

**The epidemiology of acute febrile illness in rural South and
Southeast Asian primary care, and evaluation of selected
interventions to improve its management**



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Dedicated to

Audrey Junya Chew-Dangerfield

And to the memory of Seok Leng Tan

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ABSTRACT

Acute febrile illness (AFI) accounts for a major proportion of presentations in primary care, particularly in tropical low-income and middle-income countries (LMICs). The paradigm that tropical AFI is primarily attributable to malaria is no longer valid in South and Southeast Asia, yet there is precious little high-quality contemporary evidence on its epidemiology, especially in the rural, resource-constrained, and under-studied areas containing most of the regional population. Clinical and health policy decision-making is, thus, hampered leading to larger-scale problems such as antimicrobial over-prescription and development of resistance, and hospital overcrowding from poorly-targeted referrals. Viewing this pressing but neglected problem through a pragmatic, multi-disciplinary lens, this thesis aims to lay the foundations for the development of interventions to improve primary care management of AFI in rural South and Southeast Asia at both individual patient and population levels. Beginning with two multi-national prospective studies embedded in the South and Southeast Asian Community-based Trials Network Rural Febrile Illness project, it details the baseline contextual and epidemiological realities confronting health workers and policymakers in Bangladesh, Cambodia, Laos, Myanmar, and Thailand daily, which have thus far been poorly researched. The first showed that while there were considerable differences between these sites, all relied on primary health centres and village health/malaria workers as the main providers of primary healthcare. The key results from the second, an observational study, were that in the 82,760 patients enrolled by these two provider groups the most frequent diagnoses were upper respiratory tract infection (URTI, 61.0%) and fever of unclear source (30.7%). This study also showed that targeting of antibiotic prescriptions and identification of patients with potentially severe illness could be improved, although mortality was very low (0.01%). Building on the results, a variety of research methodologies based on real-world data were used to generate evidence on potential interventions, starting with one commonly used in high-income settings

(pulse oximetry), followed by one for which the need is well-established but data for its development is lacking (a multiplex rapid diagnostic test for AFI). With regard to pulse oximetry, a systematic review concluded that it may assist clinicians in diagnosing and managing paediatric pneumonia, but for the greatest impact on patient outcomes should be implemented as part of a health systems approach. For the latter, the most important finding from a priority-setting Delphi survey was that it should be able to diagnose dengue and enteric fever at a minimum in adults and children. Health economic modelling studies showed that both these interventions were likely to be cost-effective in the settings which they were evaluated. The culminating work describes the development of a novel algorithmic electronic clinical decision support tool which integrates epidemiological and clinical data to guide diagnosis and management, and the methodology for its evaluation via a cluster-randomised trial in Cambodia. The generalisability of the knowledge gained from this thesis to other tropical LMICs, as well as the barriers to its application and implementation, are also discussed, along with potential solutions.

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CHAPTER 1 | PREFACE

1.1 Acknowledgements

The work for this thesis was carried out across the five countries of the South and Southeast Asian Community-based Trials Network (SEACTN) and involved the collection of huge amounts of data. There are, thus, many, many people to thank.

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1.2 Impact of COVID-19 on research plans

My original doctoral research plans, conceived pre-pandemic, had two main aims. The first was to conduct a large-scale observational study of acute febrile illness (AFI) in South and Southeast Asian rural primary care settings over 18–24 months, which would generate a rich dataset of presenting symptoms and vital signs, host biomarker measurements, likely causative pathogens, and outcomes of nearly 100,000 patients. The second, which is dependent on successful completion of the former, was to use this dataset to develop and validate machine learning models that would be able to predict adverse outcomes and, hence, risk-stratify patients at the time they present. The best-performing models would then be incorporated into electronic clinical decision support algorithms (eCDSAs) and evaluated in the field through a randomised clinical trial.

With this in mind, I undertook a Professional Certificate in Machine Learning and Artificial Intelligence through Imperial College London in the first year of my candidature (2020/21), concurrent with laying the foundations for the observational study. However, restrictions on travel and non-essential activities at healthcare facilities imposed to control the spread of the COronaVirus Disease of 2019 (COVID-19) meant that the observational study did not begin in earnest until the second year, delaying the end of patient recruitment to October 2023 and the availability of laboratory assay results to the second half of 2024. As such, while the findings of the observational study sans microbiological diagnoses will still form a key component of this thesis, the predictive modelling work would be impossible to complete within candidature time constraints and, hence, has been deferred to the post-doctoral phase of my academic career. The effort taken to complete the Professional Certificate, therefore, has not been wasted.

While the disruption caused by the pandemic was disappointing, it did open up avenues for me to explore other areas of interest, in particular health economics, as well as multi-faceted

methods of evaluating interventions with the potential to improve the clinical management of AFI in rural primary care settings. I was still able to conduct some modelling work through the cost-effectiveness analyses presented in this thesis; devise an eCDSA (albeit a simpler one not based on machine learning); and design the cluster-randomised trial that will evaluate this digital health intervention. In many ways, therefore, COVID-19 broadened and enriched my training experience. In addition, it made me realise how versatile I am academically since despite the need to pivot rapidly in a time of many limitations and much uncertainty, this thesis nonetheless contains new knowledge and translatable findings that will contribute to our comprehension and clinical management of AFI in rural South and Southeast Asia.

1.3 Funding

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1.4 Declarations and attributions

I declare that the contents of this thesis are my own work. Unless indicated otherwise, all text, tables, and figures were prepared by me. That said, clinical and epidemiological research is

almost always a multilateral effort and, therefore, many individuals have made substantial contributions to the work reported in here. I acknowledge them below in chapter order.

1.4.1 Chapter 2 – Background

I conceptualised and wrote this chapter. Section 2.3 describing SEACTN and the RFI project is based on work commenced by Arjun Chandna to announce the project in the journal Wellcome Open Research, which I later revised and updated as the final version of the article. Figure 2.1 was prepared by Sazid Ibna Zaman.

1.4.2 Chapter 3 – Demographic, health, and socio-economic status profiles of villages in rural South and Southeast Asia

Yoel Lubell, Richard Maude, and I conceptualised the work for this chapter, which was written by me together with the manuscript submitted for publication. I devised the data collection instrument, which was then modified to incorporate SEACTN site-specific differences with the help of the respective site coordinators (Aninda Sen, Aung Pyae Phyo, Carlo Perrone, James Callery, Koukeo Phommason, Thomas Peto, Wanlapa Roobsoong, and Moul Vanna). Mst. Asfat Ara Joly converted the questions in the data collection instrument into the KoBo Toolbox electronic form used by the data collectors. Figures 3.1 and 3.2 were prepared by Sazid Ibna Zaman, who also performed some of the data analysis with me and is joint first author on the manuscript.

1.4.3 Chapter 4 – Defining the epidemiology of acute febrile illness in rural South and Southeast Asian primary care

I conceptualised and wrote this chapter, building on the broad aims of the observational study on the epidemiology of AFI in primary care settings that comprises SEACTN Work Package A (WP-A). I developed the case report forms, wrote the Standard Operating Procedures (SOPs) and other study documents, developed staff training materials, delivered training-the-trainer

workshops remotely for healthcare workers who would go on to train their colleagues in the study procedures, and participated in on-site and remote monitoring, the last of which was led by Jaruwan Tubprasert and Akanittha Poonchai. Pimsiri Ponsap developed the electronic data collection tool and Kulthida Chaikul managed the study database, both overseen by Naomi Waithira. The site coordinators mentioned in section 1.4.2 oversaw data collection and day-to-day activities at their respective sites, with the logistical support of Watcharintorn Thongpiam and Krongkarn Nareepon. Nicholas Day, Arjun Chandna, James Callery, and Enitan Carrol, along with myself, formed the expert group that generated the algorithmic syndromic diagnosis rules. I conducted the data analysis and visualisation, aided by the statistical expertise of Alistair McLean and Mavuto Mukaka, and wrote the manuscript for publication.

1.4.4 Chapter 5 – Evaluation of pulse oximetry in the primary care management of acute febrile illness

I conceptualised and wrote this chapter, as well as the two associated manuscripts for publication. For the systematic review component, I drafted the review protocol and registered it on the International Prospective Register of Systematic Reviews (PROSPERO), along with assembling the Technical Advisory Panel. Meiwen Zhang assisted with screening of search results. Arjun Chandna adjudicated in the event of disagreement regarding study inclusion, and also checked the accuracy of extracted data. Both of them also assisted me with assessing the quality of included studies, with the person not involved in quality assessment of a particular study adjudicating in the event of disagreement. I performed the analysis and data visualisation.

