram to show the proportion of illness episodes for each inclusion criteria in the antibiotic review

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Over a third of the patients presented with a history of fever (35.3%), 13.7% had a fever on examination and 11.6% had both a history of fever and fever on examination (Table 2-2) [142].

Inclusion criteria	**Total initial presentations**	**Antibiotic prescription during the illness episode**
History of fever n/N (%)	29,246/82,976 (35.3%)	11,725/29,246 (40.1%)
Temperature > 37.5°C n/N (%)	10,508/76,644 (13.7%)	5,003/10,508 (47.6%)
ICD-10 code for infection n/N (%)	70,137/83,338 (84.2%)	27,234/70,137 (38.8%)
Antibiotic prescription n/N (%)	37,011/83,661 (44.2%)	39,242/83,661 (46.9%)

Table 2-2: The number of initial presentations for each antibiotic review inclusion criteria and the percentage prescribed antibiotics during their illness episode

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2.4.3 Antibiotic Prescriptions

At least one medication was prescribed for 81,691 illness episodes (97.7%). Antibiotics were prescribed at the first visit to 37,011 (44.2%) patients; this increased to 39,242 (46.9%) throughout their illness episode (up to 1 month).

'Antibiotics were prescribed to:

►► *49.2% of males compared with 45% of females (p<0.001).*

►► *39% of children compared with 51.8% of adults (p<0.001).*

►► *40.1% of those with a history of fever.*

►► *47.6% with a temperature >37.5°C.*

►► *38.8% with an ICD-10 code for infection'* [142].

Antibiotic prescription varied by age group; those aged 12 to 39 years old received the highest proportion of antibiotics (55.9%, Table 2-3).

Age (years)	Number of presentations n/N (%)	Number of patients receiving an antibiotic prescription n/N (%)
0 - 4	18,073/83,659 (21.6)	6,110/18,073 (33.8)
5 - 11	13,775/83,659 (16.5)	6,318/13,775 (45.9)
12 - 24	10,533/83,659 (12.6)	5,888/10,533 (55.9)
25 - 39	11,025/83,659 (13.2)	6,167/11,025 (55.9)
40 - 64	23,134/83,659 (27.7)	11,843/23,134 (51.2)
65 or over	7,119/83,659 (8.5)	2,915/7,119 (41)
Total	83,659 (100)	39,241/83,659 (46.9)

Table 2-3: The number of presentations per age group and the percentage of each group prescribed an antibiotic in the antibiotic review

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Table 2-4 shows the univariate and multivariable logistic regression analyses, accounting for clustering of patients at each PCU. Male, and adolescent and adult patients were more likely to receive antibiotics than patients who were female or children. PCUs staffed by only public health officers and no nurses, or placed 30km or further away from the provincial hospital were not associated with levels of antibiotic prescriptions. Having a documented temperature of more than 37.5°C was added to the multivariable analysis alongside sex and age category. All three variables were significantly associated with antibiotic prescription in the multivariable analysis [142].

No significant trends in the prevalence of monthly antibiotic prescriptions over time were seen (IRR = 0.99, 95% CI 0.990 to 1.007, p = 0.796, Figure 2-4). However, it is possible that a downward trend is beginning in the final 6 months. The wet season (July – October) was associated with a statistically but not clinically significant increase in antibiotic prescriptions compared to the hot and cold seasons (47.4% vs 46.6%, p value = 0.029).

Overall antibiotic prescriptions rates varied between the PCUs, with a range of 8% to 71.6% [142]. When considering antibiotic prescription alone heterogeneity between the PCUs was 0.63, $p < 0.001$. When adjusted for sex, children or adults, and temperature over 37.5°C the heterogeneity remained significant, 0.67, $p < 0.001$.

Variable	**OR (95% CI)**	**p value**	**aOR (95% CI)**	**p value**
	Univariate analysis		Multivariable analysis	
Male sex	1.18 (1.12 - 1.25)	<0.001	1.25 (1.19 - 1.32)	<0.001
Aged ≥ 12 years old	1.68 (1.48 - 1.90)	<0.001	1.72 (1.52 - 2.00)	<0.001
Temperature >37.5°C	1.05 (0.85 - 1.30)	0.627	1.24 (1.03 - 1.48)	0.020
Staffed by public health officers only	1.05 (0.40 - 2.72)	0.924	-	-
PCU ≥30 km from the provincial hospital	0.98 (0.51 - 1.88)	0.952	-	-

Table 2-4: Univariate and multivariable logistic regression analyses accounting for clustering of patients attending the same PCU, showing all included variables and their association with antibiotic prescription in the antibiotic review

*Adapted from Greer, R.C., et al., Retrospective review of the management of acute infections and the indications for antibiotic prescription in primary care in northern Thailand. BMJ Open, 2018. **8**(7): p. e022250-e022250. License CC BY [142].*

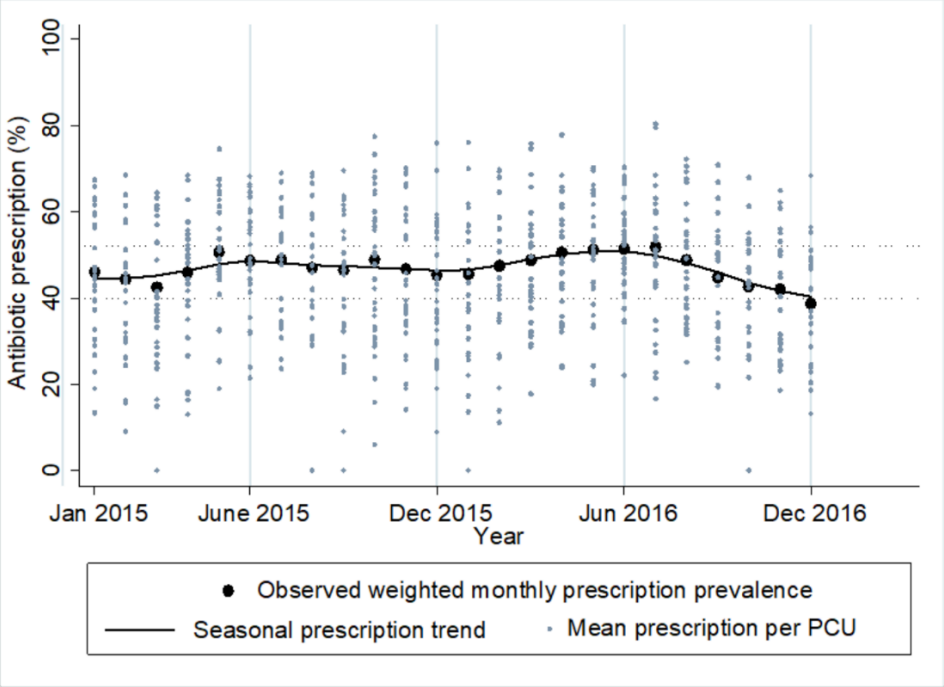

Figure 2-4: Two year trend and seasonality of antibiotic prescriptions overlaid by mean antibiotic prescription rates per primary care unit in the antibiotic review

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2.4.3.1 Classes of Antibiotics Prescribed

Amoxicillin was the most commonly prescribed antibiotic (56.7%), followed by dicloxacillin (25.1%, Table 2-5) [142]. Both of these antibiotics are classed as "Access" antibiotics in the "AWaRe" classification (Chapter 1) [53]. The most frequently prescribed "Watch" antibiotic was norfloxacin (8.9%). No "Reserve" antibiotics were prescribed.

"AWaRe" classification	**Antibiotic**	**Number of antibiotics prescribed n (%)**
"Access"	Amoxicillin	22,245 (56.7)
	Cephalexin	151 (0.4)
	Dicloxacillin	9,848 (25.1)
	Metronidazole	460 (1.2)
	Penicillin V	474 (1.2)
	Tetracycline	58 (0.2)
	Trimethoprim/sulfamethoxazole	1,641 (4.2)
	Total "Access" antibiotics	**34,877 (88.9)**

"Watch"	Erythromycin	269 (0.7)
	Norfloxacin	3,509 (8.9)
	Roxithromycin	471 (1.2)
	Total "Watch" antibiotics	**4,249 (10.8)**
Unclassed	Dual antibiotics	116 (0.3)

Table 2-5: The percentage of antibiotics prescribed by "AWaRe" classification in the antibiotic review

2.4.4 Infection Related Presentations and Antibiotic Prescriptions

The majority of infection related presentations involved the respiratory system (77.9%, Figure 2-5). The vast majority of these were diagnosed with an URTI (98.6%), with 1.1% acute LRTIs and 0.3% chronic LRTIs; antibiotics were prescribed to 36.1%, 81.8% and 53.5% respectively.

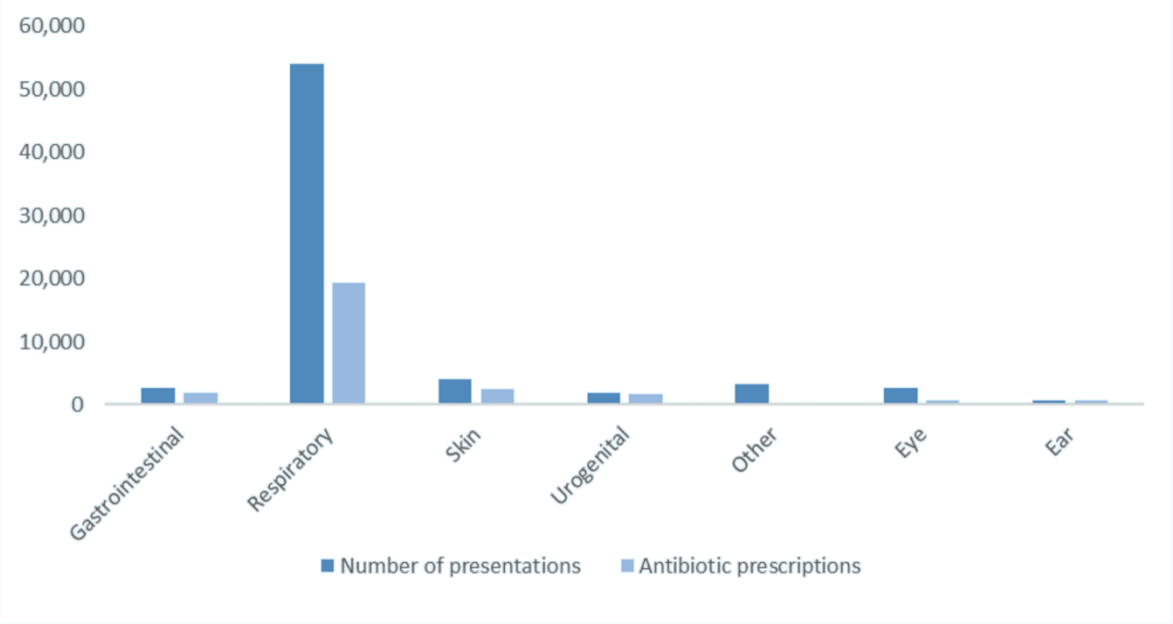

Figure 2-5: Number of acute presentations by single diagnostic systems and whether antibiotics were prescribed in the antibiotic review

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Table 2-6, shows the most common single-infection diagnoses which were common cold (34,549, 50%), acute pharyngitis (13,080, 18.9%) and acute tonsillitis (3,459, 5%), antibiotics were prescribed to 10.5%, 88.7% and 87.1% of the illness episodes, respectively.

Diagnosis	Number of presentations n/N (%)	Episode antibiotics prescribed n/N (%)	Commonest antibiotics prescribed (%)
Common cold	34,549/69,115 (50)	3,643/34,549 (10.5)	Amoxicillin (71.7), dicloxacillin (12.11), trimethoprim/ sulfamethoxazole (9.3%)
Acute pharyngitis	13,080/69,115 (18.9)	11,607/13,080 (88.7)	Amoxicillin (91.5), roxithromycin (2.4%), penicillin V (1.9%)
Acute tonsillitis	3,459/69,115 (5)	3,014/3,459 (87.1)	Amoxicillin (93.4), roxithromycin (2.0), penicillin V (1.9)
Gastroenteritis & colitis unspecified	2,412/69,115 (3.5)	1,614/2,412 (66.9)	Norfloxacin (68.8), trimethoprim/ sulfamethoxazole (22.9), amoxicillin (5.4)
Conjunctivitis	2,097/69,115 (3.0)	330/2,097 (15.7)	Amoxicillin (56.4), dicloxacillin (36.7), norfloxacin (3.0)
Other helminthiases	1,231/69,115 (1.8)	65/1,231 (5.3)	Amoxicillin (41.5), dicloxacillin (27.7), norfloxacin (21.5)
Cystitis	1,230/69,115 (1.8)	1,165/1,230 (94.7)	Norfloxacin (75.9), trimethoprim/ sulfamethoxazole (9.2), metronidazole (6.4%)

Table 2-6: Common diagnoses in patients with one single ICD-10 code for infection: the number of presentations, whether antibiotics were prescribed and which types were commonly prescribed in the antibiotic review

*Adapted from Greer, R.C., et al., Retrospective review of the management of acute infections and the indications for antibiotic prescription in primary care in northern Thailand. BMJ Open, 2018. **8**(7): p. e022250-e022250. License CC BY [142].*

The single-infection diagnoses are shown by systems, alongside the proportion prescribed antibiotics in Table 2-7. Approximately 80% of illness episodes caused by AOM, otitis externa and, hordeolum and chalazion were prescribed systemic antibiotics, while 59.4% of skin infections were prescribed antibiotics, largely due to those diagnosed with skin infections and cysts.

Diagnosis	**Number of presentations n/N (%)**	**Number of antibiotic prescriptions during the illness episode n/N (%)**
Respiratory		
Common cold	34,549/53,819 (64.2)	3,643/34,549 (10.5)
Acute sinusitis	30/53,819 (0.1)	25/30 (83.3)
Acute pharyngitis	13,080/53,819 (24.3)	11,607/13,080 (88.7)
Acute tonsillitis	3,459/53,819 (6.4)	3,014/3,459 (87.1)
Other URTIs	357/53,819 (0.7)	278/357 (77.9)
Acute bronchitis	544/53,819 (1.0)	449/544 (82.5)
Other acute LRTIs	119/53,819 (0.2)	92/119 (77.3)
Chronic bronchitis, emphysema & bronchiectasis	60/53,819 (0.1)	10/60 (16.7)
Cough	1,621/53,819 (3)	99/1,621 (6.1)
Sub total	53,819 (100)	19,217/53,819 (35.7)
Gastrointestinal		
Bacterial intestinal infections or intoxications	199/2,706 (7.4)	127/199 (63.8)
Viral enteritis	46/2,706 (1.7)	4/46 (8.7)
Gastroenteritis & colitis	2,412/2,706 (89.1)	1,614/2,412 (66.9)
Appendicitis	21/2,706 (0.8)	2/21 (9.5)
Other	9/2,706 (0.3)	2/9 (22.2)
Sialoadenitis	19/2,706 (0.7)	16/19 (84.2)
Sub total	2,706 (100)	1,765/2,706 (65.2)
Skin		
Infective dermatitis	85/4,060 (2.1)	70/85 (82.4)
Dermatophytosis	902/4,060 (22.2)	92/902 (10.2)

Other superficial mycoses	197/4,060 (4.9)	14/197 (7.1)
Candidiasis	101/4,060 (2.5)	23/101 (22.8)
Other	64/4,060 (1.6)	52/64 (81.3)
Scabies & infestations	52/4,060 (1.3)	8/52 (15.4)
Cellulitis & abscesses	841/4,060 (20.7)	618/841 (73.5)
Bacterial skin infections	533/4,060 (13.1)	464/533 (87.1)
Furuncles, caruncles & cysts	947/4,060 (23.3)	780/947 (82.4)
Other local infection of the skin & subcutaneous tissue	338/4,060 (8.3)	290/338 (85.8)
Sub total	4,060 (100)	2,411/4060 (59.4)
Eye		
Conjunctivitis	2,097/2,698 (77.7)	330/2,097 (15.7)
Hordeolum & chalazion	319/2,698 (11.8)	256/319 (80.3)
Other inflammation of the eyelid & orbit	268/2,698 (9.9)	98/268 (36.6)
Trachoma	14/2,698 (0.5)	5/14 (35.7)
Sub total	2,698 (100)	689/2,698 (25.5)
Ear		
Otitis externa	464/753 (61.6)	369/464 (79.5)
AOM	243/753 (32.3)	197/243 (81.1)
Mastoiditis	16/753 (2.1)	9/16 (56.3)
Perforation of tympanic membrane & other disorders	30/753 (4)	25/30 (83.3)
Sub total	753 (100)	600/753 (79.7)
Urogenital		
Acute tubulo-interstitial nephritis	36/1,871 (1.9)	32/36 (88.9)
Other	17/1,871 (0.9)	12/17 (70.6)
Cystitis, UTI, dysuria, urethritis & urethral syndrome	1,370/1,871 (73.2)	1,291/1,370 (94.2)
Other disorders of male genital organs	32/1,871 (1.7)	20/32 (62.5)

Other inflammatory disorders of female pelvic organs	148/1,871 (7.9)	115/148 (77.7)
Other inflammatory disorders of the vagina & vulva	268/1,871 (14.3)	149/268 (55.6)
Sub total	1,871 (100)	1,619/1,871 (86.5)
Other		
Bacterial	85/3,208 (2.7)	28/85 (32.9)
Unknown aetiology	33/3,208 (1)	14/33 (42.4)
Viral	728/3,208 (22.7)	153/728 (21)
Fungal	36/3,208 (1.1)	2/36 (5.6)
Protozoal	10/3,208 (0.3)	0/10 (0)
Parasitic	1,880/3,208 (58.6)	99/1,880 (5.3)
Nausea & vomiting	268/3,208 (8.4)	30/268 (11.2)
Fever of unknown or other origin	168/3,208 (5.2)	10/168 (6)
Sub total	3,208 (100)	336/3,208 (10.5)

Table 2-7: The number of presentations per diagnosis and system, and whether antibiotics were prescribed for that illness episode in the antibiotic review

*Adapted from Greer, R.C., et al., Retrospective review of the management of acute infections and the indications for antibiotic prescription in primary care in northern Thailand. BMJ open, 2018. **8**(7): p. e022250-e022250. License CC BY [142].*

Considering which individual conditions antibiotics were prescribed for, 29.6% were given to those with acute pharyngitis, followed by 9.3% to common colds, 7.7% to tonsillitis, 4.1% to gastroenteritis and colitis, and 3% to cystitis. Of interest, 13.8% of the total antibiotics prescribed were given to those without a fever or history of fever or an ICD-10 code classed as relating to an infection. Of these, considering only those with a single diagnosis (7,376 illness episodes), 24.6% were related to dental problems, 13.6% to ongoing surgical care, 7.1% to contact dermatitis and 6.4% to open wounds (Figure 2-6). Other indications for antibiotic use in this group include male sex (54.3%, p value < 0.001) and being older (median age of 41 vs 24 years) compared to the main patient group [142].

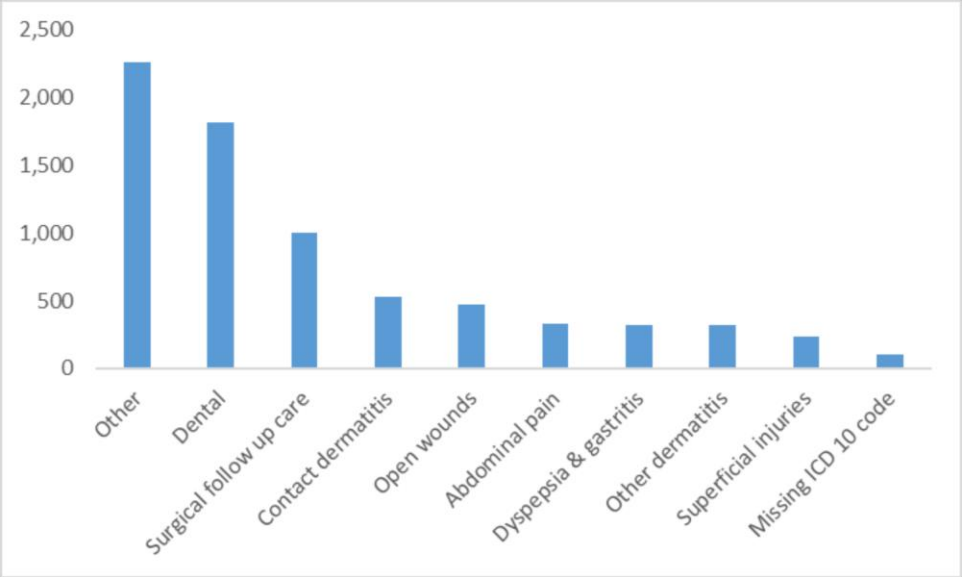

Figure 2-6: The number of common, single diagnoses made for patients with antibiotic prescriptions without a history of fever, temperature or ICD-10 code for infection included in the antibiotic review

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2.4.5 Concordance with Antibiotic Guidelines

Concordance with antibiotic guidelines was considered for the most common diagnoses (Table 2-8). We did not collect data on general examination findings so it was not possible to assess individual patients' need for antibiotics for pharyngitis and tonsillitis (Table 2-1). In order to give an estimate of appropriate antibiotic use, data were used from the sore throat subgroup enrolled into the CRP RCT, which prospectively collected data including examination findings (Chapter 3) [144]. Limitations to this data exist as lymphadenopathy was not systematically recorded so the Centor scores may have been underestimated and we made the assumption that patients presenting to six of the 32 PCUs involved in the RCT were similar to those included in this review. Of the patients enrolled in the RCT with a sore throat, only 2.4% had a Centor score of ≥ 3 [144]. Despite the limitations it is likely that the majority of the 88.4% episodes diagnosed with pharyngitis or tonsillitis and prescribed antibiotics in this review did not need antibiotics, and that only 13.9% of the cases were treated appropriately - mostly those with antibiotics withheld [142, 144]. Encouragingly, over 97% of those treated with antibiotics received an antibiotic recommended in the RDU treatment guidelines [124].

Condition	Antibiotic prescribed? n/N (%)	Indications for antibiotics n/N (%)	Appropriately prescribed or not prescribed antibiotics n/N (%)	Appropriate type of antibiotic prescribed? n/N (%)	Overall appropriate antibiotic prescribed? n/N (%)
Common cold	3,643/34,549 (10.5)	None	30,906/34,549 (89.5) -all withheld	NA	30,906/34,549 (89.5) -all withheld
Pharyngitis/ tonsillitis	14,621/ 16,539 (88.4)	Centor ≥3: 397/16,539 (2.4)	2,315/16,539 (14.0): -397 (2.4) indicated -1,918 (11.6) withheld	14,191/14,621 (97.1): -Amoxicillin: 13,432 (91.9) -Penicillin V: 273 (1.9) -Roxithromycin: 336 (2.3) -Erythromycin: 150 (1.0)	2,303/16,539 (13.9): -385 (2.3) prescribed -1918 (11.6) withheld
Gastroenteritis/ colitis	1,614/2,412 (66.9)	Temperature > 38°C: 101/2,255 (4.5) Blood: 26/2,398 (1.1) Both 0/2,249 (0)	798/2,412 (33.1) -all withheld	NA	798/2,412 (33.1) -all withheld

Table 2-8: The percentage and appropriateness of antibiotic prescriptions for common colds, sore throats and diarrhoea in the antibiotic review

Nearly 2,500 patients were diagnosed with gastroenteritis or colitis. None of them had both a temperature > 38°C and bloody diarrhoea, which according to the guidelines are the only cases which would benefit from antibiotics, therefore all of the antibiotics prescribed where deemed to be unnecessary and only the 33.1% who did not receive antibiotics were treated appropriately. If antibiotics were indicated it is likely that they would have received an appropriate type as 68.8% received norfloxacin and 22.9% received trimethoprim/ sulfamethoxazole – the two recommended antibiotics (Table 2-1 and Table 2-6) [124, 142].

In addition to the antibiotic guidelines in Table 2-1, I classed systemic antibiotics as unlikely to benefit conjunctivitis, therefore antibiotics were appropriately used in 1,767/2,097 (84.3%) of cases, all of whom did not receive antibiotics. I classed helminth infections (including non-specific worms) as not needing antibiotics, resulting in 1,166/1,231 (94.7%) having antibiotics withheld appropriately. UTIs were more difficult to class as appropriate or not because urine dipstick tests, microscopy and culture are not routinely available in the PCUs. I made the assumption that symptomatic patients needed antibiotics resulting in 1,165/1,230 (94.7%) appropriately receiving antibiotics. However, the type of antibiotic which should be prescribed is unclear due to the lack of local guidelines and limited range of antibiotics available in the PCUs. Trimethoprim, nitrofurantoin and ciprofloxacin are not routinely available.

2.5 Discussion

This is the largest detailed review of antibiotic prescriptions in primary care in Thailand, and one of the largest conducted in a LMIC. Over a 2 year period there were more than 750,000 visits to the PCUs in Mueang Chiangrai District. Over 83,500 illness episodes may have been related to an infection and were included in this review, of which nearly half received an antibiotic prescription.

Comparing overall antibiotic prescription rates between studies is challenging due to the different patient groups, diagnoses and settings involved. Overall prescribing for URTIs and acute bronchitis is

reported for all PCUs in Thailand, outside of Bangkok. In the Thai 2019 accounting year (October 2018 - September 2019), 6.2% of 9,922,274 patients received antibiotics, this was reduced from 46.3% of 4,014,665 patients in 2014 [104]. During the 2019 accounting year, 23.9% of 1,632,453 patients attending OPDs in Thailand, excluding Bangkok were prescribed antibiotics [104]. These figures are consistent with our review; 36.6% of those with URTIs or acute bronchitis received antibiotics between 2015 and 2016. It is also similar to a study of adults and children with URTIs and acute bronchitis attending a hospital OPD in central Thailand, which found that 38.4% of 9,286 patients were prescribed antibiotics in 2017 [103].

In the same study 87.3% of the 725 patients with tonsillitis received antibiotics compared to 87.1% of the 3,459 patients in our review [103]. While 77.3% of their 2,360 patients with pharyngitis received antibiotics compared to 88.7% of the 13,080 in our review [103, 142].

The Thai MOPH also reports antibiotic prescribing for diarrhoea in the PCUs in Thailand, excluding Bangkok. During the 2019 financial year, 8.1% of 692,800 patients received antibiotics, which was reduced from 2013 when 79.1% of 29,930 patients received antibiotics [104]. Our review found antibiotic use towards the higher end of this spectrum with 66.9% of the 2,412 patients with gastroenteritis and colitis receiving antibiotics.

As discussed in Chapter 1, Thailand has been actively trying to optimise antibiotic use with stewardship programmes such as ASU. The adoption of a 20% antibiotic prescribing target into the key performance indicators seems to have had a large impact on prescribing for URTIs, acute bronchitis and diarrhoea. We may be seeing the start of such a reduction in overall antibiotic use in Chiangrai in the last 6 months of this review, which coincides with the MOPH adding RDU targets into its key performance indicators for hospitals and PCUs.

Antibiotics were more likely to be prescribed to adults than children, and males than females in our review. These breakdowns are not often provided but Suttajit et al. found that antibiotics were more

likely to be given to 18 to 40 year old patients rather than older patients (no children were included) [96]. Aoybamroong et al. found that more appropriate (and presumably fewer) antibiotics were given to younger children with ARTIs compared to older children (3 months to 15 years old) [101]. A higher proportion of adults receiving antibiotics compared to children at PCUs may be a reflection of people's health-seeking behaviour. People tend to be more cautious with children and take them to the PCU, rather than buying medication for them over the counter which they are more likely to do for themselves [84, 145]. This may mean that adults are more likely than children to have a severe infection needing antibiotics when they present to PCUs. Consistent with our findings, Suttajit et al. also found that males were more likely to receive antibiotics than females aOR 1.47 (95% CI 1.26 - 1.72) [96].

Remoteness from healthcare facilities is often thought to lead to more cautious, increased antibiotic use because of concerns that patients may not be able to attend follow-up or re-attend with worsening symptoms, however in this study, distance from the provincial hospital was not associated with antibiotic prescription. Although there was heterogeneity between the PCUs in terms of overall antibiotic prescription.

Almost 90% of the antibiotics prescribed were from the "Access' category of the "AWaRe" classification. This is well within the 60% country level target set by WHO [53].

Half of the single infection diagnoses were for common colds; despite only 10.5% receiving antibiotic prescriptions these probably represent over 3,500 unnecessary antibiotic prescriptions. Tonsillitis and pharyngitis were other common diagnoses and had the highest levels of inappropriate antibiotic use, accounting for over a third of the total antibiotics prescribed. None of the episodes of gastroenteritis included in this review met the criteria for antibiotics, resulting in only a third receiving appropriate antibiotic treatments (all were withheld). The types of antibiotics used for sore throats and diarrhoea were mostly consistent with the RDU guidelines [124, 142].

Approximately 80% of the AOM, otitis externa, hordeolum and chalazion episodes received antibiotics, which is likely to represent overuse of systemic antibiotics (Table 2-7). This may be due in part to the lack of topical antibiotics available in these PCUs. Nonetheless, topical antibiotics for the eye are available yet 15.7% of the conjunctivitis cases received systemic antibiotics [142].

Areas for improvement include reducing the proportion of patients with common colds, URTIs with sore throats and simple diarrhoea receiving antibiotics in line with the ASU guidelines. Particular attention seems to be needed for pharyngitis and tonsillitis. Reducing antibiotic use in these three common conditions would affect the levels of overall antibiotic use in these PCUs. The RCT in Chapters 3 and 4 explores whether CRP POC testing can help to target antibiotic use in those attending with fever or a history of fever. Chapter 3 also looks in more detail at patients with sore throats and whether CRP testing, throat swabs and clinical scores can help to identify those who need antibiotics.

Extending antibiotic guidelines to UTIs and other common infections presenting to PCUs, such as conjunctivitis and helminth infections would help healthcare workers to manage these cases and ensure that the appropriate types of antibiotics for these infections are available in the PCUs. To inform these guidelines, more data is needed on the antibiotic susceptibility of common urinary pathogens in the community; a study from another northern Thai province found that 10.6% were not sensitive to their first line antibiotics (nitrofurantoin or ciprofloxacin for uncomplicated UTIs, and ciprofloxacin or ceftriaxone for pyelonephritis) [92]. The treatment of scrub typhus - the leading cause of local hospital admissions with acute undifferentiated fever [117], is currently overlooked in the community, with neither of the first line antibiotics (doxycycline and azithromycin) available in the PCUs.

Dental prescribing is outside of the scope of this thesis but accounted for a quarter of the antibiotics prescribed to those without a history of fever or ICD-10 code for infection. The appropriateness of this prescribing should be considered [142].

2.5.1 Strengths and Limitations

Strengths of this review are the inclusion of all the PCUs in the district and that a 2 year time period was considered. Mueang Chiangrai District is a large district covering both rural and urban areas which adds to the generalisability of the results. The wide inclusion criteria should have identified all illness episodes which may have benefitted from or been prescribed an antibiotic, rather than focusing on one or two conditions. Alongside this we included all antibiotics prescribed (even if it may not have been indicated). Collecting demographic and clinical data in addition to the diagnosis and prescription provided patient level data in order to better understand how antibiotics are being used and how appropriate these prescriptions may be. The use of routinely collected, electronic data means that this review could be reproduced in other districts or repeated in this one, allowing for further comparisons. It may also provide a more accurate picture of routine prescribing compared to a prospective study where the healthcare workers know their prescribing is being reviewed and may be influenced by The Hawthorne Effect [142].