I constructed and parameterised the models for the cost-effectiveness analysis which comprises the latter half of this chapter. Nidanuch Tasak obtained and translated relevant documents in Thai which were essential for model parameterisation. The real-world patient data on which the models were run were from earlier doctoral research by Rachel Greer, who also supplied Figure 5.3.

1.4.5 Chapter 6 – Evaluation of a putative novel multiplex rapid diagnostic test in the primary care management of acute febrile illness

Yoel Lubell and I conceptualised the modified e-Delphi survey that forms the first half of this chapter, which was written by me. I developed the survey methodology and questionnaires, assembled the expert panels, performed the data analysis, and wrote the manuscript. Matthew Mayer and Salisa Lohavittayavikant constructed the website through which panellists submitted their responses.

I conceptualised the cost-effectiveness analysis which forms the second half of the chapter, which was also written by me. Chris Painter and I constructed the models, which I parameterised. The results were obtained by running the models on software he developed, which also produced the relevant Figures 3.6, 3.7, and 3.8. I wrote the manuscript for publication.

1.4.6 Chapter 7 – Evaluation of an electronic clinical decision support algorithm to improve primary care management of acute febrile illness

I conceptualised this cluster-randomised trial, the protocol for which forms the basis for this chapter, which I wrote along with the associated published protocol paper. I am the Principal Investigator and devised the protocol, developed the case report forms, assembled the Data and Safety Monitoring Board (DSMB), obtained ethical approval from the Oxford University Tropical Research Ethics Committee (OxTREC), and registered the study with the International Standard Randomized Controlled Trial Number (ISRCTN) Registry. The last two activities were conducted with the assistance of Nhathita Panatreswas.

Thomas Peto and Moul Vanna secured the agreement of the Battambang Provincial Health Department for this study. Thomas Peto recruited the study physician, Abhijit Mishra, and, with Lek Dysoley, obtained ethical approval from the National Ethics Committee for Health

Research (NECHR) in Cambodia, where the trial is currently underway. Marco Liverani developed the mobile app through which trial data are being collected. Elke Wynberg drafted the study documents, with assistance from Jaruwan Tubprasert, Akanittha Poonchai, Arjun Chandna, James Callery, and myself. She also co-created Figures 7.1–7.3 with me. Jaruwan Tubprasert and Akanittha Poonchai are the study monitors. Greg Fegan provided statistical support, assisted by Mavuto Mukaka. Naomi Waithira and Vanapol Chamsukhee developed the study database and real-time dashboard. Elke Wynberg, Marco Liverani, Abhijit Mishra, and Moul Vanna provided staff training; Abhijit Mishra, Moul Vanna, and Phal Champheakdey also provide day-to-day supervision for the site research staff and healthcare workers involved in the study. Watcharintorn Thongpiam and Krongkarn Nareepon provided logistical support for the trial.

1.4.7 Chapter 8 – Discussion

This chapter was conceptualised and written by me.

1.5 Papers arising

During the course of my doctoral candidature I have authored the following peer-reviewed journal publications directly associated with the research in this thesis:

1. **Chew R**, Zhang M, Chandna A, Lubell Y. The impact of pulse oximetry on diagnosis, management and outcomes of acute febrile illness in low-income and middle-income countries: a systematic review. *BMJ Glob Health*. 2021;6(11):e007282.
2. Chandna A, **Chew R**, Shwe Nwe Htun N, Peto TJ, Zhang M, Liverani M, et al. Defining the burden of febrile illness in rural South and Southeast Asia: an open letter to announce the launch of the Rural Febrile Illness project. *Wellcome Open Res*. 2022;6:64.

3. **Chew R**, Lohavittayavikant S, Mayer M, Day NPJ, Lubell Y. Perceptions and priorities for the development of multiplex rapid diagnostic tests for acute non-malarial fever in rural South and Southeast Asia: An international modified e-Delphi survey. *PLoS Negl Trop Dis*. 2022;16(11):e0010685.
4. **Chew R**, Greer RC, Tasak N, Day NPJ, Lubell Y. Modelling the cost-effectiveness of pulse oximetry in primary care management of acute respiratory infection in rural northern Thailand. *Trop Med Int Health*. 2022;27(10):881-890.
5. **Chew R**, Painter C, Pan-ngum W, Day NPJ, Lubell Y. Cost-effectiveness analysis of a multiplex lateral flow rapid diagnostic test for acute non-malarial febrile illness in rural Cambodia and Bangladesh. *Lancet Reg Health Southeast Asia*. 2024;23:100389.
6. **Chew R**, Liverani M, Wynberg E, Rekol H, Nguon C, Dysoley L, et al. Evaluation of an electronic clinical decision support algorithm to improve primary care management of acute febrile illness in rural South and Southeast Asia: protocol for a cluster-randomized trial. *BMJ Open*. 2024;14(10):e089616.
7. **Chew R**, Zaman SI, Joly MAA, Uddin D, Nurullah M, Callery JJ, et al. Understanding the primary healthcare context in rural South and Southeast Asia: a village profiling study. *Int Health*. 2025;17(5):754-768.

In my concurrent role as SEACTN coordinator I have authored the publications below, which are indirectly related to my doctoral research:

1. Htun NSN, Perrone C, Phyo AP, Sen A, Phommasone K, Vanna M, et al. Ethical and cultural implications for conducting verbal autopsies in South and Southeast Asia: a qualitative study. *BMJ Glob Health*. 2023;8(12):e013462.
2. Liverani M, Phongluxa K, Phommasone K, **Chew R**, Chandna A, Pongvongsa T, et al. Prospects for the development of community-based care in remote rural areas: a stakeholder analysis in Laos. *BMC Health Serv Res*. 2024;24(1):55.

3. Dysoley L, Callery JJ, Bunreth V, Vanna M, Davoeung C, Sovann Y, et al. Expanding the roles of community health workers to sustain programmes during malaria elimination: a meeting report on operational research in Southeast Asia. *Malar J.* 2024;23(1):2.
4. Zhang M, Htun NSN, Islam S, Sen A, Islam MA, Neogi AK, et al. Defining the hidden burden of disease in rural communities in Bangladesh, Cambodia and Thailand: a cross-sectional household health survey protocol. *BMJ Open.* 2024;14(3):e081079.
5. Zhang M, Kozlowski H, **Chew R**, Htun NSN, Morris SK, Akladios C, et al. The spectrum of health conditions in community-based cross-sectional surveys in Southeast Asia 2010-21: a scoping review. *BMC Public Health.* 2024;24(1):1853.
6. Visser MT, Lek D, Adhikari B, Chandna A, Vanna M, Ol S, et al. Operational evaluation of the deployment of Malaria/CRP Duo and Dengue Duo rapid diagnostic tests for the management of febrile illness by village malaria workers in rural Cambodia. *BMC Infect Dis.* 2025; 25(1):679.
7. Liverani M, Ahmed S, Sen A, **Chew R**, Chandna A, Islam S, et al. Acute febrile illness in remote and rural communities: perspectives of health providers and managers in Chattogram, Bangladesh. *SSM Health Syst.* 2025;5:100090.

Finally, I have also authored the following publications which are outside the scope of the research for this thesis:

1. **Chew R**. Probable spinal neuroschistosomiasis manifesting as transverse myelitis. *Am J Trop Med Hyg.* 2021;105(6):1439-1441.
2. **Chew R**, Woods ML. Multibacillary mid-borderline leprosy with Type 1 lepra reaction and concurrent latent tuberculosis. *Am J Trop Med Hyg.* 2021;106(2):373-375.
3. Cox M, Paviour S, Gregory S, **Chew R**. When fever is more than infection: two cases of vancomycin-induced drug reaction with eosinophilia and systemic symptoms (DRESS). *BMJ Case Rep.* 2021;14(1):e238006.

4. Lawless R, Vickers M, Alawami M, Appasamy N, Rajasingam V, Paviour S, et al. Antimicrobial prescribing and outcomes of community-acquired pneumonia in Australian hospitalized patients: a cross-sectional study. *J Int Med Res*. 2021;49(11):3000605211058366.
5. Callum J, McDiarmid D, **Chew R**. The impact of rapid PCR testing for viral respiratory infections on acute admissions from the Emergency Department and inpatient length of stay. *J Acute Med*. 2022;12(3):96-104.
6. Callum J, Hinde D, **Chew R**. Incipient empyema as an embolic complication of group A streptococcal septic arthritis in a patient with concomitant influenza B infection. *Respirol Case Rep*. 2022;10(12):e01067.
7. Susanto M, Dunning J, **Chew R**. *Pantoea* abscess mimicking sarcoma in a HTLV-1-infected Indigenous Australian man: Case report and literature review. *Clin Case Rep*. 2023;11(5):e7351.
8. **Chew R**, Tozer S, Ulett K, Paterson DL, Whiley D, Sloots T, et al. Comparing polymerase chain reaction testing of nasopharyngeal swab and lower respiratory tract specimens for the diagnosis of *Pneumocystis jirovecii* pneumonia. *Open Forum Infect Dis*. 2024;11(3):ofae071.
9. **Chew R**, Paterson DL, Woods ML. Development and validation of supervised machine learning multivariable prediction models for the diagnosis of *Pneumocystis jirovecii* pneumonia using nasopharyngeal swab PCR in adults in a low-HIV prevalence setting. *Int Health*. 2025;17(5):804-808.

1.6 List of abbreviations

All abbreviations used in this thesis are defined when first used in each chapter for the benefit of readers who do not choose to read it in chapter order. To increase readability further, all

abbreviations used in figures and tables are also defined in the respective legend, regardless of whether they have previously been defined in the main text.

A full list of these abbreviations, in alphabetical order, is provided below as Table 1.1.

Abbreviation	Definition
AFE	Acute febrile encephalopathy
AFI	Acute febrile illness
ALRI	Acute lower respiratory tract infection
AMR	Antimicrobial resistance
aOR	Adjusted odds ratio
ARI	Acute respiratory infection
AHEAD	Action for Health Development
BCG	Bacille Calmette-Guérin
BMRC	Bangladesh Medical Research Council Ethics Committee
CABI	Commonwealth Agricultural Bureaux International
CCRU	Chiang Rai Clinical Research Unit
CENTRAL	Central Register of Controlled Trials
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHOICE	CHOosing Interventions that are Cost-Effective
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CIOMS	Council for International Organizations of Medical Sciences
CNM	National Center for Parasitology, Entomology and Malaria Control
COVID-19	COronaVirus Disease of 2019
CRedit	Contributor Roles Taxonomy
CRISPR	Clustered regularly interspaced short palindromic repeats
CRP	C-reactive protein
CTSG	Clinical Trials Support Group

DALY	Disability-adjusted life year
DARE	Database of Abstracts of Reviews of Effects
DHS	Demographic and Health Survey
DBS	Dried blood spot(s)
DSMB	Data and Safety Monitoring Board
eCDSA	Electronic clinical decision support algorithm
EDAM	Electronic clinical Decision support for Acute fever Management
EMBASE	Excerpta Medica dataBASE
GCP	Good Clinical Practice
GDP	Gross domestic product
GRAM	Global Research on Antimicrobial Resistance
HICs	High-income countries
HIV	Human immunodeficiency virus
ICAT	Implementation of C-reactive protein point of care testing to improve antibiotic targeting in respiratory illness in Vietnamese primary care
ICD	International Statistical Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ICH	International Conference on Harmonization
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMCI	Integrated Management of Childhood Illness
IR	Incidence rate
IRB	Institutional review board
IRR	Incidence rate ratio
ISRCTN	International Standard Randomized Controlled Trial Number
LF	Lateral flow
LMICs	Low-income and middle-income countries
LOMWRU	Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit

LOS	Length of stay
LRTI	Lower respiratory tract infection
MICS	Multiple Indicator Cluster Survey
MNCH	Maternal, neonatal, and child health
MORU	Mahidol Oxford Tropical Medicine Research Unit
MVRU	Mahidol Vivax Research Unit
NECHR	National Ethics Committee for Health Research
NMFI	Non-malarial febrile illness
NS1	Non-structural protein 1
OR	Odds ratio
OxTREC	Oxford University Tropical Research Ethics Committee
PO	Pulse oximetry
PRECIS-2	PRagmatic Explanatory Continuum Indicator Summary-2
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
PROSPERO	International Prospective Register of Systematic Reviews
QI	Quality improvement
RDT	Rapid diagnostic test
RFI	Rural Febrile Illness
RoB 2 CRT	Risk of Bias 2 tool for Cluster Randomised Trials
ROBINS-I	Risk of Bias in Non-randomized Studies – of Interventions
<i>robvis</i>	Risk-Of-Bias VISualization
RR	Risk ratio
SAP	Statistical Analysis Plan
SD	Standard deviation
SEACTN	South and Southeast Asian Community-based Trials Network
SEAQUAMAT	South East Asian Quinine Artesunate Malaria Trial
SMRU	Shoklo Malaria Research Unit
SOMAmer	Slow Off-Rate Modified Aptamer

SOP	Standard Operating Procedure
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SpO ₂	Peripheral oxygen saturation
URTI	Upper respiratory tract infection
US	United States
VHW	Village health worker
VMW	Village malaria worker
WHO	World Health Organization
WHO/UNICEF JMP	World Health Organization/United Nations Children's Fund Joint Monitoring Program for Water Supply, Sanitation, and Hygiene
WP-A	Work Package A
WP-B	Work Package B
WP-C	Work Package C

Table 1.1. List of abbreviations used in this thesis.

CHAPTER 2 | BACKGROUND

This chapter draws upon work published in: Chandna A, Chew R, Shwe Nwe Htun N, Peto TJ, Zhang M, Liverani M, et al. Defining the burden of febrile illness in rural South and Southeast Asia: an open letter to announce the launch of the Rural Febrile Illness project. *Wellcome Open Res.* 2022;6:64.

2.1 Acute febrile illness in rural South and Southeast Asian primary care: knowns and unknowns, challenges and opportunities

Worldwide, acute febrile illness (AFI) is an important reason for seeking healthcare.¹ It is estimated to account for over a billion healthcare encounters each year,² imposing a considerable burden in terms of morbidity, mortality, and expenditure, particularly in primary care settings.^{3,4} Relative to high-income countries, tropical low-income and middle-income countries (LMICs), such as those in South and Southeast Asia, bear a disproportionate share of this burden with most AFI episodes likely due to infective causes, reflective of the poverty in which the majority of their populations live.⁵⁻⁸ This disparity is even more apparent in rural areas of South and Southeast Asian LMICs, where health literacy is lower and health services more basic compared to their urban counterparts.⁹

Historically, malaria – the quintessential ‘tropical fever’ – constituted the bulk of AFI presentations in South and Southeast Asia, much like in Africa. Nevertheless, the success of malaria control programmes due to global investment since 2000 in distributing insecticide-treated nets and increasing the availability of rapid diagnostic tests (RDT) and artemisinin combination therapies administered by community-based healthcare workers, mean that this is no longer the case.^{10,11} In fact, mirroring the global trend, malaria incidence in South and Southeast Asia has been steadily decreasing to the point that many countries, especially those in the Greater Mekong Sub-region, are on the verge of malaria elimination.¹²

The major consequence of this epidemiological shift is the increasing proportion of AFI attributable to non-malarial febrile illness (NMFI) in the region, demonstrated by the rising numbers of patients with AFI who return negative malaria RDT results and those whose diagnosis of malaria is solely presumptive.^{13, 14} These NMFIs are caused by a myriad of pathogens from the different microbial classes (bacteria, viruses, parasites, and fungi) and may present as syndromes affecting particular organ systems e.g., community-acquired pneumonia, or as fevers of unknown source which do not localise to a particular organ system.¹⁵ In addition to the diversity of microbial aetiologies, symptoms and signs are non-specific and overlapping, making diagnosis and treatment difficult, even for highly-trained staff with access to sophisticated laboratory diagnostics.¹⁶

The complexities of NMFI stated above, and the longstanding emphasis on vertical malaria elimination efforts, have starkly exposed the inability of primary healthcare providers to diagnose and manage acute NMFI following a negative malaria RDT result. While there is huge variation, even within countries, of the many types of healthcare worker who provide primary care, there are very few doctors and most are village health workers (VHWs) or village malaria workers (VMWs) i.e., lay volunteers or semi-skilled staff with limited training in diagnosis and treatment beyond that which relates to malaria (for VMWs), or malaria and rudimentary preventive and curative care (for VHWs).¹⁷⁻²¹ Although expanding their remits to include more comprehensive management of non-malarial illness is being explored in several countries,^{18, 19,}²¹ the current clinical knowledge and skillsets, as well as workloads, of most rural primary healthcare providers do not generally allow for comprehensive medical history-taking, physical examination, and formulation of syndromic working and differential diagnoses which consider the various manifestations and causes of NMFI.²² A second major category of primary healthcare staff are those working in primary health centres or community clinics, who have

received limited paramedical or nursing training. Some primary health centres may have fully-qualified nurses, such as in Thailand.²³