There are however limitations of using routinely collected data, such as missing data and the accuracy of the data reported. A few PCUs had missing data for several months. To assess the accuracy of the data provided a subsample of case record forms (CRFs) from the CRP RCT were compared against the routine electronic data used in this review (although the patients were excluded from this review in case the RCT affected antibiotic prescription). Apart from minor discrepancies in some variables such as age, the main fields of interest such as the diagnosis and antibiotic prescriptions were consistent [142]. The number of presentations with URTIs and acute bronchitis, or diarrhoea, and antibiotic use were compared against the data released by the MOPH for this district and time period; the figures were largely reliable [104].

The diagnoses were made clinically which is standard practice in primary care and there were no diagnostics available in these PCUs to support diagnoses. The diagnoses assigned to each illness episode were reliant on the ICD-10 code given to each patient. These may vary between healthcare

workers and PCUs. Diagnosis coding may be influenced by the healthcare worker's decision to prescribe an antibiotic or not, especially for conditions monitored by the MOPH with RDU targets for antibiotic prescription [125, 142].

The dose and length of antibiotic prescription were not collected, so we were unable to calculate DDDs of antibiotics or assess the appropriateness of the dose and duration of antibiotics used. Antibiotic use was evaluated over a one month illness episode which may have incorrectly merged two separate illnesses. The 2 year study period may not have been sufficient to see longer term trends in antibiotic use in the time-series analysis. Finally, only government run PCUs were included which means we cannot generalise our findings to private clinics, hospital OPDs or pharmacies [142].

2.5.2 Conclusions

This large review provides a detailed look at antibiotic prescribing in PCUs in northern Thailand. The majority of infection presentations to the PCUs were for RTIs. Almost half of the illness episodes were prescribed antibiotics. Whilst improvements have been made in optimising antibiotic use, URTIs, particularly tonsillitis and pharyngitis remain common reasons for antibiotic overuse. There are no local antibiotic guidelines for many conditions and no diagnostic support available in the PCUs. Introducing additional antibiotic guidelines and some simple tests such as urine dipsticks, biomarkers of infection or RDTs may help guide antibiotic use. Further work is needed to explore these possible interventions' effectiveness and acceptability. Better understanding of antibiotic use in the dental and private sectors is also required.

Chapter 3 Evaluating the C-Reactive Protein Point of Care Test Intervention: Impact on Antibiotic Prescriptions and Clinical Recovery, the Detection of Group A *Streptococcus* and Healthcare Workers' Opinions

3.1 Introduction

Overuse of antibiotics is a driver of AMR and the need to optimise antibiotic use is well recognised (Chapter 1) [22, 25, 27, 28]. The majority of antibiotics are consumed in the community [27, 55]. In Thailand, most people report seeking antibiotics from healthcare workers rather than from informal sources [75, 90]. Government run PCUs are an important source of primary healthcare, so are a good target location for antimicrobial stewardship programmes. Chapter 2 describes the current use of antibiotics in PCUs in Mueang Chiangrai District, where 47% of patients with infection related presentations are prescribed an antibiotic [142]. In the six PCUs used as the Thai study sites for this RCT, antibiotics were prescribed for 29% to 72% of patients with a history of fever or fever between 2015 and 2016. In the Myanmar study sites, retrospective reviews revealed that 69% of febrile patients attending the OPD received antibiotics compared to 41% of non-routine attendees at three Medical Action Myanmar clinics [146].

One possible intervention to optimise antibiotic use is introducing a POC test for biomarkers of bacterial infection. CRP, one of the most studied biomarkers is an acute phase protein, released in response to inflammation, infection or injury. CRP levels rise within several hours and peak at 48 to 72 hours. CRP can be raised by infections as well as rheumatologic diseases, malignancies and inflammatory conditions such as pericarditis and appendicitis [147, 148]. A 2014 Cochrane review of POC biomarkers included six RCTs on CRP testing in patients with acute respiratory infections (ARIs)

presenting to primary care in Europe and Russia. They found that using CRP testing at the POC reduced antibiotic prescriptions without affecting patient outcomes [132].

As well as exploring the value of CRP testing to guide antibiotic prescriptions in LMICs we wanted to generate empirical evidence as to which CRP threshold should be used. Generally, RCTs have recommended using a CRP of < 20mg/L as an indication that antibiotics are not required and a CRP ≥ 100mg/L as an indication that antibiotics are required. Guidance for CRP values in between has varied from withholding antibiotics, giving delayed prescriptions or immediate prescriptions if there are clinical concerns [149-153]. The only previous RCT using CRP to guide antibiotics in non-severe RTIs in a LMIC was conducted in Viet Nam. They used CRP cut offs of < 10mg/L and ≥ 50mg/L for 1 to 5 year olds, and < 20 mg/L and ≥ 100mg/L for those aged 5 to 65. No guidance was given for CRP results between the two cut offs [154].

Previous observational studies from Southeast Asia evaluating CRP's ability to differentiate between viral and bacterial infections were also considered, and they had evaluated CRP cut offs of 10, 20 and 40mg/L [117, 155, 156]. CRP's diagnostic performance was evaluated in over a 1,000 febrile inpatients and outpatients in Thailand, Cambodia and Laos, who were diagnosed with a single viral, bacterial or malarial infection. CRP levels were significantly higher in bacterial infections compared to viral infections but there were no differences between bacterial and malarial infections ($p = 0.15$). A CRP cut off of 10mg/L had a sensitivity of 95% (95% CI 92% to 97%) and specificity of 49% (95% CI 46% to 53%) for differentiating bacterial from viral infections. Using a higher cut off of > 20mg/L, lowered sensitivity to 86% (95% CI 82% to 88%) but increased specificity to 67% (95% CI 63% to 71%) [155]. A study of the causes of acute undifferentiated fevers leading to admissions in a provincial hospital in Chiangrai, northern Thailand found a cause of fever in just over half of the 200 adults. In patients diagnosed with a bacterial infection, 92% had a CRP > 20mg/L and 86% had a CRP > 40mg/L; while in the viral group 73% had a CRP ≤ 20mg/L and 86% had a CRP ≤ 40mg/L. The highest proportion of correctly classed cases was achieved with a CRP cut off of 36mg/L [117].

After reviewing all the evidence, including a systematic review of laboratory tests to identify children with serious infections, which recommended using a CRP cut off of 20mg/L to rule out serious infections, we felt that it was reasonable to use the same conservative CRP cuts offs for adults and children and selected CRP cut offs of 20mg/L and 40mg/L [157].

Most of the trials conducted on CRP testing in primary care have been carried out in HICs and have tended to focus on antibiotic use for RTIs in adults [149, 150, 152, 158-160]. Children, the elderly and those with co-morbidities were often excluded from these RCTs resulting in a paucity of evidence [132]. More recent studies have been conducted in children and in LMICs to widen the generalisability of the results, although a consensus has yet to be reached on the appropriate CRP cuts off for these groups [154, 159, 161]. CRP testing to guide antibiotic use in primary care for infections other than RTIs has not been widely evaluated. To date, healthcare workers' opinions on CRP testing have mostly been explored in HICs [162-170].

To address some of these gaps we wished to extend the evaluation of CRP POC testing's role to febrile patients rather than limiting its use to those with RTIs. We also wanted to add to the evidence for CRP use in children which was more limited at the time.

The retrospective review of antibiotic use in Thailand (Chapter 2) highlighted the high use of antibiotics for patients diagnosed with sore throats, a third of the RTI consultations. However, the majority of symptomatic throat infections are caused by viruses (40 - 80%). Bacterial infections are identified in approximately 25% to 40% of children, and 5% to 25% of adults in a range of settings; the most common bacterial pathogen is GAS, followed by other BHS (group C, G and F streptococci) [140, 144, 171, 172].

Several tools including clinical scores and RDTs have been developed to identify those with a GAS infection in whom antibiotics may be beneficial. The Centor score was developed in the US to detect GAS in adults presenting to emergency departments. A point is scored for each of the following:

tonsillar exudate, tender anterior cervical lymphadenopathy or lymphadenitis, history of fever, and absence of cough [173]. The FeverPAIN score was developed more recently in the UK from a cohort of patients aged 5 years and above presenting to GPs with a sore throat; in addition to detecting GAS they also included group C and G streptococci. The score includes fever in the last 24 hours, pus on the tonsils, attendance within 3 days of symptom onset, severely inflamed tonsils, and no cough or coryza [174].

Studies on CRP testing to identify GAS infections have given varying results [171, 175-180]. There is some evidence that adding CRP testing and rapid antigen detection tests to clinician education or clinical assessment can reduce the overall use of antibiotics for RTIs [181, 182].

In Thailand, antibiotics are recommended for pharyngitis or tonsillitis if three of the following are present: fever > 39°C and a sore throat; tonsillar exudate or red uvula; painful cervical lymphadenopathy; and no cold symptoms. Despite this, antibiotics are prescribed to the majority of patients, therefore we explored if CRP testing could identify those with GAS in the subset of patients in the trial presenting with a sore throat.

3.2 Aims and Objectives

The main aim of this chapter is to evaluate the use of CRP testing to guide antibiotic use in patients presenting to primary care in Thailand and Myanmar with a fever or history of fever. Two intervention arms were included with differing CRP threshold values to guide antibiotic prescribing. Secondary objectives are to:

- Compare the clinical outcomes between the control and intervention arms.
- Review healthcare workers' concordance with the CRP test results and guidance.
- Explore healthcare workers' views towards CRP testing.
- Evaluate whether CRP testing or clinical scores can identify GAS presence in those presenting with a sore throat.

- Estimate the prevalence of GAS and other BHS.
- Assess antibiotic resistance amongst GAS isolates.

3.3 Methods

3.3.1 Study Design

We conducted a multi-centre, open label RCT in Thailand and Myanmar [146]. The RCT was powered for independent analyses of the two countries. Patients attending primary care with a fever or history of fever, were randomly assigned to one of three arms: intervention arm A (CRP cut off 20mg/L), intervention arm B (CRP cut off 40mg/L) and control arm C (routine care). CRP POC tests were used to guide antibiotic use in the intervention arms.

While CRP was measured by research staff using quantitative readers, the results were provided to healthcare workers in a binary form – being either 'low' or 'high' in relation to the threshold of the intervention arm. This was done as we assumed that if CRP testing was to be widely used in lower resource settings with less trained healthcare workers, it would be reliant on binary, qualitative CRP tests that would be easier to use and interpret, as well as having lower costs and infrastructure requirements. Nevertheless, we collected the quantitative data in order to be able to carry out a more thorough evaluation.

Given the uncertainty about the optimal CRP cut off to use in this setting we used two arms with different CRP cut offs. Evaluating two cut offs simultaneously was an efficient study design and use of resources.

Due to the extended age groups, clinical presentations and LMIC setting we repeated the CRP test at day 5 of follow-up, in order to provide further safety data in case any patients were not prescribed an antibiotic when they would have benefitted from one. Repeating the CRP test in all patients is unlikely to be useful or feasible in routine care. However, we were interested to see the results and in particular to check if any patients had a normal CRP on day 0 but a raised CRP on day 5.

We followed up the participants in person on day 5 and day 14 in order to gain some measurable secondary outcomes, such as the CRP level and temperature on day 5, as well as more subjective outcomes such as patient-reported recovery. The 14 day study period should be long enough to cover the natural history of most common infection related presentations.

3.3.2 Study Preparation

3.3.2.1 Study Approval

While planning the study we discussed the design and outcomes with our local collaborators in Thailand. After receiving the approval and support of the primary care physicians and provincial hospital director we submitted the protocol to the ethics committees. The directors of the prospective PCUs were then approached and asked whether their PCUs would be interested in becoming study sites for the RCT. A similar process was followed in Myanmar.

3.3.2.2 Study Nurse Recruitment

In order to conduct this RCT in Thailand we needed to recruit study nurses to the newly established CCRU. The positions were advertised and I conducted the interviews with CCRU's director and senior research nurse. Only one out of four nurses had previous research experience so I organised training for them. This involved shadowing sessions with current research nurses from CCRU, as well as a few days training in Bangkok organised by MORU's Clinical Trials Support Group. I reviewed the study procedures, informed consent processes and conducted roles plays on recruiting patients and the study procedures. This training was done in addition to the study specific initiation visit.

3.3.2.3 Healthcare Workers' Training

Along with a colleague responsible for the Myanmar site, I prepared the healthcare workers' training, and supported the research nurses to deliver the training sessions in Thai. The sessions discussed the challenges of clinically diagnosing viral and bacterial infections, and deciding whether antibiotics are required. They included a brief introduction to regional causes of fever, CRP and its ability to

differentiate between viral and bacterial infections. The objectives of the study and its design were discussed, focusing on the healthcare workers' roles. The guidance for interpreting and using the CRP results was then reviewed, suggesting that if the CRP test was low then antibiotics were not required, if the CRP test was high then antibiotics were likely to be beneficial. Nonetheless, healthcare workers were encouraged to use their clinical judgement and be aware of clinical danger signs, based on WHO's IMCI (Integrated Management of Childhood Illness) guidelines, such as respiratory distress and dehydration [183]. If healthcare workers were concerned, they were able to overrule the CRP guidance. The sessions ended with some sample cases and a question and answer session.

3.3.3 Study Sites

Initially two PCUs in Chiangrai city were used as study sites. They were purposively selected to include a large catchment population and to be within 30 minutes' drive of the provincial hospital. They covered rural and urban areas. An additional four PCUs were added due to an expanded research nursing team and slow participant recruitment. In Myanmar four study sites were used in Yangon: one OPD based in a government hospital and three Medical Action Myanmar clinics [146]. CRP POC tests are not routinely available at any of the study sites.

3.3.4 Study Participants

Patients were eligible to join the study if they were:

- Aged ≥ 1 year old
- Had a fever of > 37.5°C recorded at the study site or had a history of fever in the last 14 days
- Able to give written, informed consent (or parental consent in the case of children under 18 years old).
- Those presenting with a sore throat in Thailand between November 2016 and August 2017 were eligible to receive a throat swab for the nested GAS study in addition to inclusion in the main RCT.

The exclusion criteria were:

- Patients in need of referral to a higher-level facility, such as those with impaired consciousness, unable to take oral medication or with a recent history of convulsions
- Main complaint of trauma and/or injury
- Suspicion of TB
- Suspicion of UTI
- Suspicion of local skin or dental infection
- Any presenting symptom present for > 14 days
- Bleeding, including haematemesis, haemoptysis, haemorrhagic petechiae etc.
- Past or current neoplastic disease
- Unable to attend follow-up at day 5
- Positive malaria test if this was done as part of routine practice [146].

Children were included because they are frequent attendees at primary care with acute infections and there was a paucity of evidence available to optimise their antibiotic use [142]. Those under 1 year of age were not included to avoid the neonatal period, as a safety precaution and for simplicity of recruitment.

We included those with a history of fever as well as a fever because it is common for patients to present with a history of fever but to be afebrile at the consultation [142]. As fevers can fluctuate the recommendation of National Institute for Health and Care Excellence (NICE), amongst others is to take into account any reported fevers [184].

We excluded those requiring referral to a higher level facility as we wanted to focus on CRP POC testing in primary care to guide antibiotic therapy rather than its value for triaging those in need of hospital referral or admission. Differing CRP cut offs and study design may be needed to study CRP's role in triaging patients. We wanted to focus on acute infections rather than the prevention of

infections so excluded those with a main complaint of trauma. An illness duration of 14 days was chosen to exclude those with chronic fevers or infections such as TB who would need different assessment and management. We also excluded those with suspected UTIs or skin and dental infections which are more likely to have a bacterial rather than viral aetiology. Although we recognise that antibiotics can still be overused in many of these presentations the evidence for CRP's role in identifying who would benefit from antibiotics is lacking. Bleeding was excluded due to concerns about possible dengue, meningitis, haemorrhagic fevers and other more serious illnesses. Those with neoplastic disease were excluded as their CRP level may have been raised by their underlying disease rather than acute infection. Those unable to attend follow-up were excluded because we wanted to thoroughly assess the clinical outcomes of participants in this setting. Those with a positive malaria test were excluded due to concerns about CRP's ability to differentiate between malarial and bacterial infections [155].

3.3.5 Informed Consent

Study staff explained the study, procedures, and related benefits and risks to potential participants. Written informed consent was taken from those aged 18 years and above who wanted to join the study and were able to give consent. Parental consent was taken from those aged less than 18 years. Assent was sought in addition to parental consent for those aged more than 7 years and less than 18 years. In accordance with local practices and ethics committee recommendations, two witnesses were involved in the consent process for all study participants in Thailand, not just those who were illiterate. All study documents including the patient information sheets and informed consent forms were approved by the Oxford Tropical Research Ethics Committee, the Mahidol University Faculty of Tropical Medicine Ethics Committee, the Chiangrai Provincial and Public Health Office Research Ethics Committee and the Myanmar Department of Medical Research Ethics Committee.

3.3.6 Randomisation and Masking

Once eligible participants had given their informed consent, they were randomly assigned to one of the three study arms. Participants were stratified by age group (children, and adolescents and adults) and country (Thailand and Myanmar), and individually randomised 1:1:1 to one of three arms (two intervention arms and one control arm). The study statistician generated computer randomised sequences using the *ralloc* command in STATA. The Clinical Trials Support Group at MORU prepared numbered, opaque envelopes containing the next participant study number which included the study arm. These envelopes were opened on site sequentially after participant enrolment. Due to the study design it was not possible to blind participants, healthcare workers or research staff as to whether participants were in the control arm or one of the intervention arms, however, healthcare workers and participants were unaware if intervention participants were in intervention arm A or B.

3.3.7 Study Procedures

3.3.7.1 The Enrolment Visit

After patients had been screened, given their informed consent and been randomised to a study arm, they were interviewed by a study nurse. Data collected included their demographic details, past medical history, current symptoms and previous management. The screening form, CRF and medication forms are displayed in Appendix 3. If the participants were in an intervention arm (A or B), the study nurse took a capillary blood sample. They tested this on site using a POC CRP reader (NycoCard II Reader, Axis Shield, Oslo, Norway). While participants were waiting for their results a short educational video was shown to them which explained how antibiotics are only effective against bacteria and not viruses. The importance of antibiotics was discussed and the need to take them as prescribed. Following this the CRP test was explained alongside the study's follow-up procedures. The participants were given a card which said CRP test 'high' or 'low', which they passed onto the healthcare worker. If participants were in the control arm the research nurse took a venous blood sample which was retrospectively tested for CRP levels off site in the local laboratory.

Participants in Thailand who presented with a sore throat also had a throat swab taken. All participants were then reviewed by the treating healthcare worker who conducted a clinical examination, diagnosed the participant and decided how to manage them. Details of this encounter were extracted from the clinical notes and added to the participants' CRFs. This data was collected from the routine notes so that the workload for the local healthcare workers was not increased. We wanted to keep this consultation as close as possible to standard practice, especially for the control arm, and it allowed the healthcare workers to remain blind to which intervention arm the participant had been enrolled into (A or B). All of the required details were listed in the standard history and examination sheets used in routine care. During the healthcare worker training we highlighted the less common examinations and findings we were interested in e.g. cervical lymphadenopathy and made them aware that data would be extracted from the clinical notes.

3.3.7.2 Follow-Up Visits

Participants were followed up in person on day 5 (day 4 to 7) and day 14 (day 12 to 16). If participants were unable to attend the follow-up in person then a telephone follow up was conducted instead. At each follow-up visit the participant met with the research nurse who asked about their symptoms and whether they had sought any healthcare or medication since the previous visit. On day 5, a capillary CRP test was taken from all participants and tested on site. If the CRP test was ≥ 50 mg/L in children or ≥ 100mg/L in adults the treating healthcare workers were informed and the participants were referred to them for review. The participants were also seen by the healthcare worker on day 5 or day 14 if they had persisting symptoms or a temperature > 37.5°C.

On day 14 the study nurse asked the participants additional questions about their socio-economic status and their opinions toward their treatment and CRP testing (if they were in an intervention arm). These questions were asked on day 14 to reduce the inconvenience to participants, as by then we were expecting that they would have recovered from their illness.

In those also presenting with a sore throat and included in the nested GAS study Centor and FeverPAIN clinical scores were calculated and complications were screened for from the clinical data retrospectively [144]. Suppurative complications were defined as AOM, quinsy, cellulitis or sinusitis diagnosed or found on examination during the 2 week follow-up period [185]. A possible diagnosis of ARF was made if at day 14 participants reported or healthcare workers found a fever, myalgia, rash, chest pain or shortness of breath (suggestive of carditis), or if participants had been diagnosed with ARF during the 2 week follow-up period [186, 187].

3.3.7.3 Laboratory

Throat swabs were processed in the Shoklo Malaria Research Unit (SMRU) laboratory, Tak Province, Thailand. BHS were identified through Gram stain, catalase and Lancefield grouping. Isolates of GAS were tested for antimicrobial susceptibility using disk diffusion in line with the Clinical and Laboratory Standards Institute criteria [144, 188].

3.3.7.4 Monitoring Visits

MORU's Clinical Trial Support Group conducted a monitoring visit after 200 participants were recruited and at the end of the study. The site investigator files, screening logs, consent forms, CRFs and serious adverse events (SAEs) were reviewed.

3.3.7.5 Compensation

Participants received compensation for their time and travel to the enrolment visit and for the follow-up visits on day 5 and 14 if they attended in person [146].

3.3.8 Participants' and Healthcare Workers' Experiences and Opinions towards C-Reactive Point of Care Testing

All participants were asked about their experiences of the consultation and CRP testing if appropriate during the day 14 follow-up visit. Close-ended questions were asked by the research nurses (Chapter 4 and Appendix 3). All healthcare workers were approached and consent was taken from them if

they agreed to take part in semi-structure interviews (results not presented in this thesis) [84, 189]. They were also asked to self-complete a KAP questionnaire (Appendix 4). Demographic and work experience data were collected, alongside views towards antibiotics and the CRP test, if they had experience of using this. Each healthcare worker completed the KAP and interview once either before or after the RCT started. Participants' and healthcare workers' opinions were collected through a range of positively and negatively worded questions in order to try to reduce the likelihood that people would give desirable responses.

3.3.9 Study Outcomes

The primary outcomes were the overall proportion of patients in each arm prescribed an antibiotic at the study site between day 0 and day 5, and the proportion of those prescribed an antibiotic as compared with the CRP cut offs of 20mg/L and 40mg/L.

The secondary outcomes include:

- The proportion of patients prescribed an antibiotic at the study site from day 0 to day 14.
- The proportion of patients prescribed an antibiotic at the study site on day 0 compared to day 0 to day 14
- The proportion of patients with a temperature > 37.5°C on day 5 and day 14
- The median CRP results on day 5 for those with clinical recovery compared to those with ongoing illness
- Patient-reported clinical recovery at day 5 and day 14
- Patient-reported duration and severity of symptoms
- The frequency of unscheduled re-attendances within 14 days of follow-up
- The frequency of SAEs, including hospital admissions and death within 14 days of follow-up
- The indications for healthcare workers' concordance with the CRP test results and guidance
- Healthcare workers' attitudes and experiences of CRP testing.

The objectives of the nested GAS study included:

- The correlation between CRP levels, the Centor and FeverPAIN clinical scores and the presence of GAS
- The prevalence of GAS and other BHS
- The antibiotic susceptibility of GAS isolates.

Additional secondary outcomes will be discussed in Chapter 4, including the proportion of patients sourcing antibiotics and healthcare outside of the study visits, where antibiotics were sourced from, the proportion of patients with urine antibiotic activity compared to reported antibiotic use, and patient's opinions towards their care and POC CRP testing.

The control arm was also tested for a range of potential pathogens and the ability of CRP to discriminate between bacterial and viral pathogens, this is described in a subsequent publication [136], but is outside of the scope of this thesis.

3.3.10 Statistical Analysis

3.3.10.1 Sample Size Calculation

Based on previous studies from Southeast Asia and anecdotal reports from the PCUs, we expected to have a baseline antibiotic prescribing rate of 70% [190, 191]. We anticipated CRP testing to reduce antibiotic prescriptions by 25 percentage points from the baseline, but that contamination between the study arms may occur due to the study design, as healthcare workers would be treating patients in both the intervention and control arms. Therefore the hypothesised impact of CRP testing was lowered to 20 percentage points. The study was powered at 90% and to enable independent analyses for children, and adolescents and adults, and per country (Thailand and Myanmar).

Adjustments were made to allow for multiple comparisons between the study arms using Bonferroni's correction. An adjusted significance level (type I error) of 0.017 was used giving a 5% overall significance level for the three comparisons. We assumed that 15% of the participants would

be lost to follow-up. This meant that 198 participants were needed in each study arm, which we rounded to 200 participants per country, per age category (i.e. 600 children, and 600 adolescents and adults were needed in Thailand) [146].

3.3.10.2 Interim Analysis

An interim analysis was conducted after 200 children and 200 adults were recruited in Thailand. For this analysis the two interventional arms were combined and compared against the control arm. The analyses focused on safety outcomes including the proportion of symptomatic patients at day 5 and day 14, the proportion of febrile patients at day 5, the number of SAEs, the proportion of participants seeking healthcare between day 0 and 14 and the proportion of patients prescribed an antibiotic between day 0 and day 14.

3.3.10.3 Intention to Treat and Per Protocol Analyses

The results were analysed for intention to treat (all participants who were recruited and randomised) and per protocol. Participants were included in the per protocol analysis if they attended both follow-up visits on day 5 and day 14, and were in the control group or were managed in line with the CRP results and guidance. The primary outcome was analysed in the predefined subgroups of: age category and country, having a documented fever, clinical syndrome or diagnosis, and previous antibiotic use for this illness [146].

Combined analyses are made for Thailand and Myanmar, apart from the primary outcome which is also broken down into the pre-specified groups of country and age category (children or adolescents and adults), recognising that the patient group and the study context can affect the impact of CRP POC testing. The country of treatment will also be explored in relation to concordance between antibiotic prescriptions and CRP results and healthcare workers opinions of CRP testing. Throat swabs for GAS were not collected in Myanmar, so will only be presented for Thailand.

3.3.10.4 Missing Antibiotic Data

In the original analysis and publication [146], if a participant attended follow-up but had no antibiotic prescription data recorded we assumed that no antibiotic was prescribed. All other missing antibiotic data were converted to 'no antibiotics prescribed'. However, on secondary analyses it was noted that those lost to follow up were marked as not receiving an antibiotic which may have overestimated the effect of CRP testing. Statistical tests were run in order to assess the impact of these assumptions. A last observation carried forward analysis was used to replace the missing data for those who did not attend follow-up; whereby if day 5 antibiotic data were missing they were replaced by day 0 data. If day 14 data were missing they were replaced by day 5 data, or day 0 data if day 5 data were also missing. A sensitivity analysis was also conducted which replaced all missing data to 'antibiotics prescribed'. The following correspondence was sent to the journal which showed minimal effects of the assumptions made in the original analysis [192].

For this thesis chapter I will only keep the assumption that antibiotics were not prescribed if the participant attended follow-up and the antibiotic data was missing. Multiple imputation will be used to manage the missing data if more than 5% of the data are missing. This cut off was chosen because at levels less than 5% replacing or imputing the missing data has a minimal effect, can be less representative of the data and introduce more bias [193-195]. All data available will be used for the primary outcome in the intention to treat analysis. In order to be included in the primary outcome of antibiotic prescription between day 0 and 5, antibiotic prescribing data needs to be present for day 0 and day 5, unless antibiotics have been prescribed on one of those occasions (in which case it would not matter if the other time point was missing).

3.3.10.5 Descriptive Statistics

Normally distributed, continuous variables were summarised using means and standard deviations, if the data were not normally distributed medians and interquartile ranges (IQRs) were used. Categorical variables were compared using χ^2 tests or Fisher's exact test when numbers were low. T

tests were used for normally distributed groups and Mann-Whitney tests were used for those without a normal distribution. CRP values were compared between those with positive BHS throat swabs against those with negative throat swabs using rank sum. The sensitivity and specificity of CRP to detect GAS found on swab testing against those with negative throat swabs for all BHS were calculated using contingency tables. Wilson's method was used to generate 95% confidence intervals.

3.3.10.6 Other Statistical Tests

Logistic regression models were used to compare antibiotic prescriptions between the two interventional arms and the control arm, and the indicators of concordance with the CRP test results and guidance. Both models added the study sites as a random effect.

Kaplan-Meier curves were used to generate survival curves for patient-reported symptom persistence, in which the interventional arms were compared against the control arm using a Cox proportional-hazard model giving hazard ratios adjusted for study sites as a random effect.

3.3.10.7 Knowledge, Attitudes and Practices Data

KAP data for healthcare workers and participants were summarised using descriptive statistics. The design of this section was led by MH, a social scientist.

3.4 Results

The staff at the study sites conducted an initial screening and notified the research nurse if patients were attending with a fever or history of fever. Of these, 4,116 patients were screened by the research nurse and 1,706 (41.4%) were not eligible to join the study (Figure 3-1). In total, 2,410 participants were enrolled into the main RCT, 807 participants were randomised to the control arm, 803 to intervention arm A and 800 to intervention arm B. Of these participants 174 also presented with a sore throat; 169 of them had a throat swab taken and were included in the nested GAS study. Participants were recruited between the 8th of June 2016 and the 25th of August 2017. The day 5

follow-up visit was attended by 2,311/2,410 (95.9%) of the participants and day 14 by 2,317/2,410 (96.1%). The reasons for loss of follow-up are detailed in Figure 3-1. The per protocol analysis includes 1,957/2,410 (81.2%) of the study participants who attended both follow-up visits on day 5 and day 14, and were prescribed antibiotics in line with the CRP results on day 0 (in intervention arms). It consists of 767 participants in the control arm, 598 in intervention arm A and 592 in intervention arm B.