This lack of capacity among primary healthcare providers is compounded by the lack of availability of diagnostic tools to help healthcare workers make test-based diagnoses when NMFI clinical features are non-specific, as they often are, and syndromic diagnoses are insufficient to guide treatment e.g., in the case of leptospirosis or scrub typhus. Lamentably, however, there is precious little available at the point of care to identify the causative organism for the many AFIs prevalent in Asia,²⁴ much less any which are tailor-made for the high-temperature, high-humidity climate and rudimentary facilities that characterise rural primary care settings, such as the lack of stable electricity supply.^{25, 26} This problem, coupled with apprehension about withholding empirical antibiotics in difficult-to-access populations mean that antimicrobials are widely prescribed but poorly chosen and inaccurately targeted.¹⁴ For example, extrapolating the findings from a secondary care setting in Laos by Mayxay et al., the oral β -lactams commonly dispensed in primary care would be ineffective or sub-optimal in a considerable proportion of patients with bacterial NMFIs i.e., those with rickettsioses and enteric fever, while still being prescribed to the majority of patients with viral illnesses.²⁷

Such indiscriminate prescribing also contributes to the global health emergency of antimicrobial resistance (AMR).²⁸ The World Health Organization (WHO) has previously identified the threat of antimicrobial resistance to human health in the Southeast Asian region to be one of the highest in the world,²⁹ with the Global Research on Antimicrobial Resistance (GRAM) project estimating that approximately 389,000 and 254,000 deaths in the South Asia and Southeast Asia regions, respectively, were directly attributable to AMR in 2019.³⁰

Additionally, many acutely febrile patients who objectively require hospital referral based on illness severity at presentation are likely not correctly identified, extrapolating from findings in developed country pre-hospital settings where, despite better staff skill levels, considerable

gaps in early recognition of the unwell patient still exist.^{31, 32} In the context of acute infection, these patients are likely to have sepsis, which is a medical emergency and which, if not treated early, leads to excess mortality and morbidity.³³ Conversely, many patients who do not require hospital admission are referred, thus overburdening already stretched secondary care facilities,² although it should be recognised that, in addition to clinical need, contextual and cultural factors also influence decisions to refer and compliance with referral recommendations.³⁴ Therefore, a further challenge for primary healthcare workers managing patients with AFI is how to risk-stratify such patients. While there is current interest in determining biomarkers which may have prognostic value and developing machine learning or other predictive models to determine which patients will go on to develop poor clinical outcomes, this has not yet translated into tools applicable to rural primary care in LMICs.³⁵

All the above issues are not new and, in fact, were already of concern more than a decade ago.³⁶ Nonetheless, they are especially pressing now not just because little progress has been made, but also because failure to address them adequately threatens the achievement of the goal to eradicate malaria. This is because inability to diagnose and treat NMFI at the primary care level leads to decreasing patient trust in the health system and acts as a barrier to care-seeking for AFI, thus ensuring the survival of residual malaria parasite reservoirs in the population.¹⁸

One way of mitigating the challenges described previously is to base non-medically trained primary healthcare worker upskilling around common syndromes and causative pathogens, integrating this approach into broader national public health agendas. Unfortunately, such detailed but fundamentally important knowledge of the current epidemiology of AFI at the peripheries of South and Southeast Asian health systems is lacking as, to date, no robust prospective studies have been conducted in rural primary care settings in these regions.³⁷ The lack of evidence to date from large-scale studies of AFI targeting rural primary care settings in

South and Southeast Asia is, perhaps, not surprising given the high cost, geographical isolation, and scarcity of laboratory resources.^{38, 39} While some routinely-collected data on syndromic diagnoses in primary care is extant, they are not publicly available; in any case, their accuracy and comprehensiveness are debatable, given the workload and diagnostic skill limitations of primary healthcare workers mentioned above.

Therefore, not only is the epidemiological evidence on AFI in South and Southeast Asia presently available scant, but most of the studies on which it relies are focused on microbial aetiology or single diseases rather than syndromes.^{14, 40-42} This pathogen-focused approach is hampered by several weaknesses. These include the challenge of accurately attributing causation i.e., differentiating infection from colonisation,^{43, 44} the possibility of co-infections,⁴⁵ the limitations of the diagnostic assays used,⁴⁶ and absence of data on pathogens which were not looked for by design e.g., because they were not considered to have lower clinical significance or not be endemic.⁴⁷ Accordingly, the true causative pathogens in many of patients in such cause-of-fever studies could not be identified, with identification rates seldom exceeding 50% even before misclassification is accounted for.^{27, 44, 48} Furthermore, given that AFI has diverse manifestations, the strongest description of its epidemiology is one that will place equal emphasis on both syndromes and aetiology.

There are several further limitations of the available epidemiological evidence, the first of which is the heterogeneity of case definitions used.^{14, 38} The second is the high risk of bias since the bulk of the literature consists of case reports, case series, and small studies.⁴⁰ Thirdly, likely due to the cost and accessibility barriers to conducting methodologically sound epidemiological studies of AFI in rural areas of LMICs mentioned previously, these studies originate mainly from hospitals in urban centres.^{14, 40} Their findings may, therefore, not be relevant to the rural primary care context since, despite increasing urbanisation, most of the population in South and Southeast Asia still live in villages and receive the bulk of their healthcare from primary care

providers.⁴⁹ Finally, most of these studies were conducted in the upper-middle income countries of the region,⁴⁰ whereas the burden of AFI is likely heaviest in low-income and lower-middle income countries. Researchers, industry players, and policymakers in South and Southeast Asian LMICs, thus, face the challenge of allocating time, energy, and resources to programmes aiming to obtain maximal public health benefit without solid epidemiological evidence to aid their decision-making.

Nevertheless, these challenges give rise to many opportunities to improve the primary care management of AFI in rural South and Southeast Asia. The most obvious priority is to define its contemporary epidemiology systematically and prospectively in a variety of countries, primary care settings, and age groups, taking into account any seasonal variation since climate-driven surges in vector-borne and occupational exposure-related diseases are not uncommon.^{50, 51} Another reason this wide-ranging approach is important is that while overall national incidence rates of malaria have decreased substantially, this phenomenon is not likely to be uniform across patient groups and geographical areas, as evidence from sub-Saharan Africa has shown.⁵² Closely linked to this first priority is to devote resources for developing and implementing interventions with the potential to improve the clinical management of AFI by primary health workers, for example algorithmic decision support tools incorporating diagnostic and prognostic tests along with associated training. However, given that resources are scarce in South and Southeast Asian LMICs, their allocation should be based on the soundest evidence as possible.

2.2 Research rationale, and aims and objectives

The challenges and opportunities described in the previous section were the guiding principles of the research on which this thesis is based. As such, its overarching aims were to:

1. Develop an understanding of the epidemiology of AFI in the South and Southeast Asian rural primary care context in a manner that will have immediate applicability to policymakers, clinicians, and researchers.
2. Evaluate, through various lenses, tools to aid clinical management of AFI in a range of rural South and Southeast Asian primary care settings.

To achieve the above aims, this research project had the following specific objectives:

1. To provide a rich and comprehensive description of the epidemiology of AFI across a diversity of rural primary care settings, quantifying disease burden not just in terms of common presenting syndromes but also outcomes, through a large-scale observational study in five South and Southeast Asian countries.
2. To provide a high-level profile of the rural village environments in which the above observational study was done, identifying commonalities and differences in terms of health, socio-economic, and infrastructure indicators across countries, to place the epidemiological findings in their proper context.
3. To explore systematically the evidence for two interventions which can be used to aid clinical decision-making by rural primary healthcare workers, one currently available (pulse oximetry) and one with the potential to be developed through a translational pipeline (a putative multiplex rapid diagnostic test), and to evaluate the cost-effectiveness of these interventions.
4. To devise an interventional study of a novel algorithm-based electronic clinical decision support tool developed based on the findings of the previous components of this research.

2.3 The South and Southeast Asian Community-based Trials Network

This research was conducted as a key component of the multi-disciplinary Rural Febrile Illness (RFI) project of the multinational South and Southeast Asian Community-based trials Network (SEACTN).⁵³ Funded by the Wellcome Trust under its 'Innovation in low- and middle-income countries' Flagship programme,⁵⁴ the SEACTN RFI project has as its primary immediate goal the definition of the epidemiology of AFI across seven rural underserved areas (study sites) of five countries in South and Southeast Asia i.e., Thailand, Cambodia, Laos, Myanmar, and Bangladesh, through a network of community-based healthcare providers and facilities at the primary and secondary care levels serving 710 pre-defined study villages. The longer-term objective is to permanently establish the network as a platform to implement interventions targeted at improving the management of AFI and other conditions in these rural areas.

The core of the SEACTN RFI project is comprised of three work packages. Work Packages A and B (WP-A and WP-B) are observational epidemiological studies focusing on describing the syndromes, aetiologies, management, and outcomes of patients with AFI. WP-A aims primarily to determine the incidence, management, and outcomes of the presenting syndromes of 80,000–100,000 acutely febrile patients seeking care from primary care providers. In contrast, there is a greater emphasis on aetiology in WP-B, which aims to recruit fewer patients (7,200) presenting to secondary care facilities but collect a more comprehensive set of clinical data, in addition to venous blood and nasopharyngeal swab samples, from each patient. WP-C draws on data from WP-A and WP-B to design and evaluate tools which have the potential to aid diagnosis and management of AFI, with the ultimate goal of incorporating these tools as part of novel electronic clinical decision support algorithms (eCDSAs) to aid healthcare workers manage patients presenting acutely with fever. The research reported in this thesis formed key deliverables of WP-A and WP-C.

The basis of SEACTN is the strong, long-lasting collaborations between the Mahidol Oxford Tropical Medicine Research Unit (MORU), which serves as the coordinating centre of the network, and partner organisations at each site. These partner organisations had primary responsibility for identifying villages and their associated healthcare providers for inclusion in the RFI project that aligned best with the project aims, given that they know intimately the needs of, and challenges facing, the communities in which they work. These collaborations and the locations of the study sites will now be described briefly.

Three sites are located in Chiang Rai, Tak, and Yala provinces of Thailand, respectively. The Chiang Rai site is managed by the Chiang Rai Clinical Research Unit (CCRU) and the Chiang Rai Provincial Public Health Office. This site consists of 35 primary health centres (PHCs) staffed by non-medically trained health workers and whose main function is to provide basic primary care, including, but not limited to, ante-natal care, immunisations, and health promotion, in addition to seeing patients who present acutely. The other two Thai sites are in the provinces with the second (Tak) and fourth (Yala) highest malaria incidences in Thailand as of 2021.⁵⁵ They are managed by the Mahidol Vivax Research Unit (MVRU) leveraging the existing government malaria control programme infrastructure of malaria posts staffed by VMWs,¹⁷ in addition to several PHCs (seven malaria posts and ten PHCs in Tak; 22 malaria posts and five PHCs in Yala).

Similar to PHCs in Thailand, those in the other sites are also manned by health workers with limited training. The Lao site comprises 26 PHCs located in Atsaphangthong, Thaphalanxay, and Phin districts of Savannakhet province, and is overseen by the Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit (LOMWRU) and Savannakhet Provincial Health Office.

The Bangladeshi site is located in Cox's Bazar and Bandarban districts of Chattogram division and is run by BRAC, the largest non-governmental development organisation in the

world. The Cambodian site encompasses the contiguous Battambang and Pailin provinces, overseen by the National Center for Parasitology, Entomology and Malaria Control (CNM), the relevant Provincial Health Departments, and Action for Health Development (AHEAD), a local civil society organisation working to improve health in rural communities. Both these sites are comprised of a combination of mobile VMWs/VHWs and PHCs (246 VMWs and nine PHCs in Cambodia; 100 VHWs and 22 PHCs in Bangladesh).

Finally, a network of 25 PHCs and 21 VMW-manned malaria posts in the Hlaingbwe, Myawaddy, and Kawkareik townships of Karen state, Myanmar just north of the Thailand border make up the Myanmar site, supervised by the Shoklo Malaria Research Unit (SMRU). An eighth site in Myanmar located in Kachin state was initially planned, but political instability resulting from the military coup of February 2021 precluded this site from launching. Study site locations are shown in Figure 2.1, and a fuller description of the SEACTN RFI project can be found in the open letter by Chandna et al.⁵³

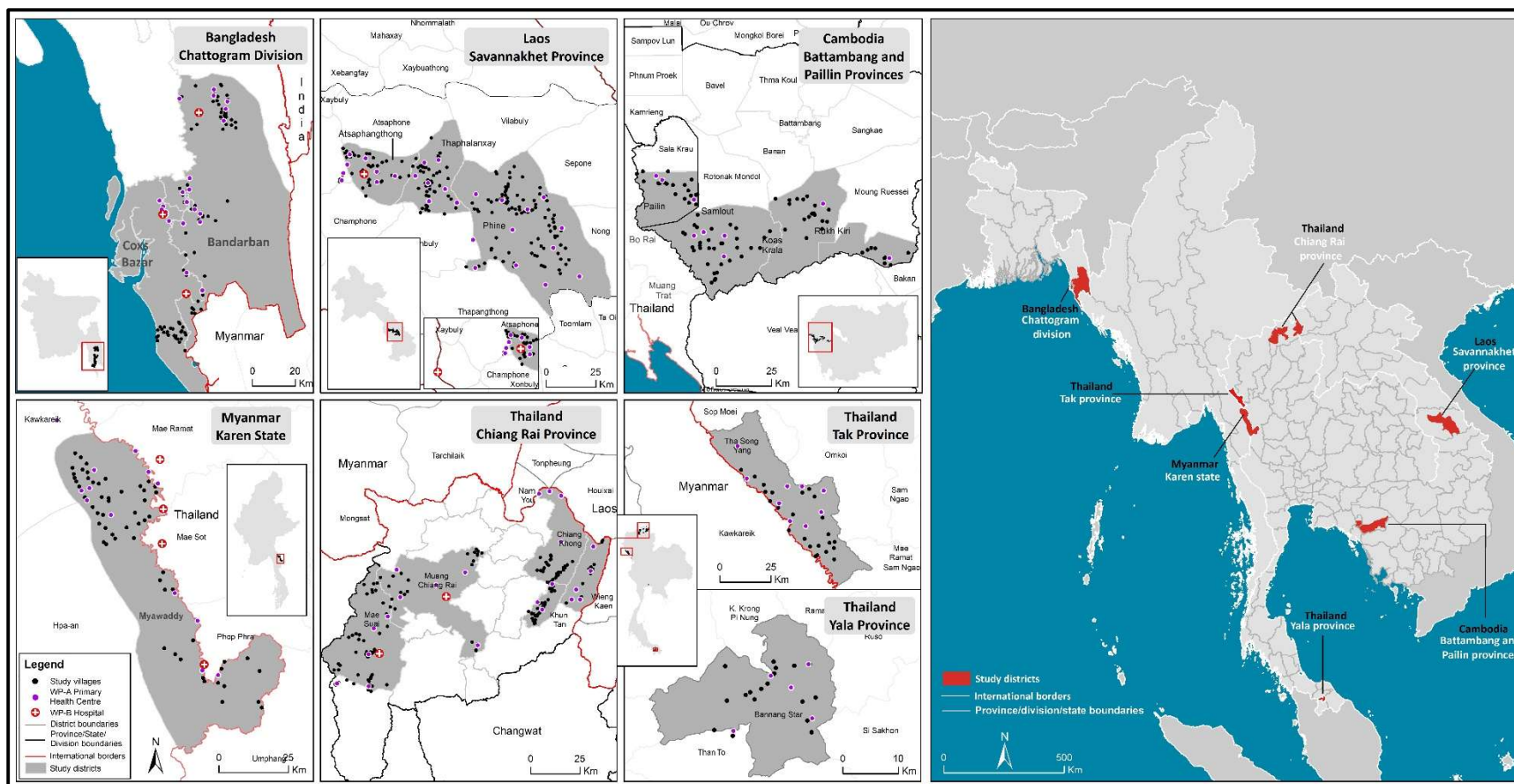


Figure 2.1. Map of the South and Southeast Asian Community-based Trials Network (SEACTN) showing the locations of the study sites in the region, and the villages and health facilities within each site. WP-A, SEACTN Work Package A which aims to define the epidemiology of acute febrile illness in primary care settings; WP-B, SEACTN Work Package B which aims to define the epidemiology of acute febrile illness in secondary care settings.

2.4 Thesis overview

This section provides brief descriptions of the chapters in the thesis, and maps their content to the relevant objectives of the project, as mentioned in section 2.2, they fulfil.

Having outlined the importance of the topic and stated the research questions to be answered in this chapter, along with a broad description of the locations in which the research was conducted, the next chapter ('Demographic, health, and socio-economic status profiles of villages in rural South and Southeast Asia') places the findings of this research in their proper context by presenting high-level profiles of the study villages at each site, addressing the second objective of this project. The content of Chapter 3, thus, sets the scene for understanding the results reported in subsequent chapters.

Chapter 4 ('Defining the epidemiology of acute febrile illness in rural South and Southeast Asian primary care') addresses the first objective by presenting the findings of the WP-A observational study of over 82,000 patients describing the epidemiology of AFI in rural South and Southeast Asian primary care settings, with an emphasis on presenting syndromes, clinical management, and outcomes. This chapter does not include microbiological diagnoses, as this is the subject of another doctoral project and will be reported separately.