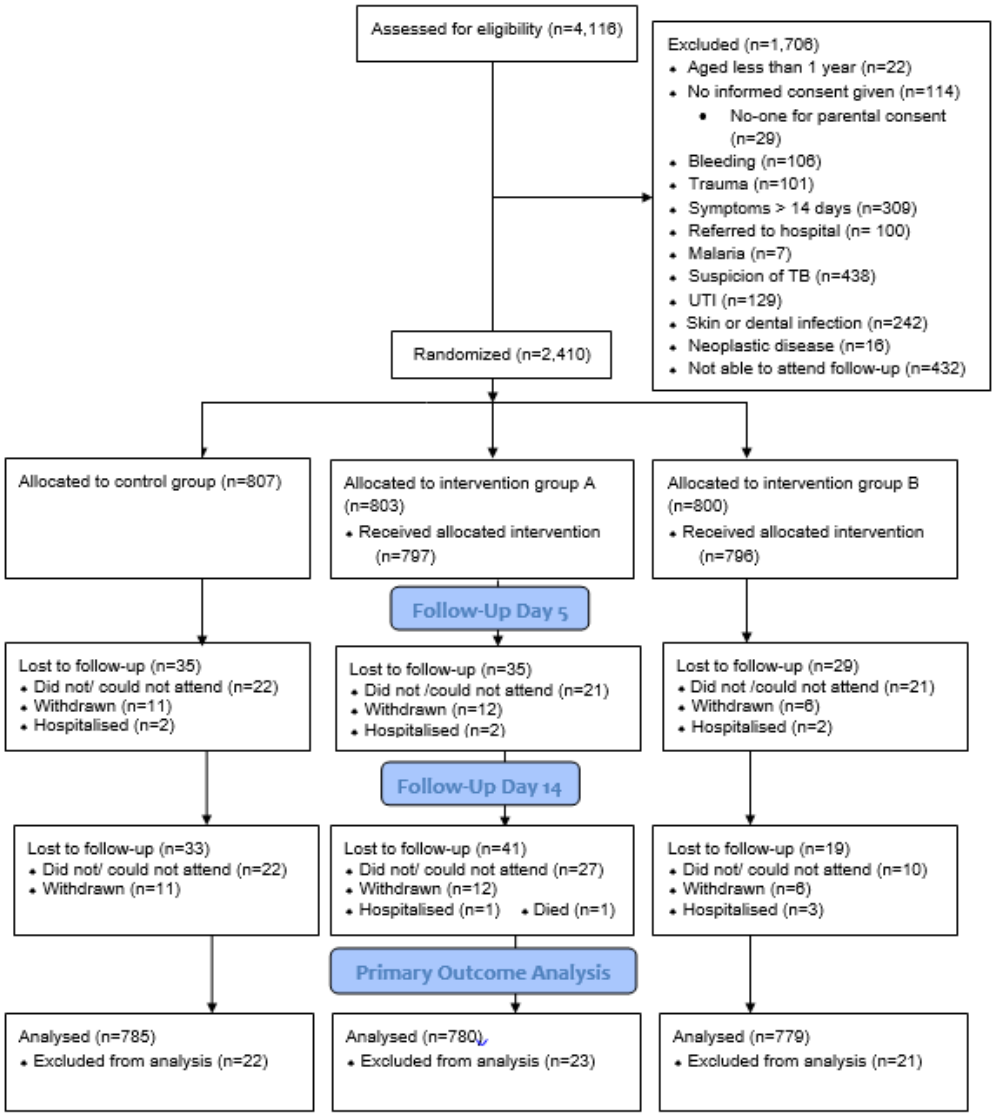


Figure 3-1: Consort flow diagram showing participant screening, randomization, follow-up and inclusion in the primary outcome analysis for the RCT

More than one exclusion reason may be present

3.4.1 Participant Characteristics

The study participants' demographic and clinical characteristics are detailed in Table 3-1. Self-reported antibiotic use in the last 2 weeks was low (5.4%). The majority of the participants were diagnosed with a single RTI (1,552, 70.8%); of these 704 (45.4%) were diagnosed with a common cold, 364 (23.5%) with an unspecified URTI, 233 (15.0%) with pharyngitis and 128 (8.3%) with tonsillitis. More than one infection was diagnosed in 102 (4.7%) participants.

	Control arm		**Intervention arm A**		**Intervention arm B**	
	Aged <12 years (N=402)	Aged ≥ 12 years (N=405)	Aged <12 years (N=400)	Aged ≥ 12 years (N=403)	Aged <12 years (N=399)	Aged ≥ 12 years (N=401)
Demographic characteristics						
Age, median (IQR), years	4 (2-7)	33 (22-52)	4 (2-7)	35 (20-53)	4 (2-7)	34 (21-51)
Male sex	204 (50.9)	159 (39.3)	209 (52.3)	156 (38.7)	204 (51.1)	174 (43.4)
≥ 30 minutes to reach the PCU	100 (24.9)	66 (16.3)	100 (25.0)	69 (17.1)	98 (24.6)	81 (20.2)
Presence of a comorbidity	15 (3.9)	112 (28.6)	16 (4.3)	100 (25.4)	20 (5.3)	88 (22.6)
Symptom onset, median (IQR), days	2 (1-3)	3 (2-4)	2 (1-3)	3 (2-4)	2 (1-3)	3 (2-4)
Sought medical care in last 14 days	195 (48.6)	244 (60.3)	219 (54.8)	239 (59.3)	215 (53.9)	260 (65.0)
Self-reported antibiotic intake in the last 2 weeks	16 (4.0)	25 (6.2)	20 (5.0)	17 (4.2)	22 (5.5)	30 (7.5)
Clinical characteristics						
Documented fever (>37.5°C)	200 (50.1)	155 (38.4)	203 (51.0)	143 (35.7)	223 (56.0)	148 (37.2)

Respiratory symptoms*	326 (81.1)	323 (79.8)	315 (78.8)	315 (78.2)	327 (82.0)	299 (74.6)
Gastrointestinal symptoms†	104 (25.9)	95 (23.5)	124 (31.0)	83 (20.6)	109 (27.3)	68 (17.0)
Respiratory diagnosis	270 (73.2)	254 (71.2)	279 (74.6)	244 (68.4)	264 (70.0)	241 (67.1)

Table 3-1: Demographic and clinical characteristics of the RCT study participants, by study arm.

Adapted from Althaus, T., et al., 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, 2019. ***7****(1): p. e119-e131. License CC BY 4.0 [146].*

*Data are number (%) unless specified. *Respiratory symptoms include cough, runny nose, sore throat, breathing difficulties and chest pain. †Gastrointestinal symptoms include nausea, vomiting, diarrhoea and abdominal pain.*

The demographic and clinical details of those included in the nested GAS study are detailed in Appendix 5.

3.4.2 Antibiotic Prescriptions

In the Thai interim analysis, antibiotic prescriptions between day 0 and day 5 were reduced by 8.8 percentage points in the intervention arms compared to the control arm (aOR 0.68, 95% CI 0.46 to 1.00). When broken down by age category this reduction was statistically significant in children but not in adolescents and adults (Table 3-2). Further details of the interim analysis are discussed in Appendix 6.

	Control Arm n/N (%)	Intervention Arms (A & B) n/N (%)	Risk Difference, percentage point (95% CI)	aOR (95% CI)
All participants				
Antibiotic prescriptions at day 0	70/164 (42.7)	104/330 (31.5)	-11.2 (-20.2 to -2.1)	0.60 (0.41 to 0.90)
Antibiotic prescriptions between day 0 and 5	**71/163 (43.6)**	**113/325 (34.8)**	**-8.8 (-18.0 to 0.04)**	**0.68 (0.46 to 1.00)**
Antibiotic prescriptions between day 0 and 14	71/163 (43.6)	113/324 (34.9)	-8.7 (-17.9 to 5.3)	0.68 (0.46 to 1.01)
Participants <12 years old				
Antibiotic prescriptions at day 0	33/68 (48.5)	43/135 (31.9)	-16.7 (-30.9 to -2.4)	0.46 (0.25 to 0.87)
Antibiotic prescriptions between day 0 and 5	**34/67 (50.8)**	**48/133 (36.1)**	**-14.7 (-29.1 to -0.2)**	**0.51 (0.27 to 0.95)**
Antibiotic prescriptions between day 0 and 14	34/67 (50.8)	48/133 (36.1)	-14.7 (-29.1 to -0.2)	0.51 (0.27 to 0.95)
Participants ≥ 12 years old				
Antibiotic prescriptions at day 0	37/96 (38.5)	61/195 (31.3)	-7.3 (-19.0 to -4.5)	0.72 (0.43 to 1.21)
Antibiotic prescriptions between day 0 and 5	**37/96 (38.5)**	**65/192 (33.9)**	**-4.7 (-16.5 to 7.1)**	**0.81 (0.49 to 1.36)**
Antibiotic prescriptions between day 0 and 14	37/96 (38.5)	65/191 (34.0)	-4.5 (-16.3 to 7.3)	0.82 (0.49 to 1.37)

Table 3-2: Antibiotic prescriptions in each study arm, by age category in the Thai RCT interim analysis

The primary outcome: antibiotic prescription between day 0 and day 5 is highlighted in bold text. The aORs are adjusted for study sites as a random effect.

Antibiotic prescriptions in the intention to treat analysis are shown in Table 3-3. For the primary outcome of antibiotic prescriptions between day 0 and day 5, there was a non-significant reduction in prescriptions when comparing intervention arm A and the control arm (RD -3.3 percentage points, aOR 0.86, 95% CI 0.70 to 1.06). Using the higher CRP cut off in intervention arm B, the reduction became statistically significant (RD -5.1 percentage points, aOR 0.78, 95% CI 0.63 to 0.97). The overall

reductions in arm B were driven by a decrease in antibiotic prescriptions amongst adults from Myanmar. In Thailand the reduction in antibiotic prescriptions was more pronounced in children compared to adolescents and adults.

	Control Arm n/N (%)	Intervention Arm A n/N (%)	Risk Difference, percentage point (95% CI)	aOR (95% CI)	Intervention Arm B n/N (%)	Risk Difference, percentage point (95% CI)	aOR (95% CI)
All participants							
Day 0	297/799 (37.2)	269/797 (33.8)	-3.4 (-8.1 to 1.3)	0.85 (0.69 – 1.05)	246/796 (30.9)	-6.3 (-10.9 to -1.6)	0.74 (0.60 to 0.92)
Between day 0 and day 5	**318/785 (40.5)**	**290/780 (37.2)**	**-3.3 (-8.2 to 1.5)**	**0.86 (0.70 to 1.06)**	**276/779 (35.4)**	**-5.1 (-9.9 to -0.3)**	**0.78 (0.63 to 0.97)**
Between day 0 and day 14	323/784 (41.2)	293/771 (38.0)	-3.2 (-8.1 to 1.7)	0.87 (0.70 to 1.07)	280/777 (36.0)	-5.2 (-10.0 to -0.4)	0.78 (0.63 to 0.97)
Thai participants aged < 12 years old							
Day 0	64/195 (32.8)	56/194 (28.9)	-4.0 (-13.1 to 5.2)	0.83 (0.53 to 1.28)	50/193 (25.9)	-6.9 (-15.9 to 2.1)	0.70 (0.45 to 1.11)
Between day 0 and day 5	**68/194 (35.1)**	**61/194 (31.4)**	**-3.6 (-13.0 to 5.8)**	**0.84 (0.55 to 1.30)**	**53/191 (27.8)**	**-7.3 (-16.5 to 1.9)**	**0.70 (0.45 to 1.09)**
Between day 0 and day 14	69/194 (35.6)	61/194 (31.4)	-4.1 (-13.5 to 5.3)	0.82 (0.53 to 1.27)	53/191 (27.8)	-7.8 (-17.1 to 1.4)	0.68 (0.44 to 1.07)

	Control Arm n/N (%)	Intervention Arm A n/N (%)	Risk Difference, percentage point (95% CI)	aOR (95% CI)	Intervention Arm B n/N (%)	Risk Difference, percentage point (95% CI)	aOR (95% CI)
Thai participants aged ≥ 12 years old							
Day 0	63/201 (31.3)	57/200 (28.5)	-2.8 (-11.8 to 6.1)	0.86 (0.56 to 1.34)	65/199 (32.7)	1.3 (-7.8 to 10.5)	1.06 (0.69 to 1.63)
Between day 0 and day 5	**64/201 (31.8)**	**60/199 (30.2)**	**-1.7 (-10.8 to 7.4)**	**0.91 (0.59 to 1.41)**	**68/196 (34.7)**	**2.9 (-6.4 to 12.1)**	**1.14 (0.74 to 1.75)**
Between day 0 and day 14	64/201 (31.8)	61/197 (31.0)	-0.9 (-10.0 to 8.2)	0.95 (0.62 to 1.47)	69/196 (35.2)	3.4 (-5.9 to 12.6)	1.17 (0.76 to 1.79)
Myanmar participants aged < 12 years old							
Day 0	78/203 (38.4)	77/204 (37.8)	-0.7 (-10.1 to 8.8)	0.98 (0.65 to 1.48)	65/204 (31.9)	-6.6 (-15.8 to 2.7)	0.74 (0.49 to 1.13)
Between day 0 and day 5	**87/195 (44.6)**	**84/194 (43.3)**	**-1.3 (-11.1 to 8.5)**	**0.96 (0.64 to 1.44)**	**79/198 (39.9)**	**-4.7 (-14.5 to 5.0)**	**0.82 (0.54 to 1.23)**
Between day 0 and day 14	88/195 (45.1)	86/188 (45.7)	0.6 (-9.4 to 10.6)	1.04 (0.69 to 1.57)	82/198 (41.4)	-3.7 (-13.5 to 6.1)	0.85 (0.57 to 1.28)
Myanmar participants aged ≥ 12 years old							

	Control Arm n/N (%)	Intervention Arm A n/N (%)	Risk Difference, percentage point (95% CI)	aOR (95% CI)	Intervention Arm B n/N (%)	Risk Difference, percentage point (95% CI)	aOR (95% CI)
Day 0	92/200 (46.0)	79/199 (39.7)	-6.3 (-16.0 to 3.4)	0.77 (0.51 to 1.15)	66/200 (33.0)	-13.0 (-22.5 to -3.5)	0.55 (0.37 to 0.84)
Between day 0 and day 5	**99/195 (50.8)**	**85/193 (44.0)**	**-6.7 (-16.6 to 3.2)**	**0.76 (0.51 to 1.13)**	**76/194 (39.2)**	**-11.6 (-21.4 to -1.8)**	**0.60 (0.39 to 0.90)**
Between day 0 and day 14	102/194 (52.6)	85/192 (44.3)	-8.3 (-18.2 to 1.6)	0.71 (0.48 to 1.06)	76/192 (39.6)	-13.0 (-22.9 to -3.1)	0.56 (0.37 to 0.85)

Table 3-3: Antibiotic prescriptions in each study arm, by age category and country, in the RCT intention to treat population

The primary outcome: antibiotic prescription between day 0 and day 5 is highlighted in bold text. The aORs are adjusted for study sites as a random effect.

Based on Althaus, T., et al., 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, 2019. 7(1): p. e119-e131. License CC BY 4.0 [146]

In the per protocol analysis, antibiotic prescriptions between day 0 and 5 were statistically and clinically significantly reduced compared to the control arm in intervention arm A (RD -12.3 percentage points, aOR 0.56, 95% CI 0.44 to 0.71), and in intervention arm B (RD -20.3 percentage points, aOR 0.35, 95% CI 0.27 to 0.45, Table 3-4). Antibiotic prescriptions remained significantly reduced when children, and adolescents and adults were considered separately in Thailand and Myanmar, apart from a non-significant reduction in antibiotics for Myanmar children in intervention arm A.

	Control Arm n (%)	Intervention Arm A n (%)	Risk Difference, percentage point (95% CI)	aOR (95% CI)	Intervention Arm B n (%)	Risk Difference, percentage point (95% CI)	aOR (95% CI)
All participants	**N = 767**	**N = 598**			**N= 592**		
Day 0	283 (36.9)	142 (23.8)	-13.2 (-18.0 to -8.3)	0.53 (0.41 to 0.67)	86 (14.5)	-22.4 (-26.8 to -17.9)	0.28 (0.21 to 0.37)
Between day 0 and day 5	**301 (39.2)**	**161 (26.9)**	**-12.3 (-17.3 to -7.4)**	**0.56 (0.44 to 0.71)**	**112 (18.9)**	**-20.3 (-25.0 to -15.6)**	**0.35 (0.27 to 0.45)**
Between day 0 and day 14	306 (39.9)	164 (27.4)	-12.5 (-17.5 to -7.5)	0.56 (0.44 to 0.71)	116 (19.6)	-20.3 (-25.0 to -15.6)	0.35 (0.27 to 0.45)
Thai participants aged < 12 years	**N=192**	**N = 162**			**N = 152**		
Day 0	62 (32.3)	30 (18.5)	-13.8 (-22.7 to -4.9)	0.47 (0.29 to 0.78)	12 (7.9)	-24.4 (-32.3 to -16.5)	0.18 (0.09 to 0.35)
Between day 0 and day 5	**66 (34.4)**	**35 (21.6)**	**-12.8 (-22.0 to -3.5)**	**0.52 (0.32 to 0.85)**	**15 (9.9)**	**-24.5 (-32.7 to -16.3)**	**0.21 (0.11 to 0.38)**
Between day 0 and day 14	67 (34.9)	35 (21.6)	-13.3 (-22.5 to -4.0)	0.51 (0.31 to 0.82)	15 (9.9)	-25.0 (-33.3 to -16.8)	0.20 (0.11 to 0.37)

	Control Arm n (%)	Intervention Arm A n (%)	Risk Difference, percentage point (95% CI)	aOR (95% CI)	Intervention Arm B n (%)	Risk Difference, percentage point (95% CI)	aOR (95% CI)
Thai participants aged ≥ 12 years	**N = 201**	**N = 145**			**N = 137**		
Day 0	63 (31.3)	16 (11.0)	-20.3 (-28.5 to -12.1)	0.26 (0.14 to 0.49)	12 (8.8)	-22.6 (-30.6 to -14.6)	0.20 (0.10 to 0.40)
Between day 0 and day 5	**64 (31.8)**	**19 (13.1)**	**-18.7 (-27.2 to -10.3)**	**0.31 (0.17 to 0.55)**	**15 (11.0)**	**-20.9 (-29.2 to -12.6)**	**0.25 (0.14 to 0.48)**
Between day 0 and day 14	64 (31.8)	20 (13.8)	-18.0 (-26.6 to -9.5)	0.33 (0.18 to 0.58)	16 (11.7)	-20.2 (-28.6 to -11.8)	0.27 (0.15 to 0.51)
Myanmar participants aged < 12 years	**N = 185**	**N = 145**			**N = 156**		
Day 0	71 (38.4)	51 (35.2)	-3.2 (-13.7 to 7.3)	0.89 (0.56 to 1.41)	33 (21.2)	-17.2 (-26.7 to -7.7)	0.44 (0.27 to 0.72)
Between day 0 and day 5	**77 (41.6)**	**57 (39.3)**	**-2.3 (-13.0 to 8.3)**	**0.91 (0.58 to 1.42)**	**46 (29.5)**	**-12.1 (-22.2 to -2.1)**	**0.60 (0.38 to 0.94)**

	Control Arm n (%)	Intervention Arm A n (%)	Risk Difference, percentage point (95% CI)	aOR (95% CI)	Intervention Arm B n (%)	Risk Difference, percentage point (95% CI)	aOR (95% CI)
Between day 0 and day 14	78 (42.2)	59 (40.7)	-1.5 (-12.2 to 9.2)	0.94 (0.61 to 1.46)	49 (31.4)	-10.8 (-20.9 to -0.6)	0.64 (0.41 to 1.00)
Myanmar participants aged ≥ 12 years	**N = 189**	**N = 146**			**N = 147**		
Day 0	87 (46.0)	45 (30.8)	-15.2 (-25.5 to -4.9)	0.52 (0.33 to 0.82)	29 (19.7)	-26.3 (-35.9 to -16.7)	0.28 (0.17 to 0.47)
Between day 0 and day 5	**94 (49.7)**	**50 (34.3)**	**-15.5 (-26.0 to -5.0)**	**0.52 (0.33 to 0.82)**	**36 (24.5)**	**-25.2 (-35.2 to -15.3)**	**0.32 (0.20 to 0.52)**
Between day 0 and day 14	97 (51.3)	50 (34.3)	-17.1 (-27.6 to -6.6)	0.49 (0.31 to 0.77)	36 (24.5)	-26.8 (-36.8 to -16.9)	0.30 (0.19 to 0.49)

Table 3-4: Antibiotic prescriptions in each study arm, by age category and country in the RCT per protocol population

The primary outcome: antibiotic prescription between day 0 and 5 is highlighted in bold text. aOR are adjusted for study site.

*Based on Althaus, T., et al., 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, 2019. **7**(1): p. e119-e131. License CC BY 4.0 [146]*

Significantly fewer participants were prescribed an antibiotic with a low CRP result and significantly more were prescribed an antibiotic with a high CRP result when comparing either intervention arm with the control arm ($p < 0.001$, Figure 3-2). When broken down by country the prescribing between the

intervention and control arms remained significantly different for all CRP cut offs in Myanmar, whereas in Thailand only those with a raised CRP were more likely to be prescribed an antibiotic in the intervention arms compared to the control arms.

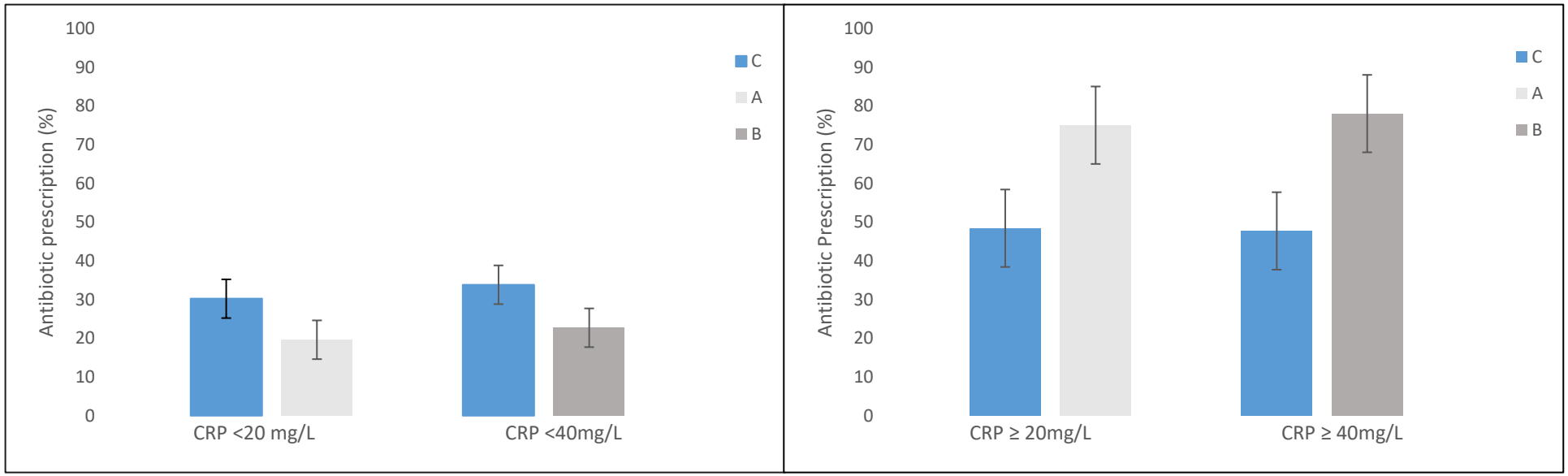


Figure 3-2: Antibiotic prescriptions on day 0 by study arm for participants with low and high CRP results using CRP cut offs of 20mg/L and 40mg/L

*Adapted from Althaus, T., et al., 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, 2019. **7**(1): p. e119-e131. License CC BY 4.0 [146]*

C = control arm, A = intervention arm A, B = intervention arm B. The error bars show the 95% CI.

Antibiotic prescribing was concordant with the CRP results on day 0 in 413/657 (62.9%) of the participants in the control arm using a CRP cut off of 20mg/L, compared to 630/797 (79.1%) of participants in intervention arm A, $p < 0.001$. Using a CRP cut off of 40mg/L, 415/657 (63.2%) of the participants

were prescribed an antibiotic in line with the CRP results in the control arm, compared to 616/796 (77.4%) in intervention arm B, p < 0.001. These differences in concordance were maintained when Thailand and Myanmar were analysed separately. Concordance with the CRP results on day 0 was similar in the intervention arms when comparing Thailand and Myanmar (77.1% vs 79.3%, p = 0.286).

Antibiotic prescriptions between day 0 and 5 were significantly reduced in the pre-defined subgroup of those with a documented fever in intervention arm B (but not arm A) compared to the control group. Antibiotic prescriptions were not affected by CRP testing in those with a respiratory diagnosis or antibiotic use in the last 2 weeks (Table 3-5).

	Control Arm n/N (%)	**Intervention Arm A n/N (%)**	**Risk Difference percentage point (95% CI)**	**aOR (95% CI)**	**Intervention Arm B n/N (%)**	**Risk Difference, percentage point (95% CI)**	**aOR (95% CI)**
Documented fever > 37.5°C	173/345 (50.1)	156/333 (46.9)	-3.3 (-10.8 to 4.2)	0.86 (0.63 to 1.16)	153/360 (42.5)	-7.6 (-15.0 to -0.3)	0.69 (0.51 to 0.94)
Respiratory diagnosis	208/520 (40.0)	199/518 (38.4)	-1.6 (-7.5 to 4.4)	0.93 (0.72 to 1.22)	183/496 (36.9)	-3.1 (-9.1 to 2.9)	0.87 (0.67 to 1.14)
Antibiotic use in the last 2 weeks	17/41 (41.5)	19/37 (51.4)	9.8 (-12.2 to 32.0)	1.42 (0.52 to 3.83)	22/49 (44.9)	3.4 (-17.1 to 24.0)	1.08 (0.44 to 2.67)

Table 3-5: Antibiotic prescription for each study arm between day 0 and 5 in the RCT for the subgroups of documented fever, respiratory diagnosis and antibiotic use in the last 2 week

3.4.3 Antibiotic Prescriptions by "AWaRe" Category

Amoxicillin was the most commonly prescribed antibiotic on day 0 (Table 3-6). The majority of antibiotics were from the "Access" category of WHO's "AWaRe" classification; none were from the "Reserve" category [53]. There were no significant differences in the proportion of "Access" and "Watch" antibiotics between the control arm and either intervention arm A or B (p = 0.570 and p = 0.573).

"AWaRe" antibiotic category	**Antibiotic prescriptions N=803, n (%)**
"Access" antibiotics	
Amoxicillin	613 (76.3)
Amoxicillin/Clavulanic acid	25 (3.1)
Cefalexin	22 (2.7)
Dicloxacillin	9 (1.1)
Trimethoprim/sulfamethoxazole	9 (1.1)
Cloxacillin	5 (0.6)
Doxycycline	4 (0.5)
Metronidazole	4 (0.5)
Others	3 (0.4)
Penicillin V	2 (0.3)
Total	**696 (86.7)**
"Watch" antibiotics	
Azithromycin	36 (4.5)
Cefixime	34 (4.2)
Ciprofloxacin	19 (2.4)
Norfloxacin	10 (1.1)
Roxithromycin	4 (0.5)
Erythromycin	2 (0.3)
Others	2 (0.3)
Total	**107 (13.3)**

Table 3-6: The percentage of antibiotic prescriptions on day 0 in the RCT by "AWaRe" categories

3.4.4 Clinical Outcomes

There were no significant differences between the control and intervention arms in the clinical outcomes of recorded fever, ongoing symptoms, symptom severity, re-attendances up to day 14 or elevated CRP results at day 5 when considering all participants (Table 3-7). When broken down into children and, adolescents and adults then more adolescents and adults in the control arm had a documented fever on day 5 compared to intervention arm A ($p = 0.033$).

There were 24 SAEs; all were admitted to hospital and one died. There were three SAEs in the control arm, compared to 10 in intervention arm A ($p = 0.050$) and 11 in intervention arm B ($p = 0.030$, Table 3-7). Only one of the SAEs may have been related to the study; a 25 year old woman in intervention arm A. She presented with a one day history of abdominal pain and fever. Her CRP was < 8 mg/L, she was diagnosed with a hypersensitivity reaction and was not prescribed an antibiotic. She was admitted to hospital the next day, diagnosed with mesenteric lymphadenitis, prescribed antibiotics and discharged. The death occurred in a 78 year old male with a history of heart disease and Chronic Obstructive Pulmonary Disease. He presented with a 5 day history of fever, sore throat, cough and myalgia. He had been seen at the study site prior to enrolment and had been given paracetamol. On day 0 he was randomly assigned to intervention arm A, had a CRP of 25mg/L, temperature of 38.2°C, heart rate of 116 beats per minute, respiratory rate of 20 per minute and blood pressure of 96/62mmHg. His examination (including the cardiovascular system, chest and throat) was otherwise normal. He was diagnosed with pharyngitis and treated with amoxicillin. He was admitted to hospital 4 days later and diagnosed with a chest infection but died 1 week later.

In the per protocol analysis there were no significant differences in clinical outcomes, re-attendances or SAEs between the study arms. There were also no differences in symptom resolution (full details of the per protocol analysis are given in Appendix 7).