Chapters 5 ('Evaluation of pulse oximetry in the primary care management of acute febrile illness') and 6 ('Evaluation of a putative novel multiplex rapid diagnostic test in the primary care management of acute febrile illness') address the third objective by evaluating two tools with the potential to improve AFI management: an existing tool (pulse oximetry) and an as-yet undeveloped tool [a multiplex lateral flow rapid diagnostic test (LF-RDT) utilizing fingerprick blood as the test substrate], respectively. Chapter 5 examines the evidence for augmenting AFI management with pulse oximetry through a systematic review, followed by a health economic evaluation of pulse oximetry in patients with acute respiratory infection (ARI), the commonest

presenting AFI syndrome found in the observational study. Chapter 6 aims to guide priority-setting for analytes to be included in a putative multiplex LF-RDT through a Delphi survey, then presents the results of an economic evaluation of this LF-RDT using data from the Bangladesh and Cambodian sites of the observational study.

Chapter 7 ('Evaluation of an electronic clinical decision support algorithm to improve primary care management of acute febrile illness') integrates the findings from Chapters 4–6 to address the final objective in the form of a clinical trial protocol for a cluster-randomised trial evaluating a novel eCDSA for AFI management in primary health centres (PHCs) that incorporates pulse oximetry, syndromic diagnosis, and RDTs. This trial is currently in progress, but the results do not form part of this thesis as they will only become available after the conclusion of my doctoral candidature.

Finally, Chapter 8 ('Discussion') synthesises the principal findings of all the components of this research, aiming to draw meaningful conclusions that will be of immediate use to policymakers, as well as identify directions to guide future research built on these conclusions.

CHAPTER 3 | DEMOGRAPHIC, HEALTH, AND SOCIO-ECONOMIC STATUS PROFILES OF VILLAGES IN RURAL SOUTH AND SOUTHEAST ASIA

This chapter draws upon work published in: **Chew R**, Zaman SI, Joly MAA, Uddin D, Nurullah M, Callery JJ, et al. Understanding the primary healthcare context in rural South and Southeast Asia: a village profiling study. *Int Health*. 2025;17(5):754-768.

3.1 Introduction

In rural South and Southeast Asia, despite differences in health systems between countries in terms of financing and structure (Table 3.1), healthcare is principally delivered at the village, or village group, level through village health workers and primary health centres, with referral facilities typically being distant and relatively difficult to access.^{56, 57} As such, interventions targeting primary healthcare would be expected to produce maximum impact. Nevertheless, as previous experience with primary health centres in India has shown, despite the apparent basing of health service provision on the principles of equity and administrative accountability, not catering to local contextual variations between villages and not involving local staff in service planning resulted in sub-optimal healthcare delivery.⁵⁸ The key variables relate to service coverage and socio-economic and geographical factors,⁵⁸ the determination of which have the benefit of being useful for micro-planning i.e., planning of health services and interventions at the village or sub-district level.⁵⁹

An understanding of these contextual factors is crucial to the successful implementation of interventions to improve healthcare delivery. Although there is no one standard definition of 'context' as it relates to healthcare,⁶⁰ one useful definition is the "situational opportunities and constraints that affect the occurrence and meaning of organisational behaviour as well as

functional relationships between variables”,⁶¹ indicating that context necessarily includes both intrinsic and extrinsic inter-related factors.⁶²

Constructing concise yet comprehensive village profiles which contain relevant key indicators is one way of characterising contextual factors important for the implementation of primary healthcare interventions and service planning. These must be as simply described as possible, widely accepted, and highly applicable to the village setting. They should also be easily comparable, sensitive to change, and yield data which is meaningful and easy to analyse.⁶³

While governmental authorities may have village-level data on some of these indicators, these may not be available from a single source and may not be current, especially as access to rural and remote locations is difficult. Correspondingly, there is also scant published research which aimed to depict the rural South and Southeast Asian primary healthcare context via the profiling of representative villages, let alone research which aimed to compare high-level village profiling data across countries. The research reported in this chapter aimed to fill these knowledge gaps, primarily to understand better the findings of the large-scale observational study on the epidemiology of acute febrile illness in the region in which patients were recruited from the selected villages as well as associated studies forming part of the South and Southeast Asian Community-based Trials Network (SEACTN) Rural Febrile Illness (RFI) project.⁵³ The aforementioned observational study and its results are described in detail in Chapter 4 (‘Defining the epidemiology of acute febrile illness in rural South and Southeast Asian primary care’). Equally importantly, it is hoped that the results of this village profiling exercise will be useful to researchers and health authorities in planning future research and guiding policy-making.

Country	Universal health coverage	Structure of primary healthcare system
Bangladesh	No (targeted for 2032)	- Delivered by public (under the Ministry of Health and Family Welfare and other ministries) and private sector providers, as well as non-governmental organisations - Public sector primary care is provided at all tiers of Ministry of Health and Family Welfare facilities from community primary health centre (PHC) to tertiary hospitals; many villages have lay village health workers (VHWs) who can treat uncomplicated malaria and provide health promotion - PHC services include maternal, neonatal, and child health (MNCH), reproductive health and family planning, nutrition, and some communicable and non-communicable disease management; these are provided for free - Each PHC, which is led by a non-medically qualified Community Health Care Provider serves a population of approximately 6,000 people
Cambodia	No (targeted for 2035)	- Delivered by public, private, and non-medical sector providers - Public sector PHCs led by nurses and midwives provide MNCH services, immunization, nutritional education, family planning, and some communicable and non-communicable disease management, as well as outreach to villages; each PHC serves approximately 12,500 people and at smaller, more remote communities >15 km from a PHC there may be a Health Post, and many villages have VHWs - Co-payment is required at PHCs unless covered by health insurance schemes, such as the Health Equity Fund for eligible low-income families - PHCs are meant to be gatekeepers for secondary care, but in practice patients are able to bypass them and go directly to public sector hospital outpatient clinics - Private providers deliver a major proportion of primary health care, often through government health staff working privately (dual practice)
Laos	No (targeted for 2025)	- Delivered by public and private sector (mainly in urban areas) providers - Rural villages have volunteer VHWs who provide health education and health promotion services - Public sector PHCs, each serving a catchment population between 1,000 and 5,000 people, provide treatment of common diseases, vaccinations, antenatal care, birth assistance, postnatal care, and home visits to patients suffering from chronic conditions or with poor mobility - Most PHCs do not meet the national minimum staffing standard of one doctor, nurse, and midwife, and are heavily dependent on semi-skilled volunteers and contractors, especially in rural areas - Co-payment is required at PHCs except for pregnant women, children, and those with a monthly income below the national poverty line
Myanmar*	No (targeted for 2030)	- Delivered by public and private sector providers - Public sector rural PHCs and sub-PHCs led by non-medically qualified Basic Health Staff (health assistants, midwives, health visitors, and public health supervisors) provide basic primary care services overseen by their respective township, district, and region and state health departments, which provide technical assistance and support - PHC and sub-PHC catchment populations vary, and patients need to pay for medications and consumables if required
Thailand	Yes (excludes non-citizens)**	Delivered by public and private sector providers

		• Each sub-district (approximately 5,000 people) has at least one nurse-led public sector PHC which provides health promotion, prevention, medical treatment, and rehabilitation services (free for Thai citizens and eligible residents); malaria posts and clinics are also present in most malaria-endemic districts • Private clinics are widely available, and patients are able to bypass PHCs and go directly to public sector hospital outpatient clinics

Table 3.1. Health system overview of South and Southeast Asian Community-based Trials Network (SEACTN) countries, with a particular focus on primary care service delivery.^{19, 64-78} Universal health coverage, as defined by the World Health Organization, means that all people have access to the full range of quality health services they need, when and where they need them, without financial hardship.⁷⁹ *An armed conflict is currently occurring in large parts of Myanmar, with many areas not under the authority of the central government; this description only applies to areas under government control. **SEACTN sites in Thailand are in border areas, where many non-Thai citizens not included in the national universal health coverage scheme access health services.

3.2 Methods

3.2.1 Setting

This study was carried out across 687 of the 710 villages (96.8%) included in SEACTN, which spans seven sites across five countries (Thailand, Laos, Cambodia, Bangladesh, and Myanmar) (Figure 3.1). As described in Chapter 2 ('Background'), the sites are located in rural areas of the following locations: Chiang Rai, Tak, and Yala provinces, Thailand; Savannakhet province, Laos; Chattogram division, Bangladesh; Battambang and Pailin provinces, Cambodia; and Karen state, Myanmar. Twenty SEACTN villages located in Tak province, Thailand and three located in Karen state, Myanmar were omitted due to logistical difficulties and security concerns, respectively.

There were no fixed criteria for selecting villages for inclusion in SEACTN. Participating villages were selected by country implementing partners, who have the most knowledge to determine which villages are representative of the areas where the target populations for the observational study and other RFI project components reside, and where prospective, directly-collected data would be most useful. Of note, one of the primary objectives of establishing SEACTN, which was to map and describe health services in under-served and under-studied rural and remote areas of South and Southeast Asia, was a guiding principle in selecting villages. Other factors influencing village selection by country partners included existing relationships, for instance participation in previous research or operational projects, and logistical considerations.

For example, an exception was made for the Myanmar site due to the ongoing armed conflict in Karen state,⁸⁰ resulting in the need to reduce inaccessibility to ensure the viability of conducting other SEACTN activities. Therefore, while all villages profiled were rural, these were in the area near the Thai border rather than in the interior of Karen state, and better connected

to transport and communication infrastructure. Because of this, and their borderland location, residents of these villages were also able to access facilities in Thailand, in particular health services.

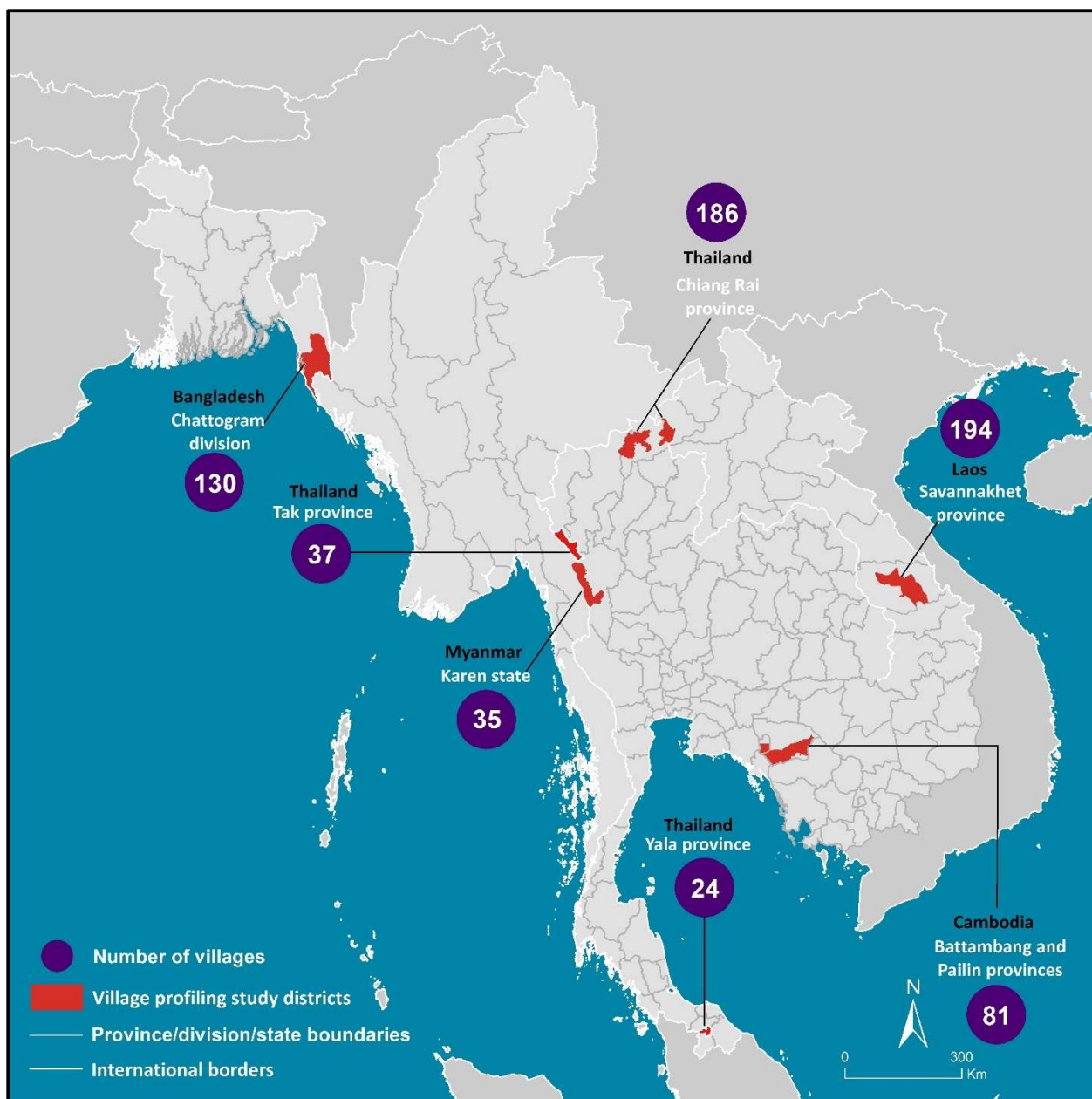


Figure 3.1. Locations of study sites in the South and Southeast Asian Community-based Trials Network and the number of villages profiled at each site.

3.2.2 Study design

Similar to previous studies which collected data on key health indicators,⁸¹ a survey-based study design was adopted, with key informants used as respondents. These key informants were identified by site research staff, and included healthcare workers, village leaders, and villagers who were judged to have the requisite knowledge. The number of key informants per village to interview was also determined by the country implementing partners, deferring to their knowledge on the prevailing conditions at each site and, thus, the most pragmatic and practicable approach to obtain the necessary information. Other data sources included Global Positioning System (GPS) data, census data, and published government documents e.g., official statistics. It should be noted, however, that a detailed exploration of health-seeking behaviour among residents of the study villages was outside the scope of this study. This very important research question will be the focus of other SEACTN projects.

3.2.3 Questionnaire development

The survey questionnaire was developed iteratively through a series of discussions with senior researchers from each site. This approach was taken to ensure that only relevant and useful data were collected and, for questions where respondents were presented with options from which to select, the options were tailored to site-specific conditions.

The questionnaire consisted of four sections, covering village location, socio-economic conditions, health services and infrastructure, and public utilities. Questions on key health and socio-economic indicators were adapted from the indicators of resources and service performance identified by Larson and Mercer as being well-defined, valid, feasibly collected, and useful i.e., literacy rate, percentage of attended deliveries, percentage of fully-immunised children, and percentage of latrine coverage.⁶³

Given country-specific differences in the definition of literacy, a proxy measure of completion of at least five years' schooling in adults aged ≥ 18 years was used instead. As per the World Health Organization (WHO), an attended birth was defined as one presided over by a skilled birth attendant i.e., an accredited health professional, such as a midwife, doctor or nurse, who has been educated and trained to proficiency in the skills needed to manage normal uncomplicated pregnancies, childbirth and the immediate postnatal period, and in the identification, management and referral of women and neonates for complications. Traditional birth attendants, whether trained or not, are not classed as skilled birth attendants.⁸² For clarity, definitions of the various healthcare worker roles are shown in Table 3.2. A fully immunised child was defined as one who has received the following vaccines: Bacille Calmette-Guérin (BCG); three doses of diphtheria, pertussis, and tetanus; three doses of polio; and measles by the age of one year.⁶³ Estimates for educational attainment, skilled birth attendance, and vaccine coverage were obtained by asking key informants to consider a representative sample of 20 persons relevant to the question, thus are rounded to the nearest 5% at the point of data collection.

The WHO/United Nations Children's Fund Joint Monitoring Program for Water Supply, Sanitation, and Hygiene (WHO/UNICEF JMP) defines 'improved drinking water sources' as those that are likely to be protected from outside contamination, particularly faeces. Examples include household connections, public standpipes, boreholes, and protected dug wells.⁸³ The WHO/UNICEF JMP also distinguishes between 'improved' and 'unimproved sanitation facilities', with the former defined as those that hygienically separate human waste from human contact including flush or pour-flush to piped sewer systems, septic tank pit latrines, ventilated-improved pit latrines, or pit latrines with slab or composting toilets. Importantly, shared or public-use sanitation facilities are not considered to be improved.⁸³

To describe access to health services and other relevant infrastructure and public utilities, respondents were asked to list the services available in the village or within 30 minutes' walk, of their residence., This 30-minute travel time was chosen as it has been widely used to define appropriate accessibility.^{84, 85}

The survey questionnaire template, which formed the basis for the study electronic data collection tool described in the next section, is shown in Appendix 3.1. Questionnaires for each site were translated into the main language used at that site to ensure that language was not a barrier.