	Control Arm n (%)	Intervention Arm A n (%)	P value	Intervention Arm B n (%)	P value
All participants	**N=807**	**N=803**		**N=800**	
Recorded temperature (>37.5 C) at day 5	27/709 (3.8)	22/715 (3.1)	0.449	25/726 (3.4)	0.712
Elevated CRP at day 5*	8/706 (1.1)	8/713 (1.1)	0.984	6/726 (0.8)	0.555
Ongoing symptoms at day 5	276/767 (36.0)	269/764 (35.2)	0.752	281/769 (36.5)	0.821
Symptom severity at day 5, median (IQR)†	1 (1-1)	1 (1-1)	0.163	1 (1-1)	0.249
Recorded temperature (>37.5 C) at day 14	9/635 (1.4)	11/655 (1.7)	0.703	11/661 (1.7)	0.719
Ongoing symptoms at day 14	34/772 (4.4)	42/760 (5.5)	0.312	46/779 (5.9)	0.181
Symptom severity at day 14, median (IQR)†	1 (1-1)	1 (1-1)	0.598	1 (1-1)	0.550
Re-attendance	16/807 (2.0)	13/803 (1.6)	0.583	22/800 (2.8)	0.311
SAE	3/807 (0.4)	10/803 (1.3)	0.050	11/800 (1.4)	0.030
Child participants (< 12 years)					
Recorded temperature (>37.5 C) at day 5	13/362 (3.6)	17/361 (4.7)	0.451	17/368 (4.6)	0.484
Elevated CRP at day 5*	3/361 (0.8)	4/360 (1.1)	0.725	2/368 (0.5)	0.684

Ongoing symptoms at day 5	144/377 (38.2)	143/379 (37.7)	0.895	145/385 (37.7)	0.879
Symptom severity at day 5, median (IQR)†	1 (1-1)	1 (1-1)	0.105	1 (1-1)	0.340
Recorded temperature (>37.5 C) at day 14	6/318 (1.9)	6/333 (1.8)	0.936	8/336 (2.4)	0.663
Ongoing symptoms at day 14	18/381 (4.7)	16/375 (4.3)	0.761	23/388 (5.9)	0.458
Symptom severity at day 14, median (IQR)†	1 (1-1)	1 (1-1)	0.351	1 (1-1)	0.849
Re-attendance	8/402 (2.0)	6/400 (1.5)	0.596	15/399 (3.8)	0.134
SAE	2/402 (0.5)	5/399 (1.3)	0.177	5/399 (1.3)	0.285
Adolescents and adult participants (≥ 12 years)					
Recorded temperature (>37.5 C) at day 5	14/347 (4.0)	5/354 (1.4)	0.033	8/358 (2.2)	0.169
Elevated CRP at day 5*	5/345 (1.5)	4/353 (1.1)	0.750	4/358 (1.1)	0.748
Ongoing symptoms at day 5	132/390 (33.9)	126/385 (32.7)	0.741	136/384 (35.4)	0.646
Symptom severity at day 5, median (IQR)†	1 (1-1)	1 (1-1)	0.764	1 (1-1)	0.502
Recorded temperature (>37.5 C) at day 14	3/317 (1.0)	5/322 (1.6)	0.725	3/325 (0.9)	1.000
Ongoing symptoms at day 14	16/391 (4.1)	26/385 (6.8)	0.101	23/391 (5.9)	0.250
Symptom severity at day 14, median (IQR)†	1 (1-1)	1 (1-1)	0.476	1 (1-1)	0.581
Re-attendance	8/405 (2.0)	7/403 (1.7)	0.802	7/401 (1.8)	0.809

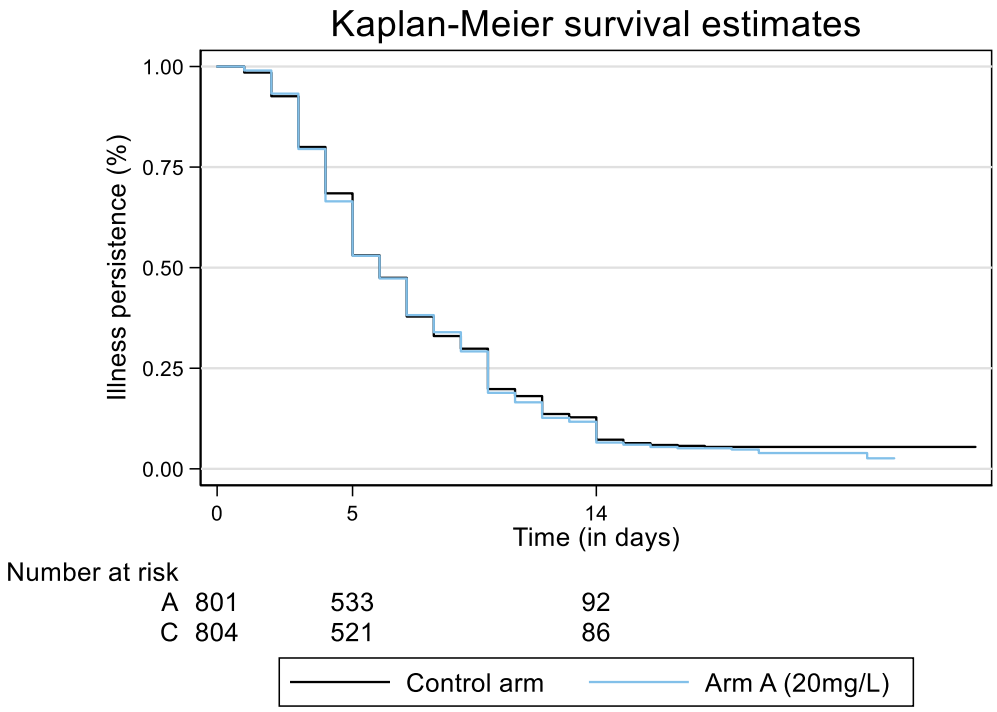
SAE	1/405 (0.3)	4/403 (1.0)	0.216	6/401 (1.5)	0.068

Table 3-7: Clinical outcomes, re-attendances and serious adverse events in each RCT study arm, by age category

** Elevated CRP on day 5: CRP ≥ 50mg/L in children and CRP ≥ 100mg/L in adolescents and adults. † Symptom severity: reported by the participant, 1 = mild, 2 = moderate, 3 = severe. 4 = life threatening*

*Adapted from Althaus, T., et al., 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, 2019. **7**(1): p. e119-e131. License CC BY 4.0 [146]*

There were no differences in symptom persistence at day 5 or day 14 when comparing either intervention arms against the control arm (log rank p values 0.557 and 0.631, Figure 3-3). The adjusted hazard ratio was 0.97 (95% CI 0.88 to 1.08), p value = 0.604 for the control arm versus intervention arm A and 0.99 (95% CI 0.94 to 1.04), p = 0.670 for intervention arm B. As such, participants' symptom resolution was unaffected by the intervention.



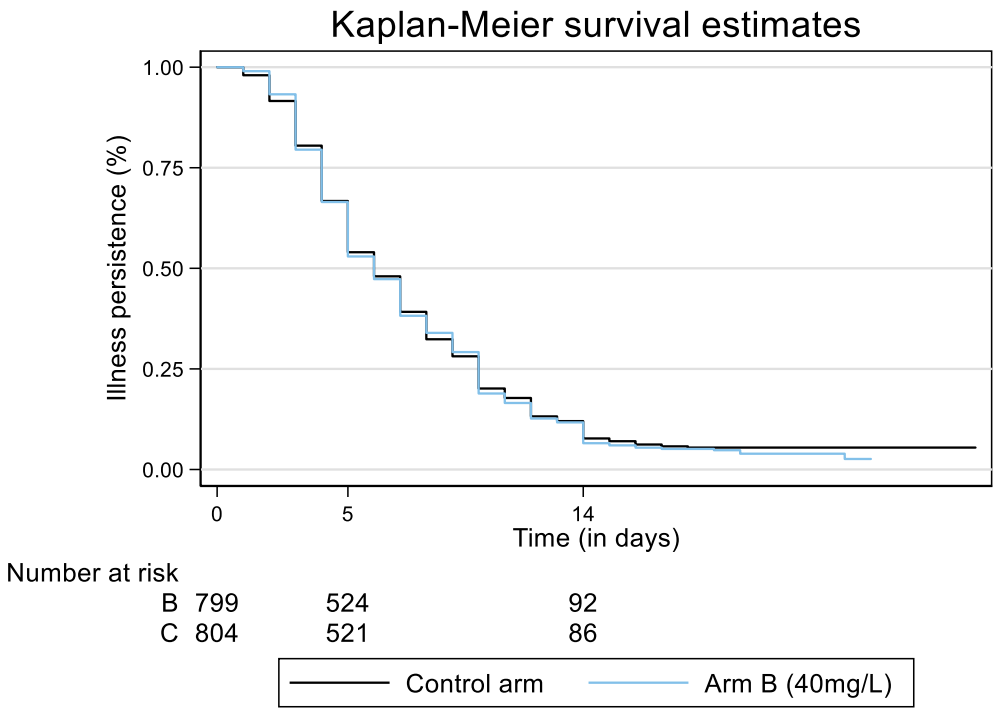
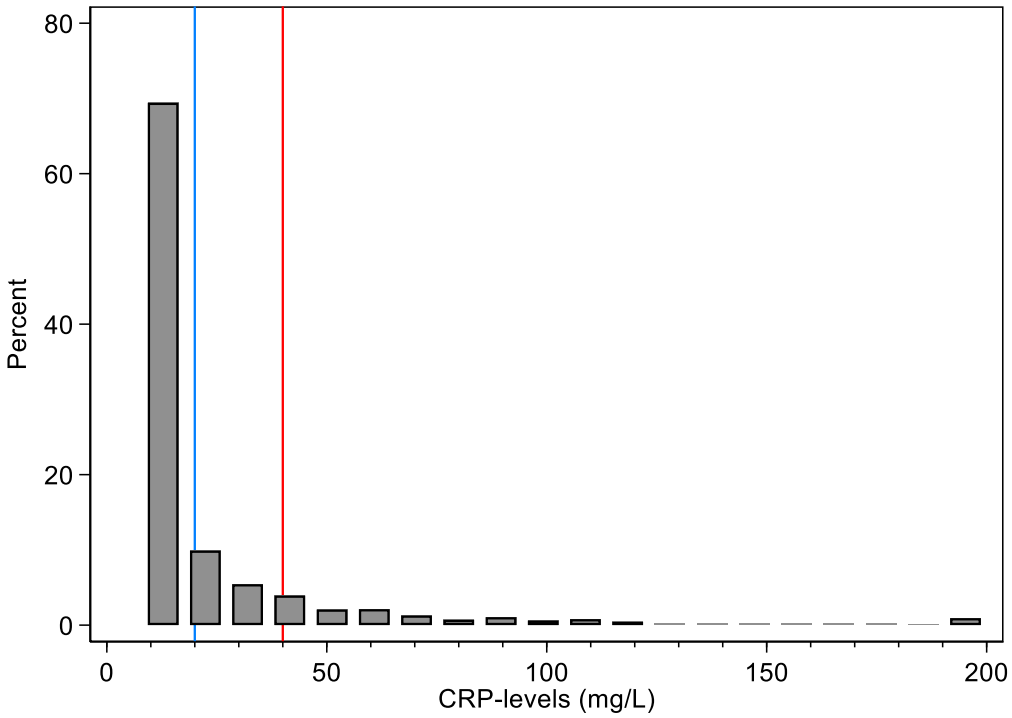


Figure 3-3: Kaplan-Meier survival estimates for symptom persistence at day 5 and day 14 comparing the control arm with intervention arm A and intervention arm B from the RCT

*Adapted from Althaus, T., et al., 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, 2019. **7**(1): p. e119-e131. License CC BY 4.0 [146]*

3.4.5 Distribution and Dynamics of CRP Results

The median CRP level on day 0 was 9mg/L (IQR < 8 to 22, Figure 3-4). The CRP level decreased between day 0 and day 5 in 935 (46.1%), remained the same in 921 (45.4%, of these 915 had a CRP of < 8mg/L) and increased in 174 (8.6%) of the 2,030 participants with CRP readings on both days. The median increase was 7mg/L (IQR 3 to 18) and 39 would have crossed their CRP cut off on day 5 (including seven controls increasing to ≥ 20mg/L). The median CRP level on day 5 was < 8mg/L regardless of whether patients reported ongoing or resolved symptoms on day 5.



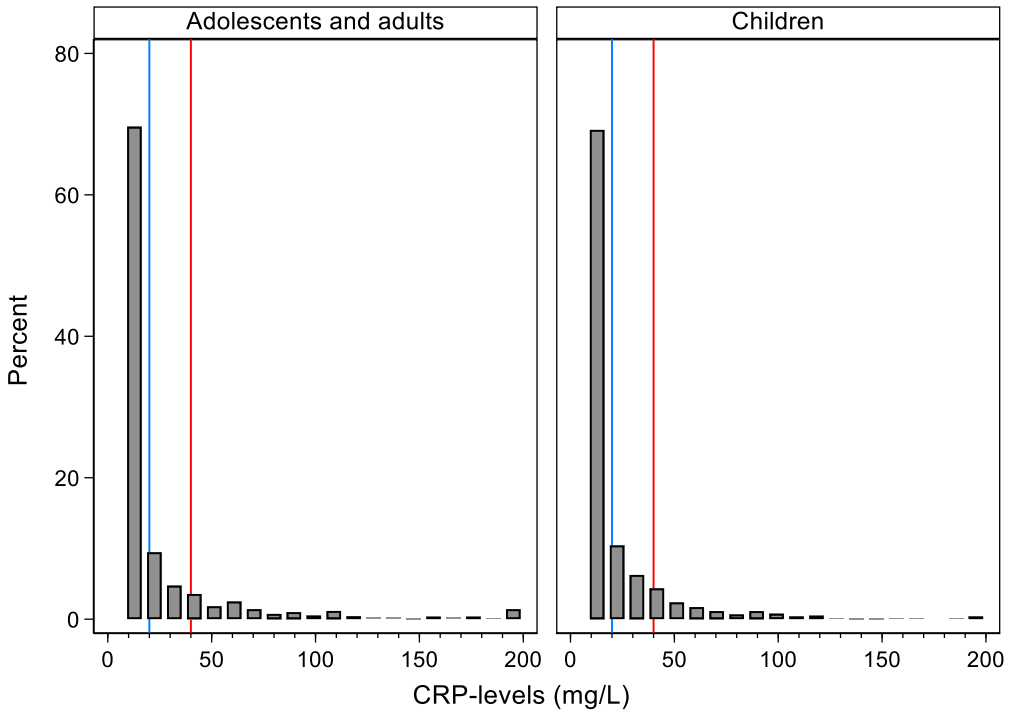


Figure 3-4: CRP levels on day 0 for all RCT participants and by age category

The blue line shows CRP = 20mg/L and the red line shows CRP = 40mg/L.

Adapted from Althaus, T., et al., 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, 2019. ***7****(1): p. e119-e131. License CC BY 4.0* [146]

3.4.6 Concordance of Antibiotic Prescriptions on Day 0 with C-Reactive Protein Results and Guidance

The healthcare workers were unaware if the participant was in intervention arm A or B, so the arms will be considered together for this section. Antibiotic prescribing was concordant with the CRP results in the intervention arms 78.2% of the time. Concordance was slightly higher if the CRP result was low (1,001/1,271, 78.8%) compared to when it was high (245/322, 76.1%). Concordance between antibiotic prescribing and the CRP results did not affect patient-reported symptom resolution by day 14, p = 0.846.

The details of the univariate logistic regression analysis are shown in Appendix 8. Overall concordance was significantly higher in children, and those with a cough or a runny nose.

Concordance was lower in those with a sore throat, muscle pain, a temperature > 37.5°C or abnormal examination findings. When compared against respiratory diagnoses, concordance was lower in GI diagnoses, non-GI and non-respiratory infections, and dual infections. Concordance was not related to the participants' sex, travel time to the study site, educational level, profession, past medical history of chronic disease, or whether they had sought healthcare or taken antibiotics in the previous 2 weeks.

Variable	**aOR (95% CI)**	**P value**
Children	1.21 (0.86 to 1.69)	0.276
Sore throat	0.52 (0.35 to 0.77)	0.009
Chest pain	0.52 (0.21 to 1.29)	0.159
Runny nose	1.57 (1.12 to 2.19)	0.009
Skin eruption or rash	0.55 (0.20 to 1.55)	0.260
Taken antibiotics in the last 2 weeks	0.77 (0.40 to 1.48)	0.434
Abnormal examination finding*	0.24 (0.17 to 0.35)	<0.001
Diagnosis body system:		
• Respiratory	Reference	Reference
• GI	0.45 (0.20 to 1.04)	0.062
• Other infections	0.55 (0.21 to 1.45)	0.226
• Fever or non-specific symptoms	1.66 (0.47 to 5.79)	0.429
• Dual infections	0.42 (0.21 to 0.85)	0.017
• Acute viral infection	0.73 (0.37 to 1.42)	0.350
• Non- infection	1	NA

Table 3-8: Multivariate logistic regression model for the concordance of antibiotic prescriptions with the CRP result in the RCT, adjusted for clustering by study site

**Abnormal examination findings excluding observations*

The global p value for the system of infection diagnosis was < 0.001, so this variable was considered for the multivariate analysis. The significant variables ($p < 0.05$) for use in the multivariate logistic regression contained 1,150/14,337 (8.0%) missing values, therefore multiple imputation of missing

values was not considered necessary. Concordance with the CRP results remained lower in those with a sore throat (aOR 0.52, 95% CI 0.35 to 0.77), abnormal examination finding (aOR 0.24, 95% CI 0.17 to 0.35) and being diagnosed with a dual rather than respiratory infection (aOR 0.42, 95% CI 0.21 to 0.85). Concordance remained higher in those with a runny nose (aOR 1.57, 95% CI 1.12 to 2.19, Table 3-8).

3.4.7 Healthcare Workers' Experiences and Opinions of Using the C-Reactive Protein Test

Table 3-9 shows the responses of the 33 healthcare workers who had used the CRP test. Over 79% were satisfied with the CRP test overall and would support its introduction. The responses between Thai and Myanmar healthcare workers were similar except Thai healthcare workers felt that the CRP test improved patients' trust and compliance with the treatment more than Myanmar healthcare workers, p = 0.008 and p = 0.004.

Knowledge, attitudes and practices	**Healthcare worker**	**Response n (%)**			
Do you feel you have understood the objectives of the test?		Yes	Neutral / so-so	No	Don't know
	All	27 (81.8)	6 (18.2)	0	0
	Thai	9 (64.3)	5 (35.7)	0	0
	Myanmar	18 (94.7)	1 (5.3)	0	0
Do you support the introduction of the test?		Strongly support/ support	Neutral	Don't support	Don't know
	All	29 (87.9)	3 (9.1)	0	1 (3.0)
	Thai	12 (85.7)	2 (14.3)	0	0
	Myanmar	17 (89.5)	1 (5.3)	0	1 (5.3)
Are the test results easy or difficult to follow?		Easy / very easy	Neutral	Difficult / very difficult	Don't know
	All	21 (63.6)	9 (27.3)	1 (3.0)	2 (6.1)
	Thai	8 (57.1)	6 (42.9)	0	0
	Myanmar	13 (68.4)	3 (15.8)	1 (5.3)	2 (10.5)

Do you find the CRP test fast enough or too time-consuming for your work?		Fast enough	Neutral	Too slow/ time-consuming	Don't know
	All	20 (60.6)	11 (33.3)	1 (3.0)	1 (3.0)
	Thai	10 (71.4)	4 (28.6)	0	0
	Myanmar	10 (52.6)	7 (38.8)	1 (5.3)	1 (5.3)
Do you think that health workers should base their antibiotics prescriptions on the test?		Yes	Yes under certain circumstances*	No	Don't know / no opinion
	All	22 (66.7)	7 (21.2)	2 (6.1)	2 (6.1)
	Thai	8 (57.1)	5 (35.7)	1 (7.1)	0
	Myanmar	14 (73.7)	2 (10.5)	1 (5.3)	2 (10.5)
Does the test influence your patients' trust in your recommendations?		Improve	No influence	Worsen	Don't know / no opinion
	All	27 (81.8)	4 (12.1)	0	2 (6.1)
	Thai	14 (100)	0	0	0
	Myanmar	13 (68.4)	4 (21.1)	0	2 (10.5)
Does the test influence your patients' compliance if you decide to prescribe or not to prescribe medication?		Improve	No influence	Worsen	Don't know / no opinion
	All	25 (75.8)	6 (18.2)	0	2 (6.1)
	Thai	14 (100)	0	0	0
	Myanmar	11 (57.9)	6 (31.6)	0	2 (10.5)
Overall are you satisfied with the CRP test?		Very satisfied / satisfied	Neutral	Dissatisfied/ very dissatisfied	Don't know
	All	26 (78.8)	7 (21.2)	0	0
	Thai	12 (85.7)	2 (14.3)	0	0
	Myanmar	14 (73.7)	5 (26.3)	0	0

Table 3-9: Healthcare workers' knowledge, attitudes and practices towards CRP testing

**Examples given: check the diagnosis, after you have done other examinations, if the test indicates antibiotics should be prescribed, or the diagnosis is uncertain*

3.4.8 Sore Throats and Group A *Streptococcus*

3.4.8.1 Throat Swab Results

BHS were isolated in 35/169 (20.7%) throat swabs; 11 (6.5%) GAS, four (2.4%) group B, four (2.4%) group C, one (0.6%) group F, 14 (8.3%) group G and one (0.6%) was non-groupable. The antibiotic susceptibility of the GAS isolates is shown in Table 3-10**Error! Reference source not found.**. Resistance was found in two isolates (18.2%) to erythromycin, clindamycin and chloramphenicol. Resistance to all three antibiotics was found in one isolate [144].

GAS isolate	Ceftriaxone	Chloramphenicol	Clindamycin	Erythromycin	Penicillin G
1	S	I	R	R	S
2	S	R	S	S	S
3	S	S	S	S	S
4	S	S	S	S	S
5	S	S	S	S	S
6	S	S	S	I	S
7	S	S	S	S	S
8	S	R	R	R	S
9	S	S	S	S	S
10	S	S	S	S	S
11	S	S	S	S	S

Table 3-10: Antibiotic susceptibility of GAS isolates from participants in the RCT

S: sensitive, I: intermediate, R: resistant

Reproduced from Greer, R., et al., Prevalence of Group A Streptococcus in Primary Care Patients and the Utility of C-Reactive Protein and Clinical Scores for Its Identification in Thailand. Am J Trop Med Hyg, 2020;102(2): p. 377-383. License CC BY 4.0 [144]

3.4.8.2 Clinical Features of Group A Streptococcus

The majority of those with GAS present on the throat swab were less than 12 years old (7/11, 63.6%, Table 3-11). Clinical diagnoses of pharyngitis and tonsillitis were no more common in those with GAS present on the throat swabs compared to those without BHS ($p = 0.473$ and $p = 0.172$, respectively).

Throat examinations were recorded as abnormal in 8/11 (72.7%) of those with GAS, compared to 69/130 (53.1%) of those without BHS on the swab ($p = 0.209$). All but one participant with GAS had a Centor score of 1 and FeverPAIN score of ≤ 3. There were no significant statistical relationships between Centor scores ≥ 3 ($p = 0.212$), and FeverPAIN scores ≥ 4 ($p = 1.000$) and the identification of GAS compared to no BHS isolation. No complications of GAS were reported during the study period.

Patient	Age (years)	Abnormal throat examination	Clinical diagnosis	CRP (mg/L)	Centor score*	FeverPAIN score	Study arm	Antibiotic prescription at enrolment	Antibiotic taken day 0-14†	Symptoms resolved by day 14•
1	13	Yes (red throat & tonsils enlarged)	Pharyngitis	12	1	3	Intervention	No	No	Yes
2	9	No	Common cold	18	1	2	Control	No	No	Yes
3	8	Yes (enlarged & swollen tonsils)	Tonsillitis	9	1	3	Control	Yes	Yes	Yes
4	6	Yes (mild infection)	Common cold	≤ 8	1	2	Intervention	No	No	Yes
5	12	No	Common cold	9	1	1	Intervention	No	No	No
6	69	Yes (red & enlarged tonsils)	Tonsillitis	34	1	3	Intervention	Yes	Yes	Yes

7	9	Yes (red throat)	Pharyngitis	≤ 8	1	2	Control	No	No	Yes
8	10	Yes (red throat)	Pharyngitis	39	1	3	Control	Yes	Yes	Yes
9	7	Yes (enlarged tonsils with exudate)	Tonsillitis	71	3	5	Intervention	Yes	Yes	Yes
10	7	No	Common cold	90	1	1	Control	No	Yes	Yes
11	22	Yes (red throat)	Pharyngitis	120	1	2	Control	No	No	Yes

Table 3-11: Individual clinical features, diagnoses, Centor and FeverPAIN scores, and antibiotic use for patients with GAS positive throat swabs

**Centor score: limited to a maximum of 3 points because no cervical lymph node examinations were recorded. †Antibiotic taken day 0-14: includes those prescribed during the study and any sourced from elsewhere. •Symptoms resolved by day 14: as reported by the patients.*

Adapted from Greer, R., et al., Prevalence of Group A Streptococcus in Primary Care Patients and the Utility of C-Reactive Protein and Clinical Scores for Its Identification in Thailand. Am J Trop Med Hyg, 2020;102(2): p. 377-383. License CC BY 4.0 [144]

3.4.8.3 C-Reactive Protein Values and Throat Swab Results

There is a trend towards increasing CRP values in those with BHS found on their throat swab compared to those with no BHS isolated (Table 3-12). This difference was statistically significant when GAS was present (p = 0.030) but only represented a modest increase in CRP values from 10mg/L to 18mg/L. A CRP cut off of > 8mg/L has a sensitivity of 81.8% (95% CI 52.3 – 94.8%) and specificity of 47.4% (95% CI 39.1 – 55.8%) for identifying GAS compared to no BHS isolation (p = 0.112) [144].

	Number of patients n/N (%)	**CRP (mg/L) median (IQR)**	**CRP ≤ 8mg/L n/N (%)**	**P value***
No sore throat†	618/1,182 (52.3)	≤ 8 (≤ 8-13)	382/617 (61.9)	N/A
Sore throat•	564/1,182 (47.7)	9 (≤ 8-19)	280/563 (49.7)	N/A
Sore throat and BHS not isolated	134/169 (79.3)	10 (≤ 8-18)	63/133 (47.4)	-
Sore throat and any BHS positive	35/169 (20.7)	14 (≤ 8-38)	12/35 (34.3)	0.052
Sore throat and GAS	11/169 (6.5)	18 (9-71)	2/11 (18.2)	0.030
Sore throat and group C or G streptococci	18/169 (10.8)	11 (≤ 8-26)	8/18 (44.4)	0.566
Sore throat and other BHS	6/169 (3.6)	17.5 (≤ 8-38)	2/6 (33.3)	0.244

Table 3-12: Median CRP values for RCT patients with and without sore throats, and by throat swab results

CRP: C-reactive protein, BHS: β-haemolytic streptococcus, GAS: group A streptococcus, N/A: not applicable

**Rank sum test to compare CRP values of positive throat swabs against no BHS isolation. †presenting with an acute fever or history of fever to the main RCT. •presenting with an acute fever or history of fever and a sore throat to the main RCT and nested study*

Reproduced from Greer, R., et al., Prevalence of Group A Streptococcus in Primary Care Patients and the Utility of C-Reactive Protein and Clinical Scores for Its Identification in Thailand. Am J Trop Med Hyg, 2020;102(2): p. 377-383. License CC BY 4.0 [144]

3.4.8.4 Group A Streptococcus and Antibiotic Prescriptions

Antibiotics were prescribed at enrolment to 53/169 (31.4%) of the patients with a sore throat. This missed 7/11 (63.6%) of those with GAS present on their throat swab; despite this only one patient with GAS had persisting symptoms at day 14. Depending on the criteria used to determine antibiotic prescribing for sore throats the proportion of patients prescribed antibiotics would vary greatly (Table 3-13).

Antibiotic Criteria	**Antibiotics indicated n/N (%)**	**Missed GAS n/N (%)**
GAS positive throat swab	11/169 (6.5)	0
Group A, G or G positive throat swab	29/169 (17.2)	0
Centor score ≥ 3	18/169 (10.7)	10/11 (90.9)
FeverPAIN ≥ 4	18/169 (10.7)	2/11 (18.2)
FeverPAIN 2 or 3	120/169 (71) delayed	
CRP > 8mg/L	93/168 (55.4)	2/11 (18.2)
CRP ≥ 20mg/L	45/168 (26.8)	6/11 (54.6)

Table 3-13: The proportion of RCT patients in whom antibiotics are indicated by throat swab, clinical scores, CRP levels and the number of GAS cases missed

3.5 Discussion

In this multicentre trial CRP POC testing significantly reduced antibiotic prescribing in those attending primary care in Thailand and Myanmar with a fever or history of fever, using the higher CRP cut off of

40mg/L (intervention arm B). There was a non-significant statistical reduction using a 20mg/L cut off (intervention arm A). When considering each country and age category separately, the reduction in antibiotic prescribing was only significant in Myanmar adolescents and adults using a 40mg/L cut off. In Thailand the limited reduction in antibiotic prescriptions was more marked in children than in adolescents and adults.

Assuming the CRP result is indicative of the need for antibiotics, CRP POC testing helped to target antibiotic prescriptions; fewer participants with a low CRP result received antibiotics and more participants with a high CRP result received an antibiotic prescription. In Myanmar this difference was maintained for all cut offs; however, in Thailand only those with a raised CRP result were more likely to receive an antibiotic in either of the intervention arms compared to the control arm. CRP testing could have a role to play in optimising antibiotic use, by ensuring that those who need antibiotics receive them.

A significant reduction in antibiotic prescriptions in both intervention arms was seen in the per protocol analysis; a greater reduction was seen in intervention arm B using the higher CRP cut off of 40mg/L. These reductions remained significant in Thailand when children, and adolescents and adults were analysed separately.

The limited impact of CRP testing found in this RCT is in contrast to other trials from LMICs. In Viet Nam, antibiotic prescriptions within 14 days were reduced from 77.9% to 64.4% (OR 0.49, 95% CI 0.40 to 0.61) in those aged 1 to 65 years old presenting to primary care with a non-severe RTI [154]. This reduction remained significant when children and adults were analysed separately. In Tanzania, CRP testing was used in an algorithm combining various POC tests as well as clinical assessments for severe respiratory distress and malnutrition, and then compared against a more basic algorithm. Over 3,000 febrile children (2 to 59 months old) were recruited and a high CRP cut off of 80mg/L was used to indicate the need for antibiotics. In the per protocol analysis antibiotic prescriptions fell from 29.7% to 11.5% (RR 0.39, 95% CI 0.33 to 0.45). These reductions were achieved with only half of the

intervention group receiving a CRP test, showing that much good could be done using clinical features alone. The primary outcome of treatment failure by day 7 was also reduced and met the non-inferiority margin. This was a safety study, with almost 100% compliance with the algorithms so an implementation study is needed to see the true effects [161]. A subgroup analysis was conducted on those children with a non-severe RTI. Antibiotic prescriptions fell from 40.4% to 2.3% (RR 0.06, 95% CI 0.04 to 0.09) and treatment failures were again reduced. It is possible that other elements of the algorithm could have contributed to these changes rather than CRP testing. In particular, increased use of salbutamol and rehydration may have improved treatment outcomes; the authors suggest that prescribing antibiotics can at times reduce the use of other (potentially more effective) treatments [196]. This more targeted approach to CRP testing with clear treatment guidelines may be more effective than testing all patients or leaving the CRP results open to interpretation by the healthcare worker [159, 160, 197]. It may also be more accepted by healthcare workers who at times have targeted their use of CRP tests even within trial settings where the protocol states to test all participants [162].

The limited impact of CRP POC testing found in our trial is more in line with a 2014 Cochrane review of CRP POC in participants with an ARI. All the studies found that POC CRP testing reduced antibiotic use; however, the RR of antibiotic prescription was 0.90 (95% CI 0.80 to 1.02) in the three individual RCTs. A greater impact was seen in the cluster RCTs (RR 0.68, 95% CI 0.61 to 0.75) [132]. Variation in the effect of CRP POC testing has been seen depending on the guidance given alongside the CRP test [132, 159, 161, 167]. Heterogeneity in prescribing has also been seen between study sites [154].

The proportion of patients receiving antibiotics in the control arm was lower than expected; in Thailand 33.4% received antibiotics between day 0 and 5 in the control arm compared to 46.9% of those presenting to all the PCUs in the same district with an infection [142]. Antibiotic prescribing between day 0 and 5 was 43.6% in the control arm during the interim analysis but fell to 33.4% during the study period overall. This is consistent with reducing antibiotic use in Thailand, as

discussed in Chapter 1. Antibiotic prescribing in the Myanmar control arm was also lower than in routine care, although higher than seen in the Thai arm of the trial [146]. The difference in control arm antibiotic use may account for the varying impact of CRP POC testing between Thailand and Myanmar as concordance with the CRP results was similar in the two countries. The effect of CRP testing in contexts with low baseline prescribing is likely to be modest compared to where baseline prescribing is higher.

Concordance between antibiotic prescriptions and the CRP results was achieved in 78.2% of the participants. This was significantly reduced in those with a sore throat, abnormal examination findings, and in those with a dual infection diagnoses. Concordance was higher in those with a runny nose. It was not affected by which country the participant was seen in. Nor was it affected by how far away the patient lived or their education level which are often given as reasons for prescribing antibiotics. It is possible that healthcare workers did not feel comfortable withholding antibiotics for certain conditions such as tonsillitis and pharyngitis which have much higher prescribing rates compared to other RTIs [142]. It is also understandable that healthcare workers would overrule the CRP result if there were abnormal examination findings causing clinical concern. Further qualitative work would be helpful to explore these areas in more detail.

There were no significant differences in clinical outcomes between the control arm and either intervention arms. A minority of participants re-attended the study site during the follow-up period, similar to most studies [132, 154]. A small number of hospital admissions occurred more frequently in the intervention arms but were thought to be unrelated to the study. This is in agreement with a few other studies, where there have been occasional reports of non-significant trends towards increasing hospitalisation [150, 197]. In contrast, clinical failures and hospital admissions were reduced in Tanzania when CRP POC testing was incorporated into a clinical algorithm [161, 196].

Overall the CRP results on day 0 were low; the median CRP result was 9mg/L and more than 80% of the participants had a CRP result under 40mg/L. These relatively low CRP results are similar to other trials conducted in Viet Nam and Tanzania [154, 196].

For any successful intervention to be implemented it is important to understand the views of those using and receiving the test. Compliance with guidelines and new interventions are more likely if they are accepted, easy to use, do not interrupt routine care and are incentivised [168-170]. Without sufficient buy-in from healthcare workers their prescribing behaviours may not change [84, 102, 166]. Healthcare workers' opinions on CRP testing have been explored in qualitative or mixed methods studies, although most have been conducted in high income settings [162-170]. Similar to other studies, our KAP data shows that most healthcare workers would welcome the introduction of CRP testing and expressed positive opinions overall [162, 164, 165, 167, 168]. Healthcare workers felt that CRP POC testing improved patients' trust in their management, which is consistent with other studies reporting that the test could be used to reassure patients that antibiotics are not needed [84, 162-164, 166, 167, 170]. The overall positive opinions towards CRP testing expressed in our KAPs were confirmed by semi-structure interviews conducted with the same healthcare workers, who felt that CRP testing helped to support their decision making and negotiation of management plans with the participants [84]. This was particularly helpful given the local and national moves in Thailand to optimise the use of antibiotics. Concordance with the test results varied amongst the nurses with some using their clinical judgement to overrule the CRP test result, while others allowed the test to overrule their judgement [84]. The context into which the CRP test was introduced was also highlighted in a case study comparing CRP testing in Thailand, Myanmar (both linked to this RCT) and Viet Nam [189]. Haenssgen at al. found three themes which seemed to particularly affect the intervention: the perceived risk of serious illness, the health system including availability of diagnostics, referrals and AMR policies, and the patients' demand for antibiotics [84, 189]. Potential barriers to implementing CRP testing were the healthcare workers' limited understanding of the test

and usability of the results which could be addressed with additional training and support. Other studies have identified costs, lack of time and interruptions to the workflow as potential barriers to implementation [162, 164-166, 168-170].

The prevalence of GAS in those presenting with a history of fever and sore throat was low (6.5%) compared to a large meta-analysis of patients presenting globally (24.1%), although most studies were conducted in HICs [198]. However, our results are similar to other studies from Thailand which found GAS prevalence rates of 3.3% to 7.9% in children and adults presenting with an URTI to ambulatory care [93, 97, 99].

The GAS isolates were fully sensitive to penicillin which was the most frequently prescribed class of antibiotic, but there were moderate levels of resistance to erythromycin, clindamycin and chloramphenicol. The GAS susceptibility of our limited number of isolates supports the ongoing use of penicillin as first line treatment. However, penicillin V may be a more appropriate choice than amoxicillin due to its narrower spectrum of action and evidence linking amoxicillin use in the community with higher levels of *E.coli* resistant UTIs [30]. Increasing levels of GAS macrolide resistance have been reported globally; in Thailand in 2019, 8.4% of 6,230 GAS isolates from 92 hospitals were resistant to erythromycin [199-201]. Ongoing AMR surveillance is required and if GAS macrolide resistance increases then antibiotic guidelines may need updating and routine susceptibility testing of patients with a penicillin allergy and suspected GAS may be needed.

Identifying the patients with GAS was challenging; the correlation between clinical diagnoses, abnormal throat examinations, raised clinical scores and CRP results were poor. Recommended antibiotic prescription levels within our cohort would vary considerably depending on the prescribing guideline used. However, we are unable to verify whether GAS positive throat swabs were due to active infection or carriage and 3/11 (27.2%) had a normal throat examination, so some may not have needed antibiotic treatment. From the data we have, it is challenging to know which strategy is most appropriate. The Centor and FeverPAIN clinical scores were not significantly correlated with

GAS identification on the throat swabs. CRP results were statistically higher in those with GAS, however the difference is not clinically significant and there was no correlation between CRP scores > 8mg/L and GAS identification [144].

3.5.1 Strengths and Limitations

This multi-centre RCT widens the participant population to those presenting with a fever or history of fever, rather than focusing on those with RTIs. We also included children aged over 12 months and did not exclude the elderly. Those who had already taken antibiotics were eligible to join, as were those with co-morbidities apart from cancer. All these factors mean that the results are more generalizable to populations attending primary care. This RCT adds to the limited evidence on CRP testing emerging from LMICs.

Having two intervention arms meant that we were able to compare two CRP cut offs against the control arm and found that the higher cut off of 40mg/L (intervention arm B) resulted in a greater reduction in antibiotic prescriptions without affecting clinical outcomes.

Another strength of the study is the range of clinical outcomes recorded. In addition to hospitalisations and re-attendances at the study site we collected patient-reported outcomes such as symptom severity and duration, as well as more objective outcomes such as recorded fevers and CRP measurements.

The RCT was complemented by the healthcare workers' KAP questionnaires and interviews (not presented in this thesis). All healthcare workers involved in the trial completed the KAP questionnaire which allows us to understand some of their opinions towards CRP testing and possible barriers to its implementation.

There are however limitations to this trial. The clinical outcomes were secondary outcomes and as such the trial was not powered to detect differences between study arms. Gillespie and colleagues make a strong case for co-powering antimicrobial stewardship interventions to consider clinical

outcomes as well as antimicrobial use; this ensures that the societal benefits of antimicrobial stewardship do not come at a cost to individual patients [202]. Powering the trial however, for the detection of differences in clinical outcome in a primary care setting with very low incidence of severe outcomes was not feasible.

The randomisation unit was the individual patient rather than the study site or healthcare worker. Conducting a cluster RCT at the site level would have reduced the chance of contamination between the study arms and may have increased the effect size. Having research staff onsite could also have influenced the effect size through The Hawthorne Effect.

This RCT was not done in isolation; in Thailand during the study period changes were made to national antimicrobial stewardship policies, including the introduction of key performance indicators for antibiotic prescribing into the FDA's RDU plan in August 2016 (Chapter 1). This could have altered prescribing behaviours in the control arm, but may have also supported the intervention. This, alongside the relatively low prescribing in the control arm, may limit the generalisability of the results to other contexts. Although we enrolled participants presenting with a history of fever the majority were diagnosed with RTIs which may limit the generalisability.

Despite all healthcare workers completing the KAP questionnaire we still have relatively small numbers. The nature of KAPs means that they only provide a snapshot of opinions and do not result in as rich or nuanced data as other methods such as in depth interviews. Although questions were worded positively and negatively it is possible that healthcare workers will have tried to give the desirable answers, especially if the KAP questionnaire was not seen as independent to the RCT. In Thailand and Myanmar, cultural attributes such as being considerate and not wanting to offend play a strong role in social interactions and may have contributed to the positive opinions reported in the KAPs. It is also possible that the answers given in the KAPs would not reflect actual practice as seen in other studies comparing questionnaire responses and observations [80, 82, 203].

The low number of GAS positive throat swabs may have hampered our ability to identify a correlation between CRP results and GAS presence. False negative swabs may have arisen from poor swab techniques, possible laboratory processing errors or prior antibiotic use. Without conducting serology or having a healthy control group we are unable to confirm if positive swab results were due to active infection, rather than carriage of BHS. The clinical scores were calculated retrospectively and some data such as lymph node examination were missing which meant that Centor scores were limited to a maximum of 3 rather than 4 points.

3.5.2 Areas for Further Work

Chapter 4 will focus on the patients' experiences of CRP testing and their health-seeking behaviour before and during the RCT. Their opinions regarding their treatment and CRP testing will be explored in order to evaluate the intervention and its acceptability. Through their viewpoint the differences in the effect of CRP testing between Thailand and Myanmar will be compared.

Implementation studies are required to understand the impact of introducing CRP testing into routine care. A large cluster randomised trial is being conducted by our sister unit in Viet Nam to evaluate this in RTIs presenting to primary care [204]. I am a co-investigator on this trial and have been involved in the study design, protocol development and provide an ongoing clinical perspective for regular meetings discussing the progress of the study. The results will help us to understand if routine CRP testing may be useful in guiding antibiotic management of RTIs in Vietnamese primary care. Further qualitative studies exploring the reasons for lower concordance with CRP guidance will help us to understand if these could be addressed or if more support and training are required.

Given the limitations of this GAS study and paucity of other Thai data there is an ongoing need to explore how antibiotic use in sore throats can be optimised without affecting patient outcomes. More data is needed on GAS infection, carriage and complication rates. Studies with larger sample sizes are required to determine how to identify which patients need antibiotics. Existing clinical

scores such as Centor and FeverPAIN need validation in the Thai primary care setting before widespread use should be recommended.

3.5.3 Conclusions

In this context with relatively low baseline antibiotic use and the introduction of new restrictive antimicrobial stewardship policies, CRP POC testing led to a modest reduction in antibiotic prescribing using a cut off of 40mg/L in patients presenting to primary care with a history of fever. CRP testing helped to target antibiotic use, with more patients prescribed an antibiotic with a high CRP result and fewer patients receiving antibiotics with a low CRP result. Clinical outcomes were not affected and healthcare workers reported positive opinions towards CRP testing. More work is required to explore the reasons for lower compliance with the CRP results in patients with a sore throat, abnormal examination findings and dual infection diagnoses.

Chapter 4 The Impact of C-Reactive Protein Testing on Treatment-Seeking Behaviour and Patients' Attitudes towards their Care

4.1 Introduction

The ability of CRP testing to optimise antibiotic use is to a great extent dependent upon the responses of patients towards the intervention and their treatment. People have hypothesised that those not receiving antibiotics after a CRP test will be dissatisfied and seek healthcare and/or antibiotics elsewhere [72, 84]. The ease with which patients will be able to do this will vary depending on their health system context. In most areas in Thailand, where there are multiple healthcare providers it is relatively easy to seek a second opinion or to purchase antibiotics directly in the private sector.

The CRP test itself could medicalise self-limiting illnesses and encourage re-attendances with similar illnesses [72, 168]. Little is known about the longer term effects of CRP testing. A 3.5 year follow-on study of a RCT evaluating CRP testing and communication skills in patients with an acute cough presenting to GPs in the Netherlands found no difference in yearly consultation rates for RTIs between the intervention arms and the control arm. Low numbers of CRP tests were done in the following years suggesting that patients were not demanding further tests [205].

The CRP test may not be acceptable due to increased costs and lengths of consultations for healthcare systems and patients [72, 167, 168]. Concerns have also been raised about the discomfort of the test, particularly for children [84]. This was explored in a mixed methods study of children attending out of hours clinics in the UK, where they found similar recruitment rates compared to other trials. The parents and study nurses interviewed had few concerns about the test and reported little discomfort for the children [167]. Overall, qualitative studies have found patients to have positive opinions towards CRP testing, although the majority have been conducted in high income settings [72, 149, 152, 154].

Patients' acceptance of an intervention to optimise antibiotic use can be measured in part by subsequent antibiotic use and seeking alternative healthcare. However, patient-reported antibiotic use can be unreliable due to several factors including a lack of awareness and understanding of the medications being taken [206-208]. Assessing urine antibiotic activity is one method that has been used to try and confirm patients' antibiotic use [154, 206, 209-211].

4.2 Aims and Objectives

In this chapter I continue to review the RCT described in Chapter 3, focusing on the patients' perspectives of CRP testing and their treatment-seeking behaviour. Differences between Thailand and Myanmar are investigated. I explore the use of antibiotics prior to attendance at the study sites, and whether CRP testing affects patients' health-seeking behaviour after attendance, including the sourcing of antibiotics. I compare self-reported antibiotic use and urine antibiotic activity. Finally, I review patients' and their caregivers' experiences and opinions towards their treatment and CRP testing.

4.2.1 Methods

The methods of the RCT are described in detail in Chapter 3. At enrolment participants were asked if they had sought healthcare or started any new medication in the 2 weeks prior to enrolment. At the follow-up visits on day 5 and 14 they were also asked about seeking additional healthcare or antibiotics outside of the study. On day 14, they were asked for additional demographic and socio-economic data, as well as their experiences of the treatment and CRP testing. This was done through close-ended questions on the CRF and conducted by the research nurses (Appendix 3).

4.2.2 Urine Antibacterial Activity

Urine samples were collected from all participants at day 0 (+ 2 days) and day 5 (+/- 2 days) to test for antibiotic activity. Due to resource constraints we were only able to test a subgroup of urine samples from day 0. All of the available day 5 urine samples were tested, given the importance of

determining the impact of CRP testing on subsequent antibiotic use within and outside of the study sites.

Aliquots of urine samples were frozen at -80°C at the local laboratories, transferred in batches to MORU's central laboratory in Bangkok, Thailand and tested for antibacterial activity. *Bacillus stearothermophilus* ATCC 7953 was used as the reference organism; it was cultured and plated onto Mueller Hinton agar [209, 211]. The urine sample was thawed and then 3µl of urine was pipetted onto a blank filter paper disc noting the position of each urine sample. The plate was then incubated for a further 18 to 24 hours, aerobically at 56°C. Antibacterial activity was declared if an inhibitory growth zone was seen around the urine. All samples were tested in duplicate and divergent results were repeated. Our methods varied from previous studies such as Liu's and Khennavong's which used three reference organisms [209, 211]. Resource constraints meant we were only able to use one reference organism and opted for *Bacillus stearothermophilus* ATCC 7953, which was selected for being the most sensitive of the three more commonly used organisms [207, 209, 211].

4.2.3 Statistical Analysis

Descriptive data was summarised and compared as described in Chapter 3. Logistic regression models were fitted for seeking additional healthcare and antibiotics during the study period, with the study arms fitted as fixed effects and the study sites as random effects. Univariate analyses were conducted to determine the indicators for seeking additional healthcare and antibiotics during the study. Any significant variables ($p < 0.05$) were added to a multivariate analysis. The kappa statistic was used to assess agreement between patient-reported antibiotic use and urine antibiotic activity.

A score for the participants' consultation experience was calculated from their opinions and attitudes, explored on day 14. Their responses were recoded as follows: positive responses received 1 point, neutral responses 0 points and negative responses -1 points. The score was made up of the sum of responses to questions 2, 3, 4, 8 and 9 (Table 4-6).

4.3 Results

A total of 2,410 participants attending primary care in Thailand and Myanmar with a fever or history of fever were enrolled into the RCT.

4.3.1 Treatment-Seeking before Study Enrolment

4.3.1.1 Health-Seeking Behaviour before Enrolment

In the 2 weeks prior to enrolment at the study site, 1,372/2,408 (57.0%) of the participants had sought healthcare; of these 31 (2.3%) sought care from two places. The majority sought care from a pharmacy or clinic (Table 4-1). Participants from Thailand were less likely to have sought care than those from Myanmar (38.4% vs 74.9%, $p < 0.001$).

Source of care	**Number of participants n (%)**
Pharmacy	755 (53.8)
Natural healer	129 (9.2)
Clinic	310 (22.1)
The study site	131 (9.3)
Hospital	39 (2.8)
Community healthcare worker	6 (0.4)
Other	2 (0.1)
Unknown	31 (2.2)
Total places*	1,403

Table 4-1: Places where participants sought healthcare before enrolment into the RCT

**Some participants sought care from more than one place*

4.3.1.2 Antibiotic Use before Enrolment

In the 2 weeks prior to enrolment in the RCT, 1,732/2,409 (71.9%) of the participants had taken a new medication; of these 367 (21.2%) had taken at least one unknown medication. In total, 130/2,409 (5.4%) of the participants reported antibiotic use in the 2 weeks prior to enrolment (Figure 4-1). Only 127/1,372 (9.3%) of those who had sought healthcare had received antibiotics. There was

no difference in antibiotic use between participants from Thailand and Myanmar. The majority of antibiotics were from clinics, including the study sites (Table 4-2).

Source of antibiotic	Number of antibiotics n (%) N=130
Clinics	82 (63.1)
Pharmacies	30 (23.1)
Hospitals	6 (4.6)
Natural healers	5 (3.8)
Street vendors	1 (0.8)
Home	3 (2.3)
Unknown	3 (2.3)

Table 4-2: Sources of antibiotics participants were taking before enrolment into the RCT

Urine antibiotic activity was present in 85/409 (20.8%) of the samples tested at enrolment. Of these 409, 22 patients (5.4%) had reported antibiotic use in the 48 hours before the urine test; 15 were positive and 7 were negative. However, 70/85 (82.4%) of the participants with antibiotic activity present in their urine did not report antibiotic use. The overall agreement between reported antibiotic use and urine antibiotic activity was fair at 81.2% (kappa=0.21).

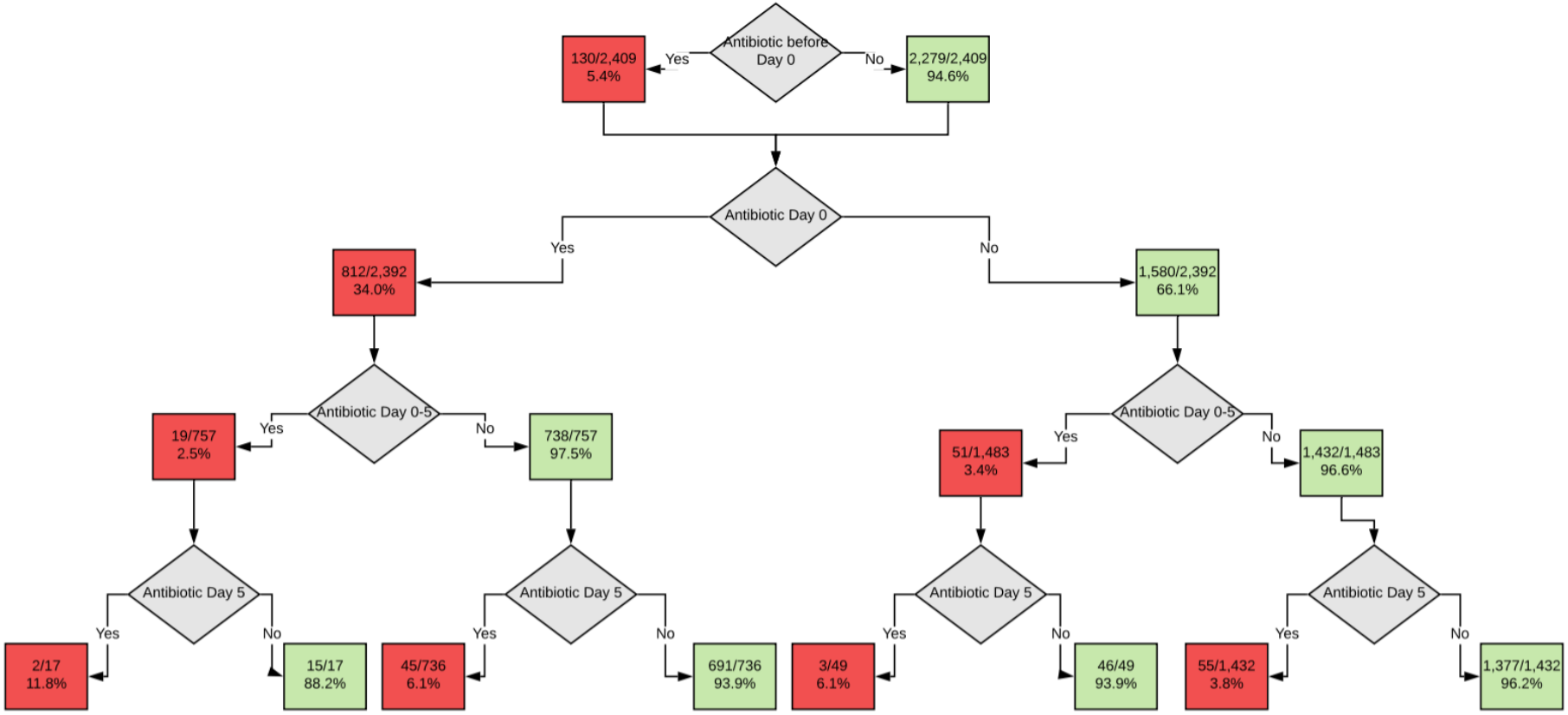


Figure 4-1: Diagram to show subsequent antibiotic use until day 5 of the RCT for participants who were and were not prescribed an antibiotic at enrolment

4.3.2 Antibiotic Prescribing at Enrolment

As detailed in Chapter 3, antibiotics were prescribed at enrolment to 515/1,593 (32.3%) of the participants in the CRP intervention arms compared to 297/799 (37.2%, p = 0.018) in the control arm.

4.3.3 Treatment-Seeking and Antibiotic Use during the Study

4.3.3.1 Health-Seeking Behaviour during the Study

Healthcare was sought by 339/2,294 (14.8%) of the participants during the study (after enrolment up to day 14, excluding study follow-up visits); of these 4 (3.7%) sought care from two places. The CRP intervention did not affect levels of health-seeking behaviour during the study (Table 4-3).

	Control arm n/N (%)	**Intervention arm A n/N (%)**	**Risk difference (95% CI)**	**aOR* (95% CI)**	**Intervention arm B n/N (%)**	**Risk difference (95% CI)**	**aOR* (95% CI)**
Sought healthcare during the study	108/766 (14.1)	106/759 (14.0)	0.1 (-3.6 to 3.4)	0.99 (0.74 to 1.32)	125/769 (16.3)	2.2 (-1.4 to 5.7)	1.17 (0.88 to 1.56)
Sourced antibiotics during the study	30/740 (4.1)	33/727 (4.5)	-0.5 (-1.6 to 2.6)	1.12 (0.67 to 1.86)	32/739 (4.3)	-0.3 (-1.8 to 2.3)	1.06 (0.63 to 1.77)

Table 4-3: Participants' seeking of healthcare and antibiotics during the RCT by study arm

Study sites were added as random effects

The details of the univariate analysis on health-seeking during the study are shown in Table 4-4. In the multivariate analysis participants from Thailand remained less likely to seek care compared to those from Myanmar. Participants were less likely to seek care if they had an antibiotic prescribed at enrolment. Those who had sought care before the study, had a fever at enrolment, higher self-reported symptom severity and higher CRP results were more likely to seek care during the study as were those diagnosed with an acute viral or dual infection compared to respiratory infections (Table 4-5).

Variable	Additional healthcare during the study		Additional antibiotics during the study	
	aOR* (95% CI)	P value	aOR* (95% CI)	P value
Thai participants	0.38 (0.22 to 0.66)	0.001	0.76 (0.33 to 1.71)	0.502
Male	1.17 (0.93 to 1.48)	0.185	1.08 (0.71 to 1.63)	0.729
Children	0.86 (0.68 to 1.09)	0.215	0.80 (0.52 to 1.22)	0.294
More than primary education†	1.03 (0.79 to 1.34)	0.805	1.21 (0.76 to 1.91)	0.420
Profession†				
• Agriculture	Reference	Reference	Reference	Reference
• Non-skilled labourer	1.03 (0.68 to 1.56)	0.895	0.82 (0.45 to 1.49)	0.522
• Skilled labourer or professional	1.12 (0.71 to 1.76)	0.630	0.91 (0.47 to 1.77)	0.474
• No employment	1.21 (0.70 to 2.08)	0.504	0.70 (0.27 to 1.85)	0.777
Sought healthcare before enrolment	1.58 (1.20 to 2.09)	0.001	1.51 (0.94 to 2.40)	0.087
Antibiotics before enrolment	1.35 (0.84 to 2.18)	0.217	0.87 (0.34 to 2.21)	0.771
Travel > 30 minutes to PCU	0.79 (0.59 to 1.08)	0.138	1.06 (0.62 to 1.81)	0.820
Chronic disease	1.35 (0.99 to 1.84)	0.057	0.93 (0.51 to 1.70)	0.812
Duration of symptoms (1 day increase)	1.02 (0.97 to 1.07)	0.477	1.08 (0.98 to 1.18)	0.113
Self-reported symptom severity (1 point increase)	1.72 (1.29 to 2.29)	< 0.001	1.26 (0.83 to 1.92)	0.282
Documented fever > 37.5°C at enrolment	1.62 (1.27 to 2.07)	< 0.001	1.57 (1.02 to 2.41)	0.038
CRP level at enrolment (1 mg/L increase)	1.01 (1.00 to 1.01)	0.001	1.01 (1.00 to 1.01)	0.002
Abnormal examination at enrolment•	0.89 (0.67 to 1.19)	0.426	0.89 (0.55 to 1.45)	0.646

Diagnosis at enrolment				
• Respiratory	Reference	Reference	Reference	Reference
• Other infections	1.30 (0.79 to 2.14)	0.304	0.75 (0.26 to 2.14)	0.586
• Acute viral infections	1.88 (1.28 to 2.75)	0.001	1.20 (0.58 to 2.51)	0.623
• Dual infection	1.72 (1.01 to 2.94)	0.045	0.68 (0.20 to 2.25)	0.525
Antibiotic prescribed at enrolment	0.71 (0.55 to 0.93)	0.012	0.75 (0.47 to 1.20)	0.227
Antibiotic prescription in concordance with CRP result	0.82 (0.58 to 1.16)	0.255	1.10 (0.59 to 2.06)	0.760

Table 4-4: Univariate analyses of variables for seeking healthcare and antibiotics during the RCT study period

**The study site was added as a random effect. †The education level and profession are for the participant unless they were under the age of 18, in which case the head of the household is used. •Abnormal examination finding: excludes observations*

Variable	Additional healthcare sought during the study period	
	aOR* (95% CI)	P value
Thai participants	0.43 (0.23 to 0.81)	0.008
Sought healthcare before enrolment	1.47 (1.07 to 2.01)	0.016
Documented fever at enrolment	1.75 (1.31 to 2.35)	< 0.001
Self-reported symptom severity score	1.81 (1.33 to 2.46)	< 0.001
Diagnosis at enrolment		
• **Respiratory**	Reference	
• **Other infections**	1.22 (0.70 to 2.12)	0.480
• **Acute viral infections**	1.71 (1.12 to 2.63)	0.014
• **Dual infection**	1.82 (1.04 to 3.18)	0.037
CRP result at day 0	1.01 (1.00 to 1.01)	0.001
Antibiotic prescribed at enrolment	0.52 (0.37 to 0.73)	< 0.001

Table 4-5: Multivariable logistic regression of variables associated with seeking healthcare during the RCT

**Study site added as a random effect*

4.3.3.2 Antibiotic Use during the Study

Antibiotics were prescribed to 110/2,311 (4.8%) of the participants at day 5 (control = 4.4%, intervention = 4.9%, p = 0.569). Antibiotics were prescribed to 15/2,317 (0.7%) of the participants at day 14 (control = 1.0%, intervention = 0.5%, p = 0.101).

In addition to the antibiotics prescribed at the study site, 95/2,206 (4.3%) of the participants sourced their own antibiotics, approximately a third of the 254 patients seeking care elsewhere. There was no difference between those seeking antibiotics in the intervention arms or the control arm (Table 4-3).

Participants were more likely to source antibiotics outside of the study if they had a higher CRP result at enrolment (aOR 1.01, 95% CI 1.00 to 1.01, p = 0.002). Sourcing antibiotics was not affected by their country, sex, age, profession or whether they were prescribed antibiotics at enrolment (Table 4-4).

Urine antibiotic activity was present in 521/2,065 (25.2%) of the day 5 urine samples (Figure 4-2). Of those with urine samples, 641 (31.0%) had reported antibiotic use in the 48 hours before the urine

test; 352 (54.9%) were positive and 289 (45.1%) were negative. In the group with positive urine antibiotic activity 352/521 (67.6%) of the participants had reported antibiotic use, while 155 (29.8%) reported no antibiotic use. The overall agreement between participant-reported antibiotic use and urine antibiotic activity was moderate at 77.4% (kappa 0.46). Approximately ¾ participants knew whether they had been prescribed an antibiotic at enrolment when asked on day 14; the rest were unsure.

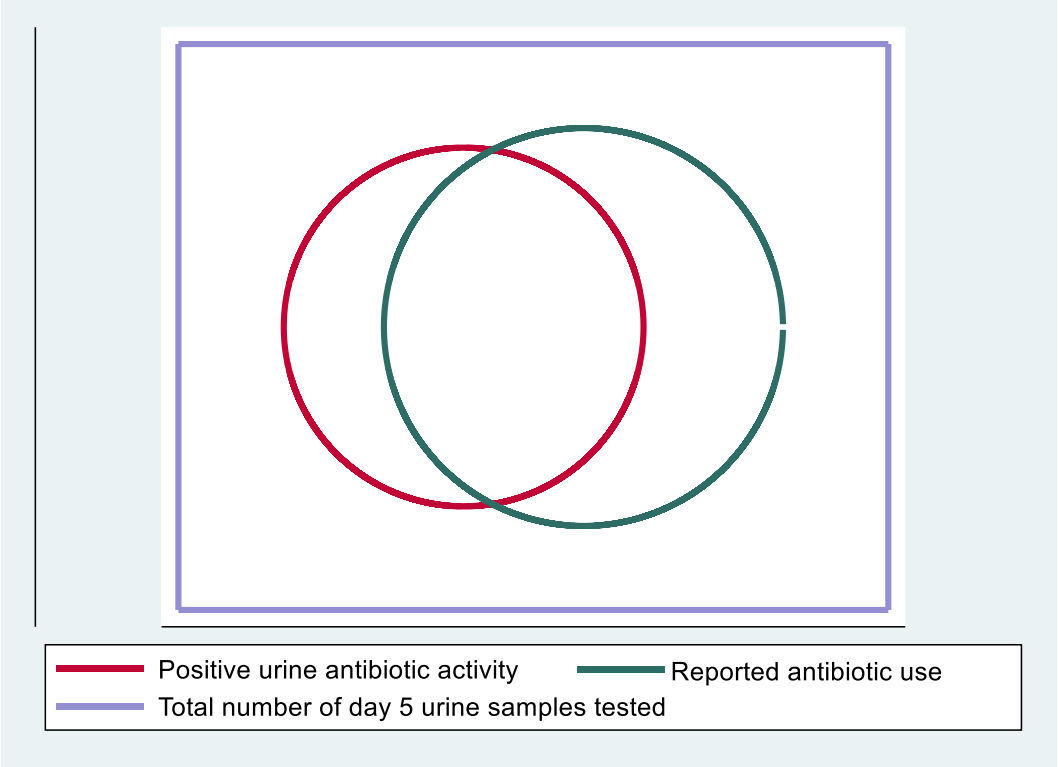


Figure 4-2: A Venn diagram to show day 5 urine antibiotic activity and RCT participant-reported antibiotic use

4.3.4 Participants' Views and Opinions of Treatment

Adherence to all courses of antibiotics was reported by 687/829 (86.7%) of the participants; 105/829 (12.7%) reported non-adherence and 37/829 (4.5%) reported adherence to some but not all courses. Other participants were unsure if they were adherent or not.

On day 14, the participants were asked about their experiences of care, and CRP testing if they were in an intervention arm. Half of the participants answered for themselves (1,096, 47.3 %) while parents or guardians answered for others. Participants expressed high levels of satisfaction with their

care (Table 4-6). The combined scores for the consultation experience (sum of answers to questions 2, 3, 4, 8 and 9) were not different between the control and intervention arms ($p = 0.980$), nor did the intervention group affect understanding ($p = 0.966$) or agreement with the treatment ($p = 0.864$). Thai participants rated their consultation experience ($p < 0.001$), understanding of the treatment ($p < 0.001$) and CRP test ($p < 0.001$), and agreement with their treatment ($p < 0.001$) higher than participants from Myanmar.

Those who sought additional healthcare during the study period had lower consultation experience scores ($p = 0.001$), less understanding of the treatment ($p = 0.007$) and of the CRP test ($p = 0.007$), and less agreement with their treatment ($p = 0.006$). Those who sought antibiotics during the study period had similar scoring for their consultations ($p = 0.313$) and understanding ($p = 0.847$) but expressed less agreement with their treatment ($p = 0.001$). Agreement with the treatment was lower in those who were not prescribed an antibiotic ($p = 0.033$), although over 80% agreed with the healthcare worker's decision to prescribe an antibiotic or not.

The majority of intervention participants reported feeling more confident as to whether or not antibiotics were needed because of the CRP test and that it improved the quality of care. Almost all of the intervention participants (91.0%) wanted the CRP test to be used again in future illnesses.

Participants' and caregivers' opinions & attitudes	**Agree n (%)**	**Neutral n (%)**	**Disagree n (%)**
I think that the healthcare worker's decision to prescribe or not to prescribe an antibiotic for my treatment was correct (Q 2)			
• Intervention arms (N = 1,377)	1,113 (80.8)	241 (17.5)	23 (1.7)
• Control arm (N = 691)	556 (80.5)	125 (18.1)	10 (1.5)
• Thailand (N = 1,172)	1,107 (94.5)	49 (4.2)	16 (1.4)
• Myanmar (N = 896)	562 (62.7)	317 (35.4)	17 (1.9)

I did <u>not</u> get enough explanation to understand the treatment (Q 3)			
• Intervention arms (N = 1,448)	79 (5.5)	394 (27.2)	975 (67.3)
• Control arm (N = 725)	37 (5.1)	200 (27.6)	488 (67.3)
• Thailand (N = 1,173)	54 (4.6)	269 (22.9)	850 (72.5)
• Myanmar (N = 1,000)	62 (6.2)	325 (32.5)	613 (61.3)
I felt that the consultation was <u>too</u> fast (Q 4)			
• Intervention arms (N = 1,451)	335 (23.1)	254 (17.5)	862 (59.4)
• Control arm (N = 726)	155 (21.4)	123 (16.9)	448 (61.7)
• Thailand (N = 1,174)	394 (33.6)	36 (3.1)	744 (63.4)
• Myanmar (N =1,003)	96 (9.6)	341 (34.0)	566 (56.4)
I fully understood the instructions for taking the prescribed antibiotic (including when, how much, how often, and how long I have to take the medication) (Q 5)			
• Intervention arms (N = 407)	388 (95.3)	15 (3.7)	4 (1.0)
• Control arm (N = 211)	195 (92.4)	14 (6.6)	2 (1.0)
• Thailand (N = 353)	343 (97.2)	8 (2.3)	2 (0.6)
• Myanmar (N = 265)	240 (90.6)	21 (7.9)	4 (1.5)
The objective of the finger-prick CRP test is <u>not</u> clear to me (Q 6)			
• Intervention arms (N = 1,453)	64 (4.4)	502 (34.6)	887 (61.1)
• Control arm (N = 723)	46 (6.4)	249 (34.4)	428 (59.2)
• Thailand (N = 1,172)	58 (5.0)	444 (37.9)	670 (57.2)
• Myanmar (N = 1,004)	52 (5.2)	307 (30.6)	645 (64.2)
The finger-prick test for CRP is painless (Q 7)			
• Intervention arms (N = 1,450)	998 (68.8)	222 (15.3)	230 (15.9)
• Control arm (N = 708)	488 (68.9)	117 (16.5)	103 (14.6)
• Thailand (N = 1,170)	1,018 (87.0)	50 (4.3)	102 (8.7)
• Myanmar (N = 988)	468 (47.4)	289 (29.3)	231 (23.4)

It is <u>too much</u> effort to come to the health centre for the treatment that I received (Q 8)			
• Intervention arms (N = 1,461)	107 (7.3)	212 (14.5)	1,142 (78.2)
• Control arm (N = 732)	58 (7.9)	101 (13.8)	573 (78.3)
• Thailand (N = 1,173)	32 (2.7)	30 (2.6)	1,111 (94.7)
• Myanmar (N = 1,020)	133 (13.0)	283 (27.8)	604 (59.2)
Overall, I am satisfied with my care (Q 9)			
• Intervention arms (N = 1,464)	1,429 (97.6)	33 (2.3)	2 (0.1)
• Control arm (N = 730)	709 (97.1)	19 (2.6)	2 (0.3)
• Thailand (N = 1,173)	1,155 (98.5)	16 (1.4)	2 (0.2)
• Myanmar (N = 1,021)	983 (96.3)	36 (3.5)	2 (0.2)
Intervention arms only	**Yes**	**Do not know**	**No**
Did the health worker explain the finger-prick test results to you in a way that you understood? (Q 10)			
• **All (N = 1,450)**	821 (56.6)	299 (20.6)	330 (22.8)
• **Thailand (N = 774)**	435 (56.2)	194 (25.1)	145 (18.7)
• **Myanmar (n = 676)**	386 (57.1)	105 (15.5)	185 (27.4)
Would you like the health worker to use the finger-prick test for CRP again the next time you have an illness? (Q 14)			
• **All (N = 1,461)**	1,329 (91.0)	103 (7.1)	29 (2.0)
• **Thailand (N = 778)**	763 (98.1)	12 (1.5)	3 (0.4)
• **Myanmar (N 683)**	566 (82.9)	91 (13.3)	26 (3.8)
Did the health worker seem to base his/her treatment decision on the test results? (Q 12)			
• **All (N = 1,443)**	782 (54.2)	557 (38.6)	104 (7.2)
• **Thailand (N = 774)**	492 (63.6)	273 (35.3)	9 (1.2)
• **Myanmar (N = 669)**	290 (43.4)	284 (42.5)	95 (14.2)
***If yes:* Do you think the health worker relied too much, enough, or not enough on the test**	**Too much**	**Enough/ adequately**	**Not enough**

results when he/she made the treatment decision? (Q 12a)	192 (24.7)	580 (74.6)	6 (0.8)
• **All (N = 778)**	181 (36.9)	309 (62.9)	1 (0.2)
• **Thailand (N = 491)**	11 (3.8)	271 (94.4)	5 (1.7)
• **Myanmar (N = 287)**			
Did the finger-prick test make you feel more or less confident that antibiotics are needed / not needed for your illness? (Q 11)	**More confident**	**Neither more or less confident**	**Less confident**
• **All (N 1,432)**	1,201 (83.9)	225 (15.7)	6 (0.4)
• **Thailand (N = 776)**	738 (95.1)	37 (4.8)	1 (0.1)
• **Myanmar (N =656)**	463 (70.6)	188 (28.7)	5 (0.8)
Do you feel that the finger-prick test for CRP improves or worsens the quality of the care you receive? (Q 13)	**Improves**	**No difference, unsure**	**Worsens**
• **All (N = 1,446)**	1,281 (88.6)	165 (11.4)	0
• **Thailand (N = 778)**	753 (96.8)	25 (3.2)	0
• **Myanmar (N = 668)**	528 (79.0)	140 (21.0)	0

Table 4-6: RCT participants' and caregivers' opinions and attitudes towards the consultation and CRP POC testing, by country

4.4 Discussion

The CRP POC test did not affect the numbers of participants seeking additional healthcare or antibiotics during the study. Despite antibiotics being readily available in Thailand and Myanmar, few participants were taking antibiotics before self-presenting at the study sites. This suggests that primary care providers are situated early enough in patients' health-seeking pathways to be effective places for antimicrobial stewardship interventions. Participants in both the control and intervention arms reported high levels of satisfaction with their care and the CRP POC test; although understanding of the treatment and CRP test was limited in some.

More than half of our participants had sought healthcare before attending the study sites and a minority of these had received antibiotics. Thai participants were less likely to have sought care than their Myanmar counterparts, although reported antibiotic use was similar. Most antibiotics were

sourced from formal care providers such as clinics, hospitals and pharmacies, suggesting that these would be effective facilities to target with antimicrobial stewardship interventions. Although our Thai study population was limited to those who presented at government run PCUs, it is consistent with provincial and national surveys which found that most antibiotics were obtained from formal healthcare sources [75, 90].

Almost 15% of the participants sought care in addition to the study follow-up visits at day 5 and 14, and this was not affected by the CRP intervention. Thai participants continued to be less likely to seek care than Myanmar participants, as were those who had an antibiotic prescribed at enrolment. Seeking care was more likely if participants had higher self-reported symptom severity scores at enrolment. No difference was seen in re-attendances between the control and intervention arms as in other trials of community based CRP POC testing from Viet Nam and Europe [149, 152-154].

Only 4.3% of the participants sourced their own antibiotics during the study; this was not affected by their study arm or whether they were prescribed an antibiotic at enrolment. These low levels of external antibiotic use are encouraging for an intervention that can optimise antibiotic use, especially coming from a context where antibiotics are freely available for purchase. There is little data available from other studies about the effect of CRP POC testing on sourcing additional antibiotics or healthcare from other facilities. A RCT on CRP testing for RTIs in the Netherlands found that more participants used their delayed antibiotic prescription in the 28 days after enrolment in the control arm compared to the CRP intervention arm [152].

Higher levels of urine antibiotic activity were found at enrolment compared to reported antibiotic use, similar to studies from Cambodia and Laos [206, 211]. This may be due to participants underreporting antibiotic use, a lack of awareness of antibiotic use (i.e. confusion with other medication) or environmental exposure [206-208, 212]. False positives may have been caused by other agents with antibacterial activity such as cranberry juice [211]. False negatives may be due to non-adherence to the antibiotics, non-renal excretion of antibiotics, freezing and thawing of urine

samples, or a lack of sensitivity of the test caused by only using one reference organism [206, 207, 209, 211]. Amoxicillin, the most commonly prescribed antibiotic, has a faster excretion time so it is possible that we may have underestimated its use [207, 209, 211].

Participants' satisfaction levels with their treatment and CRP testing were high and over 80% said that they agreed with their antibiotic treatment decisions, as half of our participants were aged less than 12 years old, this adds to the limited data on acceptability of CRP testing in children. The CRP intervention did not affect participants' consultation experience scores, understanding or agreement with treatment; however Thai participants scored higher than Myanmar participants for these variables. The satisfaction levels suggest that CRP POC testing would be acceptable to participants or might mean that a different test based intervention may be accepted. High levels of patient satisfaction have been reported in other studies of CRP POC testing [72, 149, 152, 154]. The vast majority of participants in the intervention arms felt that the CRP test improved their quality of care, increased their confidence in the antibiotic prescribing decisions and would support its use in the future, consistent with the healthcare workers' opinions explored in Chapter 3. These findings are also consistent with semi structured interviews held with our study participants who felt that CRP POC testing represented better care than clinical assessment alone. Many considered it to be a 'comprehensive' blood test, and this could raise a concern regarding over-interpretation of the test results as a clean bill of health [84, 189].

Our participants' understanding of their treatment and CRP testing could be improved. Participants who sought additional care during the study reported less understanding of their treatment, although this did not translate through to seeking antibiotics. It is intuitive that improving participants' understanding of an intervention would support its implementation and long-term use. This is particularly important if participants were not prescribed an antibiotic and disagreed with that decision as they were more likely to seek healthcare and antibiotics elsewhere. Increasing healthcare workers' understanding then training them to use enhanced communication or shared decision

making skills to discuss the CRP results and management plan with the patients may support the effect of CRP testing. However, more research is required to confirm this and the effects on consultation times [149, 150, 159, 213-216].

The CRP intervention led to a significant reduction in antibiotic prescriptions in Myanmar but not in Thailand. This difference does not seem to be driven by participants' opinions of the intervention as those from Myanmar had lower consultation experience scores, understanding of the treatment and agreement with their treatment compared to Thai participants. Myanmar participants were more likely to seek additional care during the study which could be perceived as rejection or dissatisfaction with the intervention. The vast majority of CRP RCTs have been conducted in single countries, so comparisons of the impact of CRP POC testing between countries are limited. One exception is Little's RCT which was conducted in six European countries, however the effect or acceptability in each country was not reported [150].

Another area that warrants further investigation is the effect of CRP testing on long-term antibiotic use and health-seeking behaviour. While no effects were seen during our study period of 2 weeks we cannot comment on the long-term effects. Data on the long-term effects of CRP testing are scarce [205].

4.4.1 Strengths and Limitations

Our study gives valuable insight into the effects of CRP testing on participants' health-seeking behaviour and sourcing of antibiotics outside of the study. The urine antibiotic activity tests help to validate participant-reported antibiotic use. Participants' and caregivers' opinions and attitudes towards CRP testing and their management helps to evaluate the CRP intervention, its acceptability and potential barriers to its implementation. As half of the participants were aged less than 12 years this adds to the limited data on the acceptability of CRP testing in children, as well as data for LMICs.

There are however some important limitations to consider. The participants' views towards CRP testing were collected through closed questioning which does not give as comprehensive or nuanced data as interviews. It is also possible that participants will have tried to give the correct or desirable answer, especially given the cultural norms in northern Thailand where it is unusual to express negative opinions. The questions were asked by the research nurses who recruited and followed up the patients for the main RCT; more honest opinions may have been expressed to independent researchers.

The urine antibiotic activity was not assessed in all participants in day 0 so may not reflect background antibiotic use. Only one reference organism was used which could lower the sensitivity and specificity of the test.

4.4.2 Conclusions

CRP POC testing did not affect whether participants sought healthcare or antibiotics from other sources, in a setting where multiple options are available for both. High levels of satisfaction were expressed in both arms and participants reported positive views towards CRP testing and its use in the future. If CRP testing is to be rolled out then further work is needed to assess the role of communication skills to support CRP testing and to evaluate the long-term effects of CRP testing on health-seeking behaviour.

Chapter 5 Final Reflections and Future Work

5.1 Summary of the Key Findings

The overall aim of this thesis was to evaluate if CRP testing could optimise antibiotic use in Thai primary care. The RCT demonstrated that CRP POC testing significantly reduced antibiotic prescribing for patients attending with a fever or history of fever in Thailand and Myanmar, without affecting clinical outcomes, although the reduction was non-significant when Thai participants were analysed separately. Alongside reduction in overall prescribing, in both countries and age groups CRP testing resulted in more participants with high CRP levels receiving antibiotics.

In both countries antibiotic prescribing in the control arms was lower than in the baseline antibiotic reviews. The reduced prescribing in the control arms may have been affected by the individual RCT design, the Hawthorne Effect and circumstances external to the study. In Thailand, antibiotic prescribing in the control arm continued to reduce during the study period. There is some indication that overall antibiotic prescribing in routine care in the PCUs was starting to fall as shown in Chapter 2, and this is consistent with the literature review in Chapter 1 and the aims of Thailand's NSP-AMR. Healthcare workers' concordance with the CRP results was similar between the two countries, so the non-significant reduction in Thailand may have been due to the lower control arm antibiotic prescribing in Thailand compared to Myanmar, which would make any further reductions in antibiotic prescribing harder to achieve. This all enforces the notion that the broader context, including factors such as access and availability of antibiotics will affect the impact of CRP POC testing beyond the inherent performance of the tests themselves.

Acceptance of CRP testing appears to be high in both countries. The difference in impact of the CRP tests between the countries does not seem to be explained by the patients' or healthcare workers' opinions (Chapters 3 and 4). Thai participants sought less care outside of the study which could indicate more acceptance of the CRP test and their treatment. They also had higher consultation

experience scores compared to Myanmar participants which goes against the notion of them being more expectant or demanding of antibiotics than their Myanmar counterparts. Most healthcare workers in both countries reported satisfaction with the CRP test and supported its introduction. Thai healthcare workers felt that their patients' trust and compliance was improved by the CRP test more than those in Myanmar. Pragmatic guidance was given to the healthcare workers and they were allowed to overrule the CRP result if they had clinical concerns about the patient; bearing this in mind 78% concordance with the CRP results is relatively high.

The CRP intervention did not affect treatment-seeking behaviour; only a minority of patients sought additional healthcare and antibiotics during the study. Re-consultations at the study site were also rare. These findings would be particularly encouraging if a larger effect on antibiotic prescribing was seen. Primary care clinics in both countries appear to be appropriate places to target interventions to optimise antibiotic use as few participants were taking antibiotics before attendance and the majority sought antibiotics from formal care providers (Chapter 4).

Despite the modest reduction in overall antibiotic prescribing, CRP testing did help to target antibiotic use (Chapter 3). Those with a high CRP result were more likely to receive an antibiotic and those with a low CRP were less likely to receive an antibiotic. When Thai patients were analysed alone this effect continued in those with a high CRP result. In this way, CRP testing could help to target antibiotics to those in need more than restrictive antibiotic policies (such as setting targets for < 20% antibiotics for acute bronchitis). Despite concerns about AMR, it is important to maintain access to antibiotics to patients that are likely to genuinely benefit from them, as well as ensuring that antimicrobial stewardship interventions do not adversely affect clinical outcomes. Any impact on health–seeking behaviour also needs to be monitored, and this is especially important in settings where antibiotics are available from multiple sources. In that respect, interventions that afford patients a higher degree of confidence in a healthcare worker's decision not to prescribe an antibiotic are important.

There is room to optimise antibiotic prescribing in Thai primary care (Chapter 2), however the results of the RCT do not support the widespread introduction of CRP POC testing for all febrile patients (Chapter 3). It is possible that a more targeted approach would have a greater impact on antibiotic prescribing, for example certain conditions could be targeted or CRP tests could be conducted in a subgroup of patients identified through a clinical score or algorithm. This could increase the pre-test probability that CRP testing will affect the management plan. It may also be better received by healthcare workers and be more achievable in routine care. CRP testing may be more effective if it was combined with interventions such as advanced communication skills for healthcare workers. This could help improve patients' understanding of the test and their treatment. Further training and peer support groups for healthcare workers could help to increase their understanding and support for CRP testing. Ultimately, wide scale acceptance of CRP testing and fulfilling its potential impact on prescribing is only likely to be achieved if and when this is incorporated into national guidelines.

High levels of antibiotic prescribing for sore throats were highlighted in Chapter 2. The prevalence of GAS was low in the RCT (Chapter 3) and no complications were seen which implies that antibiotic use could be reduced, however knowing who needs antibiotics remains challenging. The correlations between the Centor and FeverPAIN clinical scores, and CRP levels with GAS identification on the throat swabs were poor. Concordance with the CRP results and antibiotic prescriptions was lower in patients with a sore throat which may suggest that healthcare workers were uncomfortable to reduce their prescribing for this patient group (Chapter 3).

5.2 Improvements and Further Work

The study's strengths and limitations are discussed in detail in each chapter. However, there are some things in particular that I have learnt over the course of this thesis and looking back would try to do differently. A cluster RCT could have been a better study design to evaluate the impact of CRP testing, reducing the likelihood of contamination between the study arms. This design may give a more accurate reflection of CRP's possible impact. However, a cluster RCT would be more expensive

and require more resources including personnel, which were the main reasons why it was not chosen originally. Securing enough funding to generate the best possible evidence can be challenging.

The nested GAS study could be improved by increasing the sample size, prospectively calculating the clinical scores and including a healthy control group and/or serology in order to identify those with GAS carriage rather than active infection. The follow-up period could be extended and complications of sore throats could be specifically screened for. This study design would allow current clinical scores including the Centor score to be validated and modified if needed for the Thai population.

Extensive cost-effectiveness analyses are needed to consider whether wide scale use of CRP POC testing is appropriate. These analyses should incorporate the cost of AMR which is one of the main motivating factors for interventions to optimise antibiotic use. Capturing the costs averted by reduced antibiotic use on the development of AMR is challenging, but early attempts have shown that this could bring real savings per course of antibiotic. As an illustration of what future such cost-effectiveness analyses might capture, **Error! Reference source not found.** shows the minimal a bsolute reduction in prescribing across a range of costs for the CRP test that would be required for the CRP tests to be cost-effective, when considering the direct costs of the CRP test and antibiotics, and the societal costs of AMR associated with the consumption of the antibiotic. From this societal perspective, use of a CRP test costing 1 USD with an absolute reduction of antibiotic use of 25% would imply that CRP testing is cost-effective, whereas for a higher test cost and lower reduction in antibiotic use such as was the case in the CRP trial (Chapter 3), use of the test would not be cost-effective.

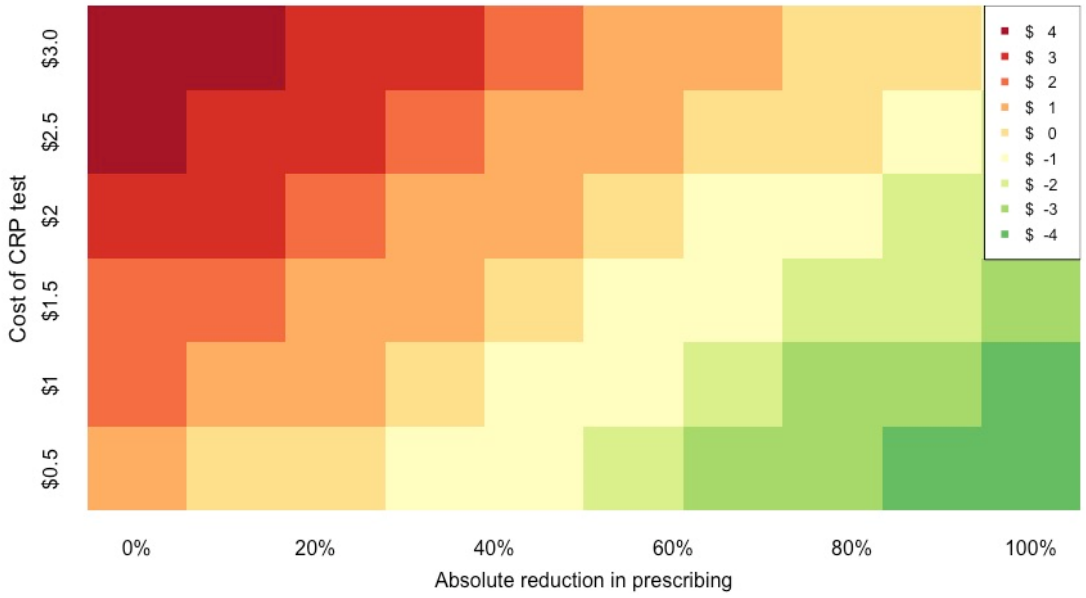


Figure 5-1: The minimal absolute reduction in antibiotic prescribing required for differing costs of the CRP test to achieve cost-effectiveness considering the cost of AMR per course of narrow spectrum penicillin

NB The negative values in the legend represent overall net gains when considering the cost of a course of narrow spectrum penicillin, AMR and the CRP test.

The main research questions arising from this thesis are:

- How do you identify which sore throat patients need antibiotics?
- How can healthcare workers' and patients' understanding of CRP testing and the need, or lack of need for antibiotics be improved?
- Would CRP testing be more effective in targeted conditions or high risk patients?
- How does context affect the impact of CRP POC testing?
- Is CRP POC testing cost-effective in Thai primary care?

5.3 Final Reflections

5.3.1 Design, Implementation and Analysis of the Studies

When I started this PhD I was a GP with little research experience. Being involved in these studies has helped me develop my skills as a researcher and given me opportunities I hadn't anticipated. Through spending time with the local primary care doctors I was able to see the range of challenges and responsibilities they had (e.g. running TB clinics, monthly prison visits, providing training for

community health volunteers, overseeing the nurses who ran the PCUs outside of the hospital etc.) in addition to the GP role I was used to in the UK. We had interesting discussions about the health needs of the local community and the potential research questions we could study together by establishing a collaboration with MORU. These discussions made me aware of the routine electronic reporting they are required to do for each patient visit. This provided an exciting opportunity to conduct a review of antibiotic use in the PCUs across the district, rather than having to rely on a manual review of paper based records which are kept in each PCU (Chapter 2). I led the design of this study, drafted the protocol, supported data collection and analysed the data with help from YL (principal investigator), PW (data manager), MM (statistician) and the other co-authors. The antibiotic review gave me my first experiences of using STATA, cleaning, managing and analysing large data sets. This was also the first community based research carried out by MORU in Chiangrai.

I was heavily involved in the design of the CRP RCT (Chapters 3 and 4) with another PhD student (TA) and the principle investigator (YL). Together we drafted the protocol and designed the study with support from the wider team. I was responsible for the Thai site, recruited the research nurses and facilitated their training. Aside from a period of maternity leave I oversaw the day to day running of the Thai sites. TA led the analysis of the primary outcome and wrote the first manuscript draft [146] but I played a key role in the data cleaning, analysis and interpretation of the results. I have adapted, re-done and added to these analyses for Chapter 3 of this thesis. I led the analysis of the patients' experiences of CRP testing (Chapter 4) and the role of CRP testing in patients presenting with a sore throat (Chapter 3).

5.3.2 Lessons Learnt

In addition to the research skills mentioned above I've seen the importance and value of integrating healthcare and research. I've learnt not to make assumptions or believe everything that is held as common knowledge, such as the notion that everyone who sees a doctor in these environments gets an antibiotic. The lower than expected prescribing levels in the control arm of the CRP RCT highlights

the need to have good quality baseline data. The policies surrounding AMR and antibiotic use in Thailand changed dramatically during the course of my PhD. Conducting research in such dynamic settings can be challenging but the Thai interest in AMR makes it an exciting place to work, where successful interventions may well be supported and rolled out in the future.

As a GP I understand that optimising antibiotic use is complex and challenging, undertaking this PhD in Thailand has made me appreciate this even more. Deciding if an antibiotic is being used optimally or not is difficult, and often much of the data needed to make an evidence-based judgement is not available. Many factors are involved and can change over time including individual patient's risks, the local context, policies and antibiotic resistance levels. Changing behaviour is difficult and can take time.

During this work I have increasingly understood the importance of assessing clinical outcomes and changes to health-seeking behaviour alongside antibiotic use. In addition to optimising antibiotic usage, we need to look for and evaluate any unintended consequences of interventions or policy changes.

5.3.3 Ethical Aspects of Conducting Research

I have reflected a lot on the ethical aspects of conducting research in LMICs. I have been involved in an embedded ethics case study in Chiangrai, although the results of this work are beyond the scope of this thesis and therefore have not been included. Ethical practice underpins all aspects of clinical and academic work. Ethical principles can be a helpful driver of research and health improvement, especially where resources are scarce and simple interventions can produce significant health gains. Yet in LMICs individual participants may be more vulnerable in their day to day lives compared to those in HICs. These vulnerabilities can be exacerbated through joining research studies or new vulnerabilities can be formed. It is important that research studies are conducted to address the needs of these communities but researchers and research ethics committees need to be aware of the difficulties faced by local communities and ensure that individual participants' circumstances are

taken into account. Studies should be designed to minimise research burdens and maximise benefits. Support and resources should be in place to address any unexpected issues that occur during a study.

Some of the ethical challenges faced during this thesis related the enrolment of children and those with low health and research understanding. Enrolling children into the CRP RCT raised questions about who was best placed to give "parental" consent for them to join (alongside assent if they were old enough). Many children in Chiangrai live with and are cared for by grandparents while their parents work away in another city. If you strictly follow international guidelines then a parent or legal guardian should give parental consent to join research studies but in Thailand like many other parts of the world these guardian roles are often not formalised. Locally and culturally, grandparents or other relatives would be considered as guardians and in many cases could arguably be able to give consent for medical treatment or for children to join research studies. It was challenging for the research nurses to explain the RCT to people who were unfamiliar with research and often had low levels of education. We practised doing role plays, explaining the study and checking participants' understanding to try and support them in this.

5.4 Conclusions

This thesis evaluated the impact of CRP POC testing to optimise antibiotic use and explored the current use of antibiotics within PCUs and the community in northern Thailand. CRP POC testing resulted in a modest reduction of antibiotic prescriptions using a CRP cut off of 40mg/L for participants with a fever in Thailand and Myanmar, however a non-significant reduction was found when Thai participants were considered separately. Despite this, CRP testing helped to ensure participants with a high CRP received antibiotics in Thailand, thus could help to target antibiotics to those who need them.

Antibiotics appear to be overprescribed for sore throat infections, despite an adapted Centor score being recommended in national RDU guidelines. Greater understanding is required of who needs

antibiotics and how they can be identified in this setting. The correlation between CRP results, the Centor and FeverPAIN clinical scores, and the identification of GAS on throat swabs in our patient cohort was poor.

Community antibiotic guidelines need to be developed for common infections using local data. Healthcare workers are well placed to optimise antibiotic use in the community and POC tests seem to be welcomed by healthcare workers and patients alike. PCUs are a good place to target community-based interventions due to their well-established infrastructure, electronic reporting of consultations, large number of patients and early position in people's health-seeking pathways. It seems likely that multi-faceted approaches are required to optimise antibiotic use in the community.

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Appendices

Appendix 1: Antibiotic Search List for the Retrospective Antibiotic Review

- Amoxicillin
- Cefixime
- Ceftriaxone
- Cephalexin
- Ciprofloxacin
- Co-amoxiclav/ Augmentin
- Co-trimoxazole/ Bactrim
- Dicloxacillin
- Doxycycline
- Erythromycin
- Metronidazole
- Norfloxacin
- Penicillin V
- Roxithromycin
- TC mycin/ tetracycline

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Appendix 2: ICD-10 Codes for Infection Used for the Retrospective Antibiotic Review

ICD-10 Code	Description	Excluded ICD-10 codes (number)
A00 - B99	Certain infectious and parasitic diseases	A15 (167), A16 (29), A18 (7), A31.9 (1), B18 (18), B24 (85), B85 (671)
G00 - 07	Inflammatory diseases of the central nervous system	-
H00 - 01	Hordeolum, chalazion and other inflammation of the eyelid	H01.1 (35)
H05.0	Acute inflammation of orbit	-
H10	Conjunctivitis	-
H60 - H70	Otitis externa, otitis media and mastoiditis	H61 (112)
H72 - 73	Perforation and other disorders of the tympanic membrane	H73.9 (2)
J00 - 43	Respiratory tract infections	J30 (150), J31 (8), J33 (1), J35.1 (1)
J47	Bronchiectasis	-
K05	Gingivitis and periodontal diseases	Exclude all (9,469)
K11 - 12	Diseases of salivary glands, stomatitis and related lesions	K11.1 (3), K11.88 (2), K11.9 (1), K12.0 (682), K12.1 (716)
K35 - 37	Appendicitis	-
K57	Diverticulitis	K57 (2)
K61	Abscess of anal and rectal regions	-
K81	Cholecystitis	-
K83 - 85	Cholangitis and pancreatitis	-
L00 - 08	Infections of the skin and subcutaneous tissue	-
L20 - 22	Dermatitis	L20 (23), L21 (19), L22 (5)
L30.3	Infective dermatitis	-
L70 - 73.2	Acne, rosacea follicular cysts and follicular disorders	-
M00 - 03	Infectious arthropathies	M0013 (1), M0023 (1), M0167 (1), M020 (1)

M60	Myositis	M60.1-M6099 (3,604)
N10 - 11	Tubulo-interstitial nephritis	-
N30	Cystitis	-
N34	Urethritis and urethral syndrome	-
N39.0	Urinary tract infection, site not specified	-
N41	Inflammatory diseases of prostate	-
N45	Orchitis and epididymitis	-
N48 - 49	Other disorders of male genital organs	N48.9 (1)
N61	Inflammatory disorders of breast	-
N70 - 76	Inflammatory diseases of female pelvic organs	-
O08.0	Genital tract and pelvic infection following abortion and ectopic and molar pregnancy	-
O23	Infections of genitourinary tract in pregnancy	-
O85 - 86	Puerperal sepsis and other puerperal infections	-
P35 - 9	Infections specific to the perinatal period	-
R05	Cough	-
R11	Nausea and vomiting	-
R30	Pain associated with micturition	-
R36	Urethral discharge	-
R50	Fever	-

Table A- 1: ICD-10 codes for infection used for the inclusion criteria for the retrospective antibiotic review

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Appendix 3: Case Record Forms for the C-Reactive Protein Trial

3A: Screening Form

SCREENING DATE	|__|__|-|__|__|__|-2016 (e.g. *01-JAN-2016*)			
INCLUSION / EXCLUSION CRITERIA				
Inclusion Criteria (all should be "Yes")		**YES**	**NO**	
1	Aged ≥ 1 year old	○	○	
2	Tympanic temperature >37.5°c (or axillary temperature >37˚C) or history of fever ≤ 14 days	○	○	
3	Written informed consent (by the parent/guardian in the case of children)	○	○	
Exclusion Criteria (all should be "No" or "N/A")		**YES**	**NO**	**NA**
1	Signs of any bleeding*	○	○	
2	The main complaint is trauma and/or injury	○	○	
3	Any presenting symptom present for more than 14 days	○	○	
4	Patients requires referral to a higher level facility**	○	○	
5	Malaria rapid test positive (if done)	○	○	○
6	Suspicion of tuberculosis (TB)***	○	○	
7	Suspicion of Urinary Tract Infection (UTI)****	○	○	
8	Suspicion of skin / dental infection and/or abscess*****	○	○	
9	Past/current neoplastic disease	○	○	○
10	Not able to comply with the Day 5 (+/-1 day) of the follow-up	○	○	

*** Signs of any bleeding: Any of these symptoms**

- ✓ Otorrhagia
- ✓ Hematemesis
- ✓ Hemoptysis
- ✓ Hemorrhagic petechiae
- ✓ Hematuria
- ✓ Bloody diarrhea

**** Presence of any of these symptoms**

- ✓ Impaired consciousness
- ✓ Inability to take oral medication
- ✓ Convulsions

***** Suspicion of Tuberculosis (TB)**

- ✓ Long-lasting cough or dyspnoea, chest pain, or hemoptysis (>2 weeks) with weight loss, night sweats, and weakness
- ✓ Personal exposure to TB with incomplete treatment (less than 6 months of treatment)
- ✓ Active TB among member(s) of the households and or relatives.

****** Suspicion of Urinary Tract Infection (UTI)**

- ✓ Dysuria (discomfort when passing urine)
- ✓ Urine Smelly
- ✓ High frequency of urination

******* Suspicion of skin/dental and soft tissue infections / abscess**

- ✓ Erythematous eruption / Erysipelas
- ✓ Dental / skin abscess

ELIGIBILITY

CONSENT DATE |__|__|-|__|__|__|-2016 *(e.g. 01-JAN-2016)*

Is the subject eligible for the study? ○ YES ○ NO

Is the subject enrolled into study? ○ YES ○ NO

If **ENROLLED**, Subject No. |__|__|__|__|__|-|__|-|__|__|__|__|

*Provide the **subject enrollment number** and **randomization arm** from the randomization envelope.*

If **NOT ENROLLED**, please provide the reason(s) other than exclusion criteria:

_____

_____

_____
RANDOMIZATION
RANDOMIZATION DATE |__|__|-|__|__|__|-2016 *(e.g. 01-JAN-2016)*
RANDOMIZATION ARM: ○ Group A: Low cut-off ○ Group B: High cut-off ○ Group C: Controls

CRF completed by _____ (initials) Date I__I__I-I__I__I__I- 2016 *(e.g. 01-JAN-2016)*

CASE REPORT FORM

Version 2.0 (20-June-2016)

THE IMPACT OF CRP TESTING ON ANTIBIOTIC PRESCRIPTION IN FEBRILE PATIENTS ATTENDING PRIMARY CARE IN LOW RESOURCES SETTINGS

Subject Number: |__|__|__|__|__|-|__|-|__|__|__|__|
(*e.g. TH001-A-001*)

Subject Initials: |__|__|__|

Randomization Arm: ○ Group A ○ Group B ○ Group C

DATE OF VISIT |__|__|-|__|__|__|-2016 *(e.g. 01-JAN-2016)*		
1.	**Who is the person answering the questions?** ○Patient ○Mother ○Father ○Other_____	
DEMOGRAPHICS AT BASELINE		
2.	Date of birth |__|__|-|__|__|__|-|__|__|__|__| *(e.g. 01-JAN-2016)* Or Age *(if DOB not known)* |__|__|years, |__|__|months old.	
3.	Sex	○ Male ○ Female
4.	How did you travel to this facility?	○ Walking ○ Bicycle ○ Motorcycle/Tricycle ○ Car/Tractor/Four-wheeler ○ Taxi ○ Bus ○ Other _____
5.	How long does it take you to travel to this facility?	○ < 30 minutes ○ 30-60 minutes ○ 1-2 hours ○ >2 hours ○ Not applicable
MEDICAL HISTORY AT BASELINE		
6.	**6.1 Do you have a chronic disease?** ○ Yes ○ No ○ Do not know ○ Not willing to answer	
	6.2 If **Yes**, please fill out: ☐ HIV ☐ Hepatitis B / C ☐ Diabetes ☐ Cirrhosis ☐ Pregnant: gestation _____weeks ☐Other _____	

MEDICATION HISTORY AT BASELINE

7. **7.1 Have you sought any medical care in the last 14 days for this illness?**
○ Yes ○ No ○ Do not know

7.2 If **Yes**, please fill out where:
☐ This facility ☐ Another Clinic ☐ Pharmacy ☐ Hospital
☐ Community healthcare worker ☐ Natural healer ☐ Other_____

8. **8.1 Have you taken any medication in the last 14 days?** ○ Yes ○ No ○ Do not know

8.2 If **Yes**, please fill out:
☐ Antibiotic ☐ Antimalarial ☐ Paracetamol ☐ Anti-inflammatory ☐ Unknown
☐ Other _____

8.3 If **Yes**, how much did you spend to buy the **medication**? ○ Do not know
|__|__|__|__| Baht

If the patient has taken any ANTIBIOTICS in the last 14 days**,** please fill out the **MEDICATION FORM**

SYMPTOM QUESTIONNAIRE AT BASELINE (within the last 14 days)
(#Grading 1=mild, 2=moderate, 3=severe, 4=life-threatening).

Symptoms	Yes	No	NK	If Yes, #Grading (1-4)	If Yes, Duration (days)	Symptoms	Yes	No	NK	If Yes, #Grading (1-4)	If Yes, Duration (days)
1. Fever	○	○	○	|__|	|__|__|	10. Jaundice	○	○	○	|__|	|__|__|
2. Headache	○	○	○	|__|	|__|__|	11. Abdominal pain	○	○	○	|__|	|__|__|
3. Confusion	○	○	○	|__|	|__|__|	12. Loss of appetite	○	○	○	|__|	|__|__|
4. Earache	○	○	○	|__|	|__|__|	13. Diarrhoea	○	○	○	|__|	|__|__|
5. Sore throat	○	○	○	|__|	|__|__|	14. Nausea / vomiting	○	○	○	|__|	|__|__|
6. Difficulty breathing	○	○	○	|__|	|__|__|	15. Skin eruption / rash	○	○	○	|__|	|__|__|
7. Chest pain	○	○	○	|__|	|__|__|	16. Muscle pain	○	○	○	|__|	|__|__|
8. Cough	○	○	○	|__|	|__|__|	17. Weakness, tiredness	○	○	○	|__|	|__|__|
9. Runny nose	○	○	○	|__|	|__|__|	18. Others _____	○	○	○	|__|	|__|__|

FOR PATIENTS IN GROUP A or GROUP B: **CRP Value** |__|__|__| mg/L

VITAL SIGNS AT BASELINE **Weight** |__|__|__|.|__| **kg** **Height** |__|__|__| **cm**

1. Tympanic temperature |__|__|.|__| °C Axillary temperature (*if tympanic is not possible*) |__|__|.|__| °C	3. Pulse rate |__|__|__| beats per minute
2. Respiratory rate |__|__| breaths per minute	4. Blood pressure |__|__|__|/|__|__|__|mmHg *(eg.120/080)*

Abnormal lymph nodes? ○ Yes ○ No ○ Not examined

If **Yes**, please specify the location of the abnormal lymph nodes:

☐ Cervical & occipital ☐ Hepatomegaly

☐ Axillary & pectoral ☐ Splenomegaly

☐ Inguinal & femoral

Body system	Normal	Abnormal	Not examined	Body system	Normal	Abnormal	Not examined
1. Head	○	○	○	7. Respiratory System	○	○	○
2. Eyes	○	○	○	8. Gastrointestinal System	○	○	○
3. Ears	○	○	○	9. Eschar	○	○	○
4. Nose	○	○	○	10. Other 1: _____ _____	○	○	○
5. Throat	○	○	○	11. Other 2: _____ _____	○	○	○
6. Cardiovascular System	○	○	○	12. Other 3: _____ _____	○	○	○

Specify if abnormal:

_____

_____

CLINICAL DIAGNOSIS		
DRUG PRESCRIPTION AT BASELINE ○ Yes ○ No		
Antibiotic prescribed?	**Paracetamol prescribed?**	**Anti-inflammatory prescribed?**
○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
If the patient has been prescribed any ANTIBIOTICS, please fill out the "MEDICATION FORM"		
FOR PATIENTS IN GROUP A or GROUP B: Has the patient been shown the video? ○ Yes ○ No, please specify why _____ ○ NA		

DAY 5 FOLLOW-UP

1. **1.1 Did the patient have Day-5 follow-up?** ○ Yes ○ No

   1.2 If **Yes** ○ Face-to-face interview

   ○ Telephone interview if Yes, please specify why: _____

   Date |__|__|-|__|__|__|__|-2016 *(e.g. 01-JAN-2016)*

   1.3 If **No**, please specify why:

   ○ Admitted to hospital (please complete SAE report) ○ Did not attend & unable to contact

   ○ Withdrawn ○ Died ○ Other (specify) _____

2. **Who is the person answering the questions?** ○ Patient ○ Mother ○ Father

   ○ Other_____

MEDICATION HISTORY AT DAY 5

3. **3.1 Have you sought any medical care since Day 0?** ○ Yes ○ No

   3.2 If **Yes**, where?

   ☐ This facility ☐ Another clinic ☐ Pharmacy ☐ Hospital

   ☐ Community healthcare worker ☐ Natural healer ☐ Other _____

4. **4.1 Have you taken any new medication apart the ones prescribed to you on Day 0 or at any unscheduled visits here?** ○ Yes ○ No

   4.2 If **Yes**, please fill out:

   ☐ Antibiotic ☐ Antimalarial ☐ Paracetamol ☐ Anti-inflammatory ☐ Unknown

   ☐ Other _____

   4.3 If **you have taken a new medication**, how much did you spend on the medication?

   ○ Do not know

   |__|__|__|__|__| Baht

   If the patient has started any NEW antibiotics since the last visit, please fill out the "MEDICATION FORM"

Has your illness resolved since the first time you consulted the health facility? ○ **Yes** ○ **No**

If **Yes**, what was the total duration of your illness? |__|__| Days

TEMPERATURE MEASUREMENT AT DAY 5

Tympanic temperature |__|__|.|__| °C Axillary temperature if tympanic is not possible |__|__|.|__| °C

FOR ALL PATIENTS: **CRP Value** |__|__|__| mg/L

Did the patient meet the health worker? ○ **Yes** ○ **No**

- ✓ If the illness has <u>not</u> resolved
- ✓ If tympanic temperature >37.5°C (or axillary temperature >37˚C)
- ✓ If CRP ≥ 50mg/L for *children* or ≥ 100mg/L in *adults*
- ✓ If the patient met the health worker

1. Fill out the symptom questionnaire if **at least one** of the conditions is met.
2. If the patient met the health worker, fill out the vital signs, physical examination and the medication form using the health facility form.

SYMPTOM QUESTIONNAIRE AT DAY 5 *(#Grading 1=mild, 2=moderate, 3=severe, 4=life-threatening).*

Symptoms	Yes	No	NK	If Yes, # Grading (1-4)	If Yes, Duration (days)	Symptoms	Yes	No	NK	If Yes, # Grading (1-4)	If Yes, Duration (days)
1. Fever	○	○	○	|__|	|__|__|	10. Jaundice	○	○	○	|__|	|__|__|
2. Headache	○	○	○	|__|	|__|__|	11. Abdominal pain	○	○	○	|__|	|__|__|
3. Confusion	○	○	○	|__|	|__|__|	12. Loss of appetite	○	○	○	|__|	|__|__|
4. Earache	○	○	○	|__|	|__|__|	13. Diarrhoea	○	○	○	|__|	|__|__|
5. Sore throat	○	○	○	|__|	|__|__|	14. Nausea / vomiting	○	○	○	|__|	|__|__|
6. Difficulty breathing	○	○	○	|__|	|__|__|	15. Skin eruption / rash	○	○	○	|__|	|__|__|
7. Chest pain	○	○	○	|__|	|__|__|	16. Muscle pain	○	○	○	|__|	|__|__|
8. Cough	○	○	○	|__|	|__|__|	17. Weakness, tiredness	○	○	○	|__|	|__|__|

9. Runny nose	○	○	○	|__|	|__|__|	18. Others _____	|__|	|__|__|

VITAL SIGNS AT DAY 5	
1. Respiratory rate |__|__| breathes per minute	2. Pulse |__|__|__| beats per minute
3. Blood pressure *(eg.120/080)* |__|__|__|/|__|__|__| mmHg	
Abnormal lymph nodes? ○ Yes ○ No ○ Not examined If **Yes**, please specify the location of the abnormal lymph nodes:	☐ Cervical & occipital ☐ Axillary & pectoral ☐ Splenomegaly ☐ Hepatomegaly ☐ Inguinal & femoral

PHYSICAL EXAMINATION AT DAY 5

Body system	Normal	Abnormal	Not examined	Body system	Normal	Abnormal	Not examined
1. Head	○	○	○	7. Respiratory System	○	○	○
2. Eyes	○	○	○	8. Gastrointestinal System	○	○	○
3. Ears	○	○	○	9. Eschar	○	○	○
4. Nose	○	○	○	10. Other 1: _____	○	○	○
5. Throat	○	○	○	11. Other 2: _____	○	○	○
6. Cardiovascular System	○	○	○	12. Other 3: _____	○	○	○

Specify if abnormal:

_____

_____

_____

CLINICAL DIAGNOSIS

DRUG PRESCRIPTION TODAY – DAY 5	○ Yes	○ No

Antibiotic prescribed?	Paracetamol prescribed?	Anti-inflammatory prescribed?
○ Yes ○ No	○ Yes ○ No	○ Yes ○ No

If the patient has been prescribed any NEW antibiotics, please fill out the "MEDICATION FORM"

DAY 14 FOLLOW-UP

1.	**1.1 Did the patient have Day-14 follow-up?** ○ Yes ○ No
	1.2 If **Yes** ○ Face-to-face interview ○ Telephone interview if Yes, please specify why: _____ Date |__|__|-|__|__|__|__|-2016 *(e.g. 01-JAN-2016)*
	1.3 If **No**, please specify why: ○ Admitted to hospital (please complete SAE report) ○ Did not attend & unable to contact ○ Withdrawn ○ Died ○ Other (specify)_____
2.	**Who is answering the questions ?** ○ The patient ○ Mother ○ Father ○ Other _____

MEDICATION HISTORY AT DAY 14

3.	**3.1 Have you sought any medical care since the Day 5 visit?** ○ Yes ○ No
	3.2 If **Yes**, where? ☐ This setting ☐ Another clinic ☐ Pharmacy ☐ Hospital ☐ Community healthcare worker ☐ Natural healer ☐ Other _____
4.	**4.1 Have you taken any NEW medication since the Day 5 visit or any unscheduled visits here?** ○ Yes ○ No
	4.2 If **Yes**, please fill out: ☐ Antibiotic ☐ Antimalarial ☐ Paracetamol ☐ Anti-inflammatory ☐ Unknown ☐ Other _____
	4.3 If **Yes**, how much did you spend to buy the **medication**? ○ Do not know |__|__|__|__| Baht

If the patient has started any NEW antibiotics since the last visit, please fill out the "MEDICATION FORM"

Please fill out the "End dates" for any antibiotics recorded on the "MEDICATION FORM" (from D0-14)

Has your illness resolved since the first time you consulted the health facility? ○ **Yes** ○ **No**

If **Yes**, what was the total duration of your illness? |__|__| Days

TEMPERATURE MEASUREMENT AT DAY 14

Tympanic temperature |__|__|.|__| °C

Axillary temperature if tympanic is not possible |__|__|.|__| °C

Did the patient meet the health worker? ○ **Yes** ○ **No**

- ✓ If the illness has not resolved
- ✓ If tympanic temperature >37.5°C (or axillary temperature >37˚C)
- ✓ If CRP ≥ 50mg/L for *children* or ≥ 100mg/L in *adults*
- ✓ If the patient met the health worker

1. Fill out the symptom questionnaire if **at least one** of the conditions is met.
2. If the patient met the health worker, fill out the vital signs, physical examination and the medication form using the health facility form.

SYMPTOM QUESTIONNAIRE AT DAY 14 *(#Grading 1=mild, 2=moderate, 3=severe, 4=life-threatening).*

Symptoms	Yes	No	NK	If Yes, #Grading (1-4)	If Yes, Duration (DAYS)	Symptoms	Yes	No	NK	If Yes, #Grading (1-4)	If Yes, Duration (DAYS)
1. Fever	○	○	○	|__|	|__|__|	10. Jaundice	○	○	○	|__|	|__|__|
2. Headache	○	○	○	|__|	|__|__|	11. Abdominal pain	○	○	○	|__|	|__|__|
3. Confusion	○	○	○	|__|	|__|__|	12. Loss of appetite	○	○	○	|__|	|__|__|
4. Earache	○	○	○	|__|	|__|__|	13. Diarrhoea	○	○	○	|__|	|__|__|
5. Sore throat	○	○	○	|__|	|__|__|	14. Nausea / vomiting	○	○	○	|__|	|__|__|
6. Difficulty breathing	○	○	○	|__|	|__|__|	15. Skin eruption / rash	○	○	○	|__|	|__|__|
7. Chest pain	○	○	○	|__|	|__|__|	16. Muscle pain	○	○	○	|__|	|__|__|
8. Cough	○	○	○	|__|	|__|__|	17. Weakness, tiredness	○	○	○	|__|	|__|__|
9. Runny nose	○	○	○	|__|	|__|__|	18. Others _____				|__|	|__|__|

VITAL SIGNS AT DAY 14	
1. Respiratory rate |__|__| breathes per minute	2. Pulse |__|__|__| beats per minute
3. Blood pressure *(eg.120/080)* |__|__|__|/|__|__|__| mmHg	
Abnormal lymph nodes? ◯ Yes ◯ No ◯ Not examined If **Yes**, please specify the location of the abnormal lymph nodes:	☐ Cervical & occipital ☐ Axillary & pectoral ☐ Splenomegaly ☐ Hepatomegaly ☐ Inguinal & femoral

PHYSICAL EXAMINATION AT DAY 14

Body system	Normal	Abnormal	Not examined	Body system	Normal	Abnormal	Not examined
1. Head	◯	◯	◯	7. Respiratory System	◯	◯	◯
2. Eyes	◯	◯	◯	8. Gastrointestinal System	◯	◯	◯
3. Ears	◯	◯	◯	9. Eschar	◯	◯	◯
4. Nose	◯	◯	◯	10. Other 1: _____	◯	◯	◯
5. Throat	◯	◯	◯	11. Other 2: _____	◯	◯	◯
6. Cardiovascular System	◯	◯	◯	12. Other 3: _____	◯	◯	◯

Specify if abnormal:

_____

_____

_____

CLINICAL DIAGNOSIS

DRUG PRESCRIPTION AT DAY 14	○ Yes ○ No	
Antibiotic prescribed?	**Paracetamol prescribed?**	**Anti-inflammatory prescribed?**
○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
If the patient has been prescribed any ANTIBIOTICS, please fill out the "MEDICATION FORM"		
DEMOGRAPHIC CHARACTERISTICS		
1.	Household members	1.1 How many people live in your household (residence of ≥6 months per year) |__|__| 1.2 Age category; Number of people: ☐ <5 years |__|__| ☐ 5-17 years |__|__| ☐ 18-34 years |__|__| ☐ 35-59 years |__|__| ☐ ≥ 60 years |__|__|
2.	Profession *(profession of the head of the household if patient<18 years old)*	○ Agriculture / farming ○ Fishing ○Housemaid ○ Vendor ○ Office worker ○ Student ○ Monk / religious ○ Professional (doctor, teacher, lawyer, engineer) ○ Non-skilled labourer ○ No employment ○ Skilled labourer (mechanic, factory work, hotel employee, government employees) ○ Other: _____
3.	Education level of the patient	3.1 Have you completed your education: ○Yes ○No ○NA 3.2 What is your **highest** education level? ○ None ○ Primary school ○ Secondary school ○ High school ○ Higher education ○ Do not know ○ Other, please specify _____
4.		4.1 Is the patient the head of the household? ○ Yes ○ No 4.2 If **no,** what is the **highest** education level of the household head? ○ None ○ Primary school ○ Secondary school

	Education of the head of the household	○ High school ○ Higher education ○ Do not know ○ Other, please specify _____
5.	Characteristics of the household	How many main meals did you have on a typical day last week (excluding snacks and tea)? |__|__| meals per day

ECONOMIC IMPACT OF THE ILLNESS AT DAY 14	
1. How many days of work/school or your normal activites have you missed because of the illness?	|__|__| days ○ Do not want to answer ○ NA
2. [If the respondent is the parent or guardian of the patient:] How many days of work or your normal activites have you missed because of the illness of your child?	|__|__| days ○ Do not want to answer ○ NA
EXPERIENCE OF TREATMENT AND CRP TESTING	
Please indicate whether you agree or disagree with the following statements	
1. Did the health worker precribe an antibiotic on the first day of your visit (Day 0)?	○ Yes ○ No ○ Don't know
2. I think that the healthcare worker's decision to prescribe or not to prescibe an antibiotic for my treatment was correct.	○ Agree ○ Neutral ○ Disagree ○ Not applicable ○ Do not want to answer
3. I did <u>not</u> get enough explanation to understand the treatment.	○ Agree ○ Neutral ○ Disagree ○ Not applicable ○ Do not want to answer
4. I felt that the consultation was too fast.	○ Agree ○ Neutral ○ Disagree ○ Not applicable ○ Do not want to answer
5. [If patient answered "Yes" to **Question 1:**] I fully understood the instructions for taking the prescribed antibiotic (including when, how much, how often, and how long I have to take the medication).	○ Agree ○ Neutral ○ Disagree ○ Not applicable ○ Do not want to answer
6. The objective of the finger-prick CRP test is <u>not</u> clear to me.	○ Agree ○ Neutral ○ Disagree ○ Not applicable ○ Do not want to answer
7. The finger-prick test for CRP is painless.	○ Agree ○ Neutral ○ Disagree ○ Not applicable ○ Do not want to answer
8. It is too much effort to come to the health centre for the treatment that I received.	○ Agree ○ Neutral ○ Disagree ○ Not applicable ○ Do not want to answer
9. Overall, I am satisfied with my care.	○ Agree ○ Neutral ○ Disagree ○ Not applicable ○ Do not want to answer

Finally, please answer the following questions IF you had the finger-prick test for CRP on your first visit.	
10. Did the health worker explain the finger-prick test results to you in a way that you understood?	○ Yes ○ No ○ Don't know ○ Not applicable ○ Do not want to answer
11. Did the finger-prick test make you feel more or less confident that antibiotics are needed / not needed for your illness?	○ More confident ○ Neither more nor less confident ○ Less confident ○ Not applicable ○ Do not want to answer
12. Did the health worker seem to base his/her treatment decision on the test results?	○ Yes ○ No ○ Don't know ○ Not applicable ○ Do not want to answer
	If **yes**: Do you think the health worker relied too much, enough, or not enough on the test results when he/she made the treatment decision? (**Explanation if patient is unsure**: "Too much" would mean that the healthcare worker did not pay enough attention to you as the patient; "not enough" would mean that the healthcare worker considered the test results but decided on a different treatment in spite of them in a way that you disagree with.) ○ Too much ○ Enough / adequately ○ Not enough ○ No opinion / do not want to answer
13. Do you feel that the finger-prick test for CRP improves or worsens the quality of the care you receive?	○ Improves ○ No difference, unsure ○ Worsens ○ Not applicable ○ Do not want to answer
14. Would you like the health worker to use the finger-prick test for CRP again the next time you have an illness?	○ Yes ○ No ○ Don't know ○ Not applicable ○ Do not want to answer

FINAL STATUS AT DAY 14 FOLLOW-UP

Subject has completed the study

○ **Yes**, specify date |__|__|-|__|__|__|-2016 *(eg. 01-JAN-2016)*

○ **No**, please provide reason and date of last contact

|__|__|-|__|__|__|-2016 *(eg. 01-JAN-2016)*

○ Did not have any Day 14 follow-up

○ Consent withdrawn

○ Death

○ Other, please specify briefly_____

Remarks

_____

_____

Investigator's Statement

I have reviewed the data recorded in this CRF and confirm that the data are complete and accurate.

Complete Name: _____

Signature: _____ Date |__|__|-|__|__|__|-2016

(e.g. 01-JAN-2016)

CRF completed by _____ (initials) Date I__I__I-I__I__I__I- 2016 *(e.g. 01-JAN-2016)*

Health worker ____ (initials)

3C: Medication Form

To be filled if the patient has started any NEW antibiotics									
ANTIBIOTIC NAME		**ROUTE***	**DOSE (per day)**	**DOSE UNIT**	**TYPE OF VISIT**	**SOURCE OF THE MEDICATION**	**START DATE & TREATMENT DURATION**	**ACTUAL END DATE** To be filled out at Day 14	**COMPLETED BY & DATE**
○ Amoxycillin ○ Amox-clavulanic acid (co-amoxiclav) ○ Ciprofloxacin ○ Cotrimoxazole ○ Dicloxacillin	○ Doxycycline ○ Erythromycin ○ Metronidazole ○ Penicillin V ○ Other antibiotic: _____	○ PO ○ IM ○ IV ○ IR ○ Other** _____	|__|__|__|__|	○ mcg ○ mg ○ g ○Other _____	○ Prior Day 0 ○ Day 0 ○ Day 5 ○ Day 14 ○ Unscheduled ○ NA	○ Home ○ This facility ○ Pharmacy ○ Hospital ○ Another clinic ○ Street vendor ○ Other: _____	|__|__|- |__|__|__|- 2016 *(e.g. 01-JAN-2016)* Treatment duration: *(from prescription)* ____ days	|__|__|- |__|__|__|- 2016 Or ☐ Ongoing Full compliance with treatment? ○ Yes ○ No ○ NK	_____ (initials) |__|__|- |__|__|__|- 2016 *(e.g. 01-JAN-2016)*
○ Amoxycillin ○ Amox-clavulanic acid (co-amoxiclav) ○ Ciprofloxacin ○ Cotrimoxazole ○ Dicloxacillin	○ Doxycycline ○ Erythromycin ○ Metronidazole ○ Penicillin V ○ Other antibiotic: _____	○ PO ○ IM ○ IV ○ IR ○ Other** _____	|__|__|__|__|	○ mcg ○ mg ○ g ○Other _____	○ Prior Day 0 ○ Day 0 ○ Day 5 ○ Day 14 ○ Unscheduled ○ NA	○ Home ○ This facility ○ Pharmacy ○ Hospital ○ Another clinic ○ Street vendor ○ Other: _____	|__|__|- |__|__|__|- 2016 *(e.g. 01-JAN-2016)* Treatment duration: *(from prescription)* ____ days	|__|__|- |__|__|__|- 2016 Or ☐ Ongoing Full compliance with treatment? ○ Yes ○ No ○ NK	_____ (initials) |__|__|- |__|__|__|- 2016 *(e.g. 01-JAN-2016)*
○ Amoxycillin ○ Amox-clavulanic acid	○ Doxycycline ○ Erythromycin	○ PO ○ IM ○ IV	|__|__|__|__|	○ mcg ○ mg ○ g	○ Prior Day 0 ○ Day 0	○ Home ○ This facility ○ Pharmacy	|__|__|- |__|__|__|- 2016	|__|__|- |__|__|__|- 2016	_____ (initials)

(co-amoxiclav) ○ Ciprofloxacin ○ Cotrimoxazole ○ Dicloxacillin	○ Metronidazole ○ Penicillin V ○ Other antibiotic: _____	○ IR ○ Other** _____		○Other _____	○ Day 5 ○ Day 14 ○ Unscheduled ○ NA	○ Hospital ○ Another clinic ○ Street vendor ○ Other: _____	*(e.g. 01-JAN-2016)* Treatment duration: *(from prescription)* ____ days	Or ☐ Ongoing Full compliance with treatment? ○ Yes ○ No ○ NK	|__|__|-|__|__|__|-2016 *(e.g. 01-JAN-2016)*
○ Amoxycillin ○ Amox-clavulanic acid (co-amoxiclav) ○ Ciprofloxacin ○ Cotrimoxazole ○ Dicloxacillin	○ Doxycycline ○ Erythromycin ○ Metronidazole ○ Penicillin V ○ Other antibiotic: _____	○ PO ○ IM ○ IV ○ IR ○ Other** _____	|__|__|__|__|	○ mcg ○ mg ○ g ○Other _____	○ Prior Day 0 ○ Day 0 ○ Day 5 ○ Day 14 ○ Unscheduled ○ NA	○ Home ○ This facility ○ Pharmacy ○ Hospital ○ Another clinic ○ Street vendor ○ Other: _____	|__|__|-|__|__|__|-2016 *(e.g. 01-JAN-2016)* Treatment duration: *(from prescription)* ____ days	|__|__|-|__|__|__|-2016 Or ☐ Ongoing Full compliance with treatment? ○ Yes ○ No ○ NK	_____ (initials) |__|__|-|__|__|__|-2016 *(e.g. 01-JAN-2016)*

***ROUTE:** PO=per os (by mouth), IM=intramuscular, IV=intravenous, IR=intra-rectal

****Other:** PAR=parenteral (other injections, infusion, implantation); TOP=topical; VG=vaginal; IH=inhalation; TD=transdermal; OPH=ophthalmic; UNK= unknown

Appendix 4: Knowledge, Attitudes and Practices Questionnaire for Healthcare Workers Involved in the C-Reactive Protein Trial

Part I: Introduction: [For HCW in Pre-intervention & Intervention sites]	
*As part of the interview on your everyday work practice and medicine use, I am inviting you to share with me your opinions and views about antibiotics. This will take no more than **ten** minutes and will help us to better understand your work. Nothing of what we discuss will be used for any purposes other than those of this research project. No one will be able to identify you based on what you tell me. If you do not wish to answer any of the questions during the interview, you may say so and I will move on to the next question.*	
i. Date of interview	|__|__|-|__|__|__|-2016 *(e.g. 01-JAN-2016)*
ii. Interviewer Initials	Initials: _____
Part II: Main Questionnaire Let us begin with a few questions about yourself and your work.	
1. [***record as observed***] Sex	○ Male ○ Female
2. How old are you? [***in years***]	Age in years: _____
3. How many years of medical training have you received? [***in years***]	Number of years: _____
4. How many years have you worked after you completed your medical training? [***in years***]	Number of years: _____
5. How many years have you worked here? [***in years***]	Number of years: _____
6. How many patients do you treat in a normal day?	Number of patients / day: _____

7. I would now like to ask you about your work with antibiotics.	
7.1. How often do you normally prescribe antibiotics? [if “daily” or “weekly” etc., probe: Once a day / week or more often than that?]	○ A few times per day ○ Once per day ○ A few times per week (2-6 times per week) ○ Once per week ○ A few times per month (2-3 times per month) ○ Once a month ○ Less often (1-11 times per year) ○ Never ○ I don’t know
7.2. Approximately what share of your patients with acute illness receives antibiotics from you (as prescription)?	○ 100% (all of them) ○ 76% – 99% (most of them, almost all) ○ 51% – 75% (a small majority, more than half) ○ 50% (half of them) ○ 49% – 25% (a large minority, almost half) ○ 1% – 24% (very few of them, almost none) ○ 0% (none of them) ○ I don’t know
7.3. How good is your knowledge of antibiotics?	○ Very good (I know everything) ○ Good (I know most things) ○ Neither good nor bad (I know some things) ○ Not very good (I know few things) ○ Bad (I don’t know anything)
7.4. Do you find it sometimes difficult to prescribe an antibiotic?	○ Yes → [***Go to next question***] ○ Neither difficult nor easy → [***Go to next question***] ○ No → [***Go to question 7.5***] ○ Don’t know → [***Go to question 7.5***]

7.4.1.[***if "yes" to Q7.4***] What are these difficulties?	☐ Lack of supply / stock-out ☐ Costs to health facilities ☐ Costs to patient ☐ Diagnosis not clear ☐ Patient does not want antibiotics ☐ Lack of prescription guidelines ☐ Unsure which antibiotics to use ☐ Other (Specify: _____) ☐ Don't know
7.5. How often do you consult a co-worker before prescribing an antibiotic?	○ Always……..1 ○ Most of the time……..2 ○ About half of the time……3 ○ Sometimes ……4 ○ Never ……5
7.6. How often are antibiotics available in your health centre when they are needed?	○ Always ○ Most of the time ○ About half of the time ○ Sometimes ○ Never
8. I would now like to know more about your training and experience with antibiotics.	
8.1. Have you received any information about antibiotics in the past year?	○ Yes → [***Go to next question***] ○ No → [***Go to question Q8.2***]

8.1.1. [***If "yes" to Q8.1***] What were these sources of information? [***mark all that are mentioned, and probe for "any others?"***]	☐ Colleagues ☐ Sales representatives ☐ Courses / training / teaching material ☐ Information event ☐ Information brochures in health centre ☐ Official guidelines ☐ Mail / advertisement ☐ Television ☐ Newspaper ☐ Internet (specify: _____) ☐ Other (specify: _____)
8.2. Have you ever received specific training about antibiotics?	○ Yes → [***Go to next question***] ○ No → [***Go to question Q8.3***]
8.2.1. [***If yes to Q8.2***] How many courses and training units about antibiotics have you received in the last year? [***this also includes training and introductions from sales representatives***]	Number of training units: _____
8.2.2. [***If yes to Q8.2***] When was the last time you received such training? [***date – complete at least the year***]	|__|__|-|__|__|__|-20|__|__| *(e.g. 01-JAN-2016)*
8.3. Have you actually needed information about antibiotics in the past year?	○ Yes ○ No
9. Can you please tell me the answers to the following questions?	

9.1. Are antibiotics a kind of medicine to treat bacterial infections?	○ Yes ○ No ○ Don't know
9.2. Are antibiotics a kind of medicine to treat viral infections, such as cold and flu?	○ Yes ○ No ○ Don't know
9.3. Are antibiotics a kind of medicine to treat muscle pain and inflammation from hard work or sports injuries?	○ Yes ○ No ○ Don't know
9.4. Should unfinished antibiotics be kept for future use?	○ Yes ○ No ○ Don't know
10. Can you please tell me whether you agree or disagree with the following statements?	
10.1. In case of doubt, it is better to give the patient an antibiotic.	○ Agree ○ Neutral ○ Disagree ○ I don't know
10.2. Antibiotic resistance is a problem.	○ Agree ○ Neutral ○ Disagree ○ I don't know
10.3. Bacteria in the body are generally harmful.	○ Agree ○ Neutral ○ Disagree ○ I don't know

10.4. It would be useful if everyone knew more about antibiotics.	○ Agree ○ Neutral ○ Disagree ○ I don't know
10.5. People don't use antibiotics often enough.	○ Agree ○ Neutral ○ Disagree ○ I don't know
10.6. Antibiotics prescription in this health facility can lead to antimicrobial resistance.	○ Agree ○ Neutral ○ Disagree ○ I don't know
11. [***For HCW in Intervention sites only***] Lastly, I would like to ask you some questions about your experience with the CRP test.	
11.1. Do you feel that you have understood the objectives of the test?	○ Yes / understood ○ Neutral / So-so ○ No / not understood ○ I don't know
11.2. Do you support the introduction of the test?	○ Support / strongly support ○ Neutral ○ Don't support ○ I don't know
11.3. Are the test results easy or difficult to follow?	○ Easy / very easy ○ Neutral ○ Difficult / very difficult ○ I don't know

11.4. Do you find the CRP test fast enough or too time-consuming for your work?	○ Fast enough ○ Neutral ○ Too slow / time-consuming ○ I don't know
11.5. Do you think that health workers should base their antibiotics prescriptions on the test?	○ Yes ○ Yes, under certain conditions (specify: _____) ○ No ○ I don't know / no opinion
11.6. Does the test influence your patients' trust in your recommendations? [***If "yes," probe: Does it improve or worsen trust?***]	○ Improve ○ No influence ○ Worsen ○ I don't know / no opinion
11.7. Does the test influence your patients' compliance if you decide to prescribe or not to prescribe medication? [***If "yes," probe: Does it improve or worsen compliance?***]	○ Improve ○ No influence ○ Worsen ○ I don't know / no opinion
11.8. Are you overall satisfied or dissatisfied with the CRP test?	○ Satisfied / very satisfied ○ Neutral ○ Dissatisfied / very dissatisfied ○ I don't know
That was the last question of the survey. Thank you very much for participating in this research.	

Part III: Interviewer observations [to be completed by interviewer after interview]	
i. Was the interview completed?	○ Yes ○ Yes, with difficulties ○ No

ii.	Was someone else present during the interview? [***mark all that apply***]	☐ Patient ☐ Colleague ☐ Research team member ☐ Other ☐ None of the above
iii.	What is your evaluation of the accuracy and trustworthiness of the informant's answers?	○ Very good ○ Satisfactory ○ Doubtful ○ Very low
iv.	Were there any unusual circumstances during the interview?	○ Yes (Describe: _____) ○ No

Appendix 5: Demographic and Clinical Details of Participants included in the Nested Group A *Streptococcus* Study

	All patients N = 169	**BHS not isolated N = 134**	**GAS isolated N = 11**	**Other BHS isolated N = 24**
Age: adolescents & adults (≥ 12 years) Total= 78 (46.2%), median (IQR)	47 (20 - 59)	49 (24 - 60)	17.5 (12.5 - 45.5)	24 (20 - 59)
Age: children (<12 years) Total=91 (53.9%), median (IQR)	6 (4 - 9)	6 (4 - 9)	8 (7 - 9)	6 (4 - 7)
Male sex n/N (%)	79/169 (46.8)	61/134 (45.5)	4/11 (36.4)	14/24 (58.3)
Antibiotic within last 2 weeks n/N (%)	12/169 (7.1)	11/134 (8.2)	0/11 (0)	1/24 (4.2)
Chronic disease n/N (%)	29/169 (17.2)	18/134 (13.4)	5/11 (45.5)	6/24 (25)
Respiratory diagnosis (single) n/N (%)	164/169 (97)	129/134 (96.3)	11/11 (100)	24/24 (100)
• **Common cold**	94/164 (57.3)	79/129 (61.2)	4/11 (36.4)	11/24 (45.8)
• **Pharyngitis**	42/164 (25.6)	32/129 (24.8)	4/11 (36.4)	6/24 (25)
• **Tonsillitis**	26/164 (15.9)	16/129 (12.4)	3/11 (27.3)	7/24 (29.2)
• **Acute LRTI**	2/164 (1.2)	2/129 (1.6)	0/11 (0)	0/24 (0)

Duration of illness (days) Median (IQR)	2 (2 - 4)	2 (2 - 4)	2 (2 - 4)	2 (2 - 3)
Abnormal throat examination n/N (%)	92/164 (56.1)	69/130 (53.1)	8/11 (72.7)	15/23 (65.2)
• **Exudate***	16/92 (17.4)	11/69 (15.9)	1/8 (12.5)	4/15 (26.7)
• **Injected or red***	68/92 (73.9)	52/69 (75.4)	5/8 (62.5)	11/15 (73.3)
Swollen or enlarged*	43/92 (46.7)	33/69 (47.8)	4/8 (50)	6/15 (40)

Table A- 2: Demographic and clinical details of the RCT participants included in the nested GAS study

BHS: β-haemolytic streptococcus, GAS: group A Streptococcus

** Recorded as free text under details of abnormal examination, the denominator is those with an abnormal throat examination, can have more than one.*

Symptom	Day 0 n (%) N=169	Day 5 n (%) N=169	Day 14 n (%) N=169
Sore throat	169 (100)	18 (10.7)	2 (1.2)
Fever	169 (100)	4 (2.4)	0
Cough	140 (82.8)	70 (41.4)	9 (5.3)
Runny nose	100 (59.2)	44 (26)	5 (3)
Headache	38 (22.5)	0	0
Weakness	28 (16.6)	1 (0.6)	1 (0.6)
Muscle pain	26 (15.4)	2 (1.2)	0
Nausea / vomiting	22 (13)	2 (1.2)	0
Loss of appetite	14 (8.3)	0	0
Abdominal pain	9 (5.3)	0	0
Diarrhoea	9 (5.3)	0	0
Difficulty breathing	5 (3)	0	0
Chest pain	2 (1.2)	1 (0.6)	0
Skin eruption / rash	1 (0.6)	1 (0.6)	0
Jaundice	0	1 (0.6)	0
Confusion	0	0	0
Earache	0	0	0
Others:	5 (3.0)	1 (0.6)	0
• **Dizziness**	4 (2.4)	1 (0.6)	0
• **Chills**	1 (0.6)	0	0
No symptoms	0	79 (46.8)	154 (91.1)

Table A- 3: Participant-reported symptoms at enrolment, day 5 and day 14 included in the GAS study

Appendix 6: Interim Analysis for the C-Reactive Protein Trial

The interim analysis was conducted after 200 children, and 200 adolescents and adults had been recruited in Thailand, this included participants enrolled up to and including the 14th of October 2016. The control arm had 164 participants, intervention arm A had 166 participants and intervention arm B had 164 participants. For the interim analysis the intervention arms were combined and compared against the control arm.

Antibiotic prescriptions between day 0 and 5, at the study sites are shown in Chapter 3, Table 3-2. There were no statistical differences in recorded temperature at day 5, elevated CRP at day 5, antibiotic prescriptions at day 5, ongoing symptoms at day 5 or 14, and seeking healthcare between day 1 and 14 between the control and intervention arms (Table A- 4). Of the antibiotics prescribed on day 5, 1/2 (50%) were prescribed to participants who had not received antibiotics on day 0 in the control arm and 9/12 (75%) in the intervention arms.

	Control Arm N = 164 n/N (%)	**Intervention Arms N = 330 n/N (%)**	**P value**
All participants			
Recorded temperature (> 37.5 C) at day 5	1/161 (0.6)	5/321 (1.6)	0.669
Elevated CRP at day 5*	0	2/321 (0.6)	0.554
Ongoing symptoms at day 5	56/161 (34.8)	116/322 (36.0)	0.788
Antibiotic prescription at day 5	2/161 (1.2)	12/322 (3.7)	0.125
Ongoing symptoms at day 14	2/164 (1.2)	11/324 (3.4)	0.235
Sought healthcare between day 1 and 14	18/163 (11.0)	34/323 (10.5)	0.862

Child participants (< 12 years)	**N = 68**	**N = 135**	
Recorded temperature (> 37.5 C) at day 5	1/65 (1.5)	5/130 (3.8)	0.666
Elevated CRP at day 5*	0	1/130 (0.8)	1.000
Ongoing symptoms at day 5	25/65 (38.5)	48/131 (36.6)	0.804
Ongoing symptoms at day 14	0	6/133 (4.5)	0.098
Sought healthcare between day 1 and 14	11/67 (16.4)	14/131 (10.7)	0.251
Adolescent and adult participants (≥ 12 years)	**N = 96**	**N = 195**	
Recorded temperature (>37.5 C) at day 5	0	0	NA
Elevated CRP at day 5*	0	1/191 (0.5)	1.000
Ongoing symptoms at day 5	31/96 (32.3)	68/191 (35.6)	0.578
Ongoing symptoms at day 14	2/96 (2.1)	5/191 (2.6)	1.000
Sought healthcare between day 1 and 14	7/96 (7.3)	20/192 (10.4)	0.391

Table A- 4: Clinical outcomes, new antibiotic prescriptions on day 5 and healthcare-seeking during the study for participants included in the Thai RCT interim analysis, by age category

** Elevated CRP on day 5: CRP ≥ 50mg/L in children and CRP ≥ 100mg/L in adults. † Symptom severity: reported by the participant, 1 = mild, 2 = moderate, 3 = severe. 4 = life threatening*

Only three SAEs occurred in participants included in the interim analysis; one in the control arm and two in the intervention arms. All were classed as unrelated to the study but one SAE resulted in the death of an elderly male (Chapter 3).

Appendix 7: Per Protocol Analysis for the C-Reactive Protein Trial

	Per protocol population N = 1,957	**Intention to treat population N = 2,410**	**P value**
Demographic characteristics			
Age, median (IQR), years	11 (4-35)	11 (4-34)	0.945
Male sex	888 (45.4)	1,106 (45.9)	0.724
≥ 30 minutes to reach the PCU	419 (21.4)	514 (21.3)	0.953
Presence of a comorbidity	292 (15.6)	351 (15.2)	0.719
Symptom onset, median (IQR), days	2 (2-3)	2 (2-3)	0.482
Sought medical care in last 14 days	1,094 (55.9)	1,372 (57.0)	0.476
Self-reported antibiotic intake in the last 2 weeks	97 (5.0)	130 (5.4)	0.515
Clinical characteristics			
Documented fever (>37.5°C)	848 (43.4)	1,072 (44.7)	0.388
Respiratory symptoms*	1,574 (80.4)	1,905 (79.1)	0.259
Gastrointestinal symptoms†	457 (23.4)	583 (24.2)	0.518
Respiratory diagnoses	1,299 (71.8)	1,552 (70.8)	0.471

Table A- 5: Demographic and clinical characteristics of the per protocol and intention to treat RCT populations

Based on Althaus, T., et al., 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, 2019. ***7****(1): p. e119-e131. License CC BY 4.0.*

*Data are number (%) unless specified. *Respiratory symptoms include cough, runny nose, sore throat, breathing difficulties and chest pain. †Gastrointestinal symptoms include nausea, vomiting, diarrhoea and abdominal pain.*

The per protocol populations includes 1,957/2,410 (81.2%) of the participants from the intention to treat population. The demographic and clinical characteristics of the per protocol and intention to treat populations were similar (Table A- 5).

In addition to antibiotic prescriptions being significantly reduced in the intervention arms, antibiotic prescriptions were significantly reduced in the subgroups of participants with a documented fever and a respiratory diagnosis on day 0 (Table A- 6). In those who had taken antibiotics in the previous 2 weeks, antibiotic prescribing was not significantly reduced in the intervention arm A compared to the control arm, although a borderline significant reduction was seen between intervention arm B and the control arm.

	Control Arm n/N (%)	Intervention Arm A n/N (%)	Risk Difference, percentage point (95% CI)	aOR (95% CI)	Intervention Arm B n/N (%)	Risk Difference, percentage point (95% CI)	aOR (95% CI)
Documented fever > 37.5°C	164/336 (48.8)	101/250 (40.4)	-8.4 (-16.6 to -0.3)	0.70 (0.50 to 0.98)	68/262 (26.0)	-22.9 (-30.4 to -15.3)	0.35 (0.25 to 0.51)
Respiratory diagnosis	198/510 (38.8)	121/416 (29.1)	-9.7 (-15.8 to -3.7)	0.60 (0.44 to 0.81)	67/373 (18.0)	-20.1 (-26.6 to -15.1)	0.31 (0.22 to 0.44)
Antibiotic use in the last 2 weeks	17/41 (41.5)	10/26 (38.5)	-3.0 (-27.0 to 21.0)	0.87 (0.28 to 2.68)	6/30 (20.0)	-21.5 (-42.2 to -0.7)	0.28 (0.08 to 1.00)

Table A- 6: Antibiotic prescription between day 0 and 5 in the subgroups of documented fever, respiratory diagnosis and antibiotic use in the last 2 weeks in the RCT per protocol population

As in the intention to treat population, amoxicillin was the most frequently prescribed antibiotic for the per protocol participants (Table A- 7). The majority of the antibiotics prescribed (87.5%) were from the "Access" group.

"AWaRe" category of antibiotics	**Number of antibiotics N=505 n (%)**
"Access" antibiotics	
Amoxicillin	398 (78.8)
Amoxicillin/Clavulanic acid	18 (3.6)
Cefalexin	9 (1.8)
Dicloxacillin	4 (0.8)
Trimethoprim/sulfamethoxazole	5 (1.0)
Doxycycline	3 (0.6)
Metronidazole	2 (0.4)
Penicillin V	2 (0.4)
Ampicillin	1 (0.2)
Total	**442 (87.5)**
"Watch" antibiotics	
Cefixime	23 (4.6)
Azithromycin	21 (4.2)
Ciprofloxacin	13 (2.6)
Norfloxacin	4 (0.8)
Roxithromycin	1 (0.2)
Erythromycin	1 (0.2)
Total	**63 (12.5)**

Table A- 7: Antibiotic prescriptions on day 0 by "AWaRe" category for the RCT per protocol population

There were no significant differences in clinical outcomes, re-attendances or SAEs between the study arms (Table A- 8). There were also no differences in symptom resolution (Figure A-1). The log-rank p value for the Kaplan-Meier curves was 0.482 for intervention arm A compared to the control arm, and p = 0.723 for intervention arm B and the control arm. The cox proportional-hazards model gives an adjusted hazard ratio of 0.97 (95% CI 0.86 to 1.08, p = 0.537) for intervention arm A compared to

the control arm. The adjusted hazard ratio was 0.99 (95% CI 0.94 to 1.05, p = 0.755) for intervention arm B compared to the control arm.

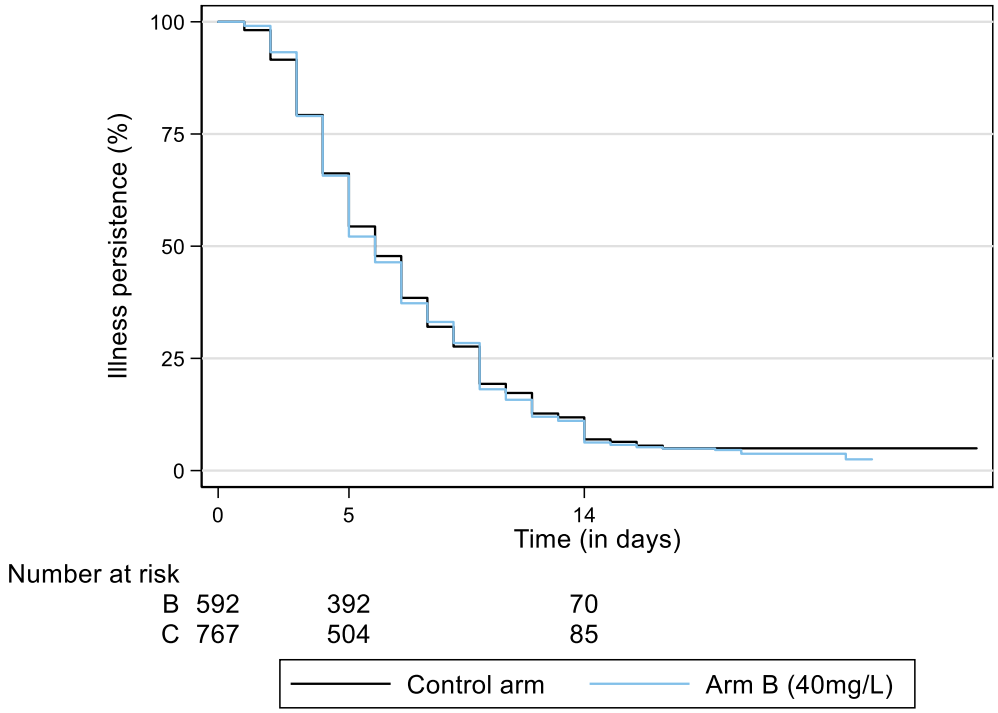

Figure A- 1: Kaplan-Meier survival estimates for symptom persistence at day 5 and day 14 comparing the control arm with intervention arm A and intervention arm B for the RCT per protocol population

*Adapted from Althaus, T., et al., 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, 2019. **7**(1): p. e119-e131. License CC BY 4.*

	Control Arm n (%)	Intervention Arm A n (%)	P value	Intervention Arm B n (%)	P value
All participants	**N = 767**	**N = 598**		**N = 592**	
Recorded temperature (>37.5 C) at day 5	26/706 (3.7)	17/555 (3.1)	0.547	18/558 (3.2)	0.660
Elevated CRP at day 5*	8/703 (1.1)	5/553 (0.9)	0.684	4/558 (0.7)	0.444
Ongoing symptoms at day 5	272/762 (35.7)	214/596 (35.9)	0.936	219/591 (37.1)	0.606
Symptom severity at day 5, median (IQR)†	1 (1 – 1)	1 (1 – 1)	0.321	1 (1 – 1)	0.761
Recorded temperature (>37.5 C) at day 14	9/631 (1.4)	8/516	0.863	7/501	0.967
Ongoing symptoms at day 14	34/765 (4.4)	35/597 (5.9)	0.236	32/590 (5.4)	0.406
Symptom severity at day 14, median (IQR)†	1 (1 – 1)	1 (1 – 1)	0.978	1 (1 – 1)	0.422
Re-attendance	13/767 (1.7)	10/598 91.7)	0.974	17/592 (2.9)	0.143
SAE	3/767 (0.4)	4/598 (0.7)	0.706	6/592 (1.0)	0.189
Thai child participants (< 12 years)	**N = 192**	**N = 162**		**N = 152**	
Recorded temperature (>37.5 C) at day 5	2/192 (1.0)	4/158 (2.5)	0.415	1/149 (1.3)	1.000
Elevated CRP at day 5*	1/192 (0.5)	1/158 (0.6)	1.000	1/149 (0.7)	1.000

Ongoing symptoms at day 5	92/192 (47.9)	91/162 (56.2)	0.121	84/152 (55.3)	0.176
Symptom severity at day 5, median (IQR)†	1 (1 – 1)	1 (1 – 1)	0.302	1 (1 – 1)	0.804
Recorded temperature (>37.5 C) at day 14	1/182 (0.6)	0/157	1.000	0/144	1.000
Ongoing symptoms at day 14	10/192 (5.2)	8/162 (4.9)	0.908	13/152 (8.6)	0.217
Symptom severity at day 14, median (IQR)†	1 (1 – 1)	1 (1 – 1)	0.371	1 (1 – 1)	0.254
Re-attendance	0	0	NA	0	NA
SAE	1/192 (0.5)	2/162 (1.2)	0.595	1/152 (0.7)	1.000
Thai adolescents and adult participants (≥ 12 years)	**N = 201**	**N = 145**		**N = 137**	
Recorded temperature (>37.5 C) at day 5	0/200	0/144	NA	0/137	NA
Elevated CRP at day 5*	0/200	0/144	NA	1/137 (0.7)	0.407
Ongoing symptoms at day 5	76/201 (37.8)	60/145 (41.4)	0.503	58/137 (42.3)	0.404
Symptom severity at day 5, median (IQR)†	1 (1 – 1)	1 (1 – 1)	0.660	1 (1 – 1)	0.804
Recorded temperature (>37.5 C) at day 14	0/195	0/138	NA	0/130	NA
Ongoing symptoms at day 14	5/201 (2.5)	8/145 (5.5)	0.144	3/137 (2.2)	0.860
Symptom severity at day 14, median (IQR)†	1 (1 – 1)	1 (1 – 1)	0.429	1 (1 – 1)	NA

Re-attendance	0	0	NA	0	NA
SAE	0	0	NA	1/137 (0.7)	0.405
Myanmar child participants (< 12 years)	**N = 185**	**N = 145**		**N = 156**	
Recorded temperature (>37.5 C) at day 5	11/168 (6.6)	9/133 (6.8)	0.940	11/144 (7.6)	0.707
Elevated CRP at day 5*	2/167 (1.2)	1/132 (0.8)	1.000	1/144 (0.7)	1.000
Ongoing symptoms at day 5	50/182 (27.5)	30/144 (20.8)	0.167	32/156 (20.5)	0.137
Symptom severity at day 5, median (IQR)†	1 (1 – 1)	1 (1 – 1)	0.845	1 (1 – 1)	0.874
Recorded temperature (>37.5 C) at day 14	5/133 (3.8)	5/119 (4.2)	1.000	6/120 (5)	0.761
Ongoing symptoms at day 14	8/184 (4.4)	7/144 (4.9)	0.825	7/154 (4.6)	0.930
Symptom severity at day 14, median (IQR)†	1 (1 – 1)	1 (1 – 1)	-	1 (1 – 1)	0.277
Re-attendance	5/185 (2.7)	3/145 (2.1)	1.000	14/156 (9.0)	0.012
SAE	1/185 (0.5)	2/145 (1.4)	0.584	3/156 (1.9)	0.336
Myanmar adolescents and adult participants (≥ 12 years)	**N = 189**	**N = 146**		**N = 147**	
Recorded temperature (>37.5 C) at day 5	13/146 (8.9)	4/120 (3.3)	0.065	5/128 (3.9)	0.096
Elevated CRP at day 5*	5/144 (3.5)	3/119 (2.5)	0.732	1/128 (0.8)	0.218
Ongoing symptoms at day 5	54/187 (28.9)	33/145 (22.8)	0.209	45/146 (30.8)	0.700

Symptom severity at day 5, median (IQR)†	1 (1 – 1)	1 (1 – 1)	0.226	1 (1 – 1)	0.168
Recorded temperature (>37.5 C) at day 14	3/121 (2.5)	3/102 (2.9)	1.000	1/107 (0.9)	0.625
Ongoing symptoms at day 14	11/188 (5.9)	12/146 (8.2)	0.397	9/147 (6.1)	0.917
Symptom severity at day 14, median (IQR)†	1 (1 – 1)	1 (1 – 1)	0.952	1 (1 – 1)	0.283
Re-attendance	8/189 (4.2)	7/146 (4.8)	0.805	3/147 (2.0)	0.359
SAE	1/189 (0.5)	0/146 (0)	1.000	1/147 (0.7)	1.000

Table A- 8: Clinical outcomes, re-attendances and serious adverse events by study arm in the RCT per protocol population, by age category and country

** Elevated CRP on day 5: CRP ≥ 50mg/L in children and CRP ≥ 100mg/L in adults. † Symptom severity: reported by the participant, 1 = mild, 2 = moderate, 3 = severe. 4 = life threatening*

*Based on Althaus, T., et al., 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, 2019. **7**(1): p. e119-e131. License CC BY 4.0.*

Appendix 8: Univariate Logistic Regression Model for the Concordance of Antibiotic Prescribing and the C-Reactive Protein Result in the Trial

Variable	aOR (95% CI)	P value
Male sex	0.98 (0.76 – 1.25)	0.845
Children	1.34 (1.05 – 1.71)	0.021
Travel ≥ 30 minutes to the study site	1.30 (0.95 – 1.79)	0.105
Education level higher than primary school*	0.83 (0.63 – 1.09)	0.189
Profession:*		
• Agricultural	Reference	Reference
• Non-skilled labourer	0.90 (0.62 – 1.31)	0.587
• Unemployed	0.81 (0.47 – 1.40)	0.456
• Skilled labourer or professional	0.91 (0.60 – 1.36)	0.630
Chronic disease	1.06 (0.74 – 1.51)	0.764
Country		
• Myanmar	Reference	Reference
• Thailand	1.22 (0.55 – 2.68)	0.625
Sought healthcare in the last 2 weeks	0.82 (0.63 – 1.08)	0.157
Taken antibiotics in the last 2 weeks	0.48 (0.30 – 0.77)	0.003
Headache	0.98 (0.72 – 1.35)	0.912
Earache	0.74 (0.07 – 7.27)	0.793
Sore throat	0.41 (0.30 – 0.57)	<0.001
Difficulty breathing	0.65 (0.33 – 1.29)	0.223
Chest pain	0.50 (0.26 – 0.97)	0.040
Cough	1.09 (0.83 – 1.43)	0.528
Runny nose	1.52 (1.17 – 1.97)	0.002
Abdominal pain	0.76 (0.46 – 1.23)	0.264
Loss of appetite	0.75 (0.46 – 1.21)	0.237
Diarrhoea	0.71 (0.45 – 1.14)	0.158
Nausea or vomiting	0.81 (0.58 – 1.14)	0.233
Skin eruption or rash	0.36 (0.16 – 0.83)	0.016
Muscle pain	0.86 (0.63 - 1.19)	0.364
Weakness	0.73 (0.49 – 1.10)	0.137

Temperature > 37.5°C	0.86 (0.67 – 1.11)	0.251
Abnormal examination finding†	0.20 (0.15 – 0.27)	<0.001
Diagnosis body system:		
• Respiratory	Reference	Reference
• GI	0.60 (0.33 – 1.10)	0.097
• Other infections	0.47 (0.23 – 0.96)	0.037
• Fever or non-specific symptoms	1.68 (0.74 – 3.85)	0.216
• Dual infections	0.31 (0.18 – 0.54)	<0.001
• Acute viral infection	1.57 (0.96 – 2.59)	0.074
• Non infection	4.12 (0.52 – 32.34)	0.178

Table A- 9: Univariate logistic regression model for the concordance of antibiotic prescribing and the CRP result, adjusted for clustering by study site

**Education and profession are for the participant, unless the participant is under 18 years old where it is replaced by the head of the household. †Abnormal examination findings excluding observations*