Role	Definition
Doctor	A healthcare worker who has completed a course of training in allopathic medicine at a medical school accredited or recognised in the country of practice
Nurse	A healthcare worker who has completed a course of training in nursing at a nursing school accredited or recognised in the country of practice
Pharmacist	A healthcare worker who has completed a course of training in pharmacy at a pharmacy school accredited or recognised in the country of practice
Primary health centre worker	A healthcare worker who is not a doctor, nurse, or midwife and who has completed a course of training conducted by the local health authority to equip them to work in a para-medical capacity in a primary health centre
Auxiliary midwife	A healthcare worker who assists in the provision of maternal and newborn health care, particularly during childbirth but also in the prenatal and postpartum periods. They may have had a period of on-the-job training, sometimes formalised in apprenticeships and possess some midwifery competencies but are not fully qualified as midwives. They also have basic nursing skills and no training in nursing decision-making
Village health worker	A layperson who has received some para-medical training (up to two years) but is not considered a health professional, and who is based in their village of residence i.e., they provide services outside of health facilities or at peripheral facilities not staffed by health professionals
Village malaria worker	A village health worker with a narrower remit focusing solely or primarily on the diagnosis and treatment of malaria in the community
Malaria post worker	Equivalent to a village malaria worker but who works in a malaria post
Traditional birth attendant	A layperson who assists a mother during childbirth and initially acquired their skills by delivering babies themselves, or through apprenticeship to other traditional birth attendants
Traditional healer	A layperson who has not had any formal medical training, but is considered by the local community as being competent to provide healthcare using animal, plant and mineral substances and certain other techniques based on social, cultural and religious background as well as the knowledge, attitudes and beliefs that are prevalent in the community regarding physical, mental and social well-being and the causation of disease and disability
Informal healthcare provider	A layperson who does not have any formal healthcare training, whether allopathic or traditional, but who claims to be competent to provide healthcare

Table 3.2. Definitions of healthcare worker roles used in this study. World Health Organization definitions were used to define ‘auxiliary midwife’,⁸⁶ ‘village health worker’,⁸⁷ ‘traditional birth attendant’,⁸⁸ and ‘traditional healer’.⁸⁹

3.2.4 Data collection instrument and study procedures

Electronic versions of the survey questionnaire tailored to each site was developed using KoboToolbox (Kobo Organization, Cambridge, USA) and loaded onto tablet devices. Data collection was then carried out electronically for each village by site research staff using a combination of visits to the village, telephone interviews, and desk-based research. Data collection at each site was conducted over a period of one to two months. However, this was not carried out simultaneously at all sites as research staff were also engaged in other projects; the first site commenced data collection on 5 January 2023 and the last site to finish did so on 2 August 2024. Using the translated questionnaires as scripts, three to five local research staff at each site were tasked with data collection. These staff received appropriate training on conducting interviews and using the electronic data collection instrument by the relevant site study coordinator. Interviews were not recorded and transcribed, since the vast majority of the questions did not require free-text responses and could be answered either through selecting from a range of options or by providing a short response in the form of a number.

Village population figures were obtained from the latest available official statistics; for villages where these were not available, estimates were obtained through key informant interviews.

Key informants were interviewed either in person or by telephone. At sites where more than one key informant was interviewed per village, the mean of the responses to questions requiring numerical answers was entered as the final value if the responses were broadly similar. Otherwise, research staff were allowed to use their discretion in selecting the preferred response based on how well-suited the knowledge and expertise of the key informant was to the question e.g., the response of a health worker key informant would be preferred over that of a village head for the question on percentage of attended deliveries.

3.2.5 Statistical analysis

Data were analysed and presented using descriptive statistics to depict an ‘average’ village for each site. Count data at the site level were reported directly, while medians and upper and lower quartiles were calculated for continuous data captured at the village level. Percentages were calculated for binary and categorical data captured at the village level.

Responses to questions requiring the selection of one or more responses e.g., types of water source available at each village, were summarised graphically to show the percentage of villages per site with access to a particular service. Analyses were carried out using Excel (Microsoft, Redmond, USA).

3.2.5 Ethical approval

Ethical approval was not required for this study.

3.3 Results

The locations of the villages profiled in this study within each study site are shown in Figure 3.2.

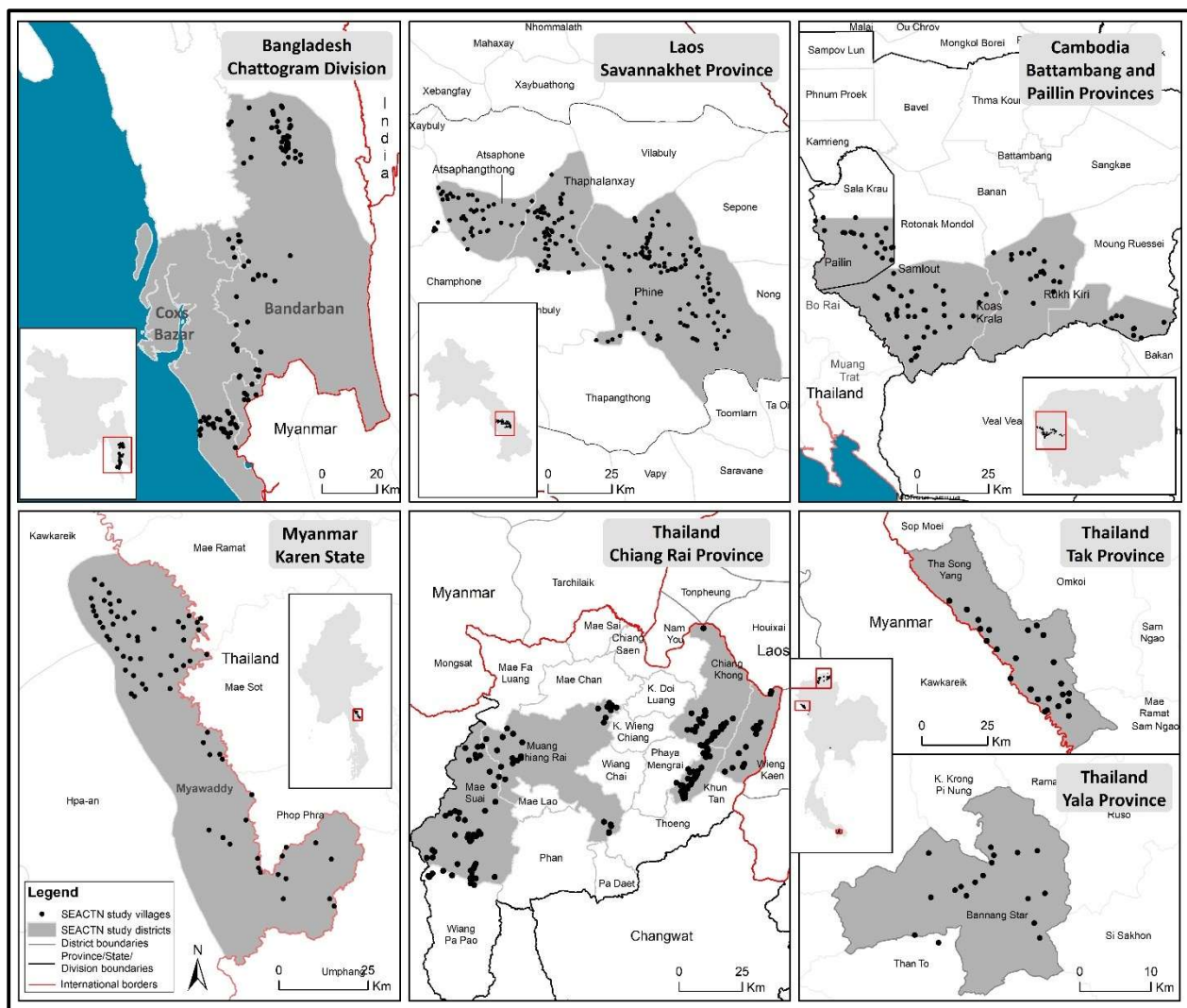


Figure 3.2. Locations of profiled villages within each study site of the South and Southeast Asian Community-based Trials Network.

3.3.1 Demographic details and health and socio-economic status indicators

Site-specific demographic and health and socio-economic status indicator data are shown in Table 3.3.

In the profiled SEACTN villages, the median village population for any given site ranged between 345 and 902 people. Despite this, there was a high level of cultural, religious, and linguistic diversity with several languages being spoken and religions practised at all sites, except in Cambodia and Yala province of Thailand which were more homogenous.

In general, the median percentage of adults with five years' schooling was no greater than 75% except in Cambodia where this figure was 100%. There was little difference in educational attainment between genders except in Yala, where a median of 70% of females had achieved this level of education compared to 50% of males.

Except for Chiang Rai and Yala provinces in Thailand, latrine coverage did not exceed the 90% threshold generally accepted as the coverage required to have a positive impact on the health of the community.⁹⁰ Latrine coverage was particularly low in Bangladesh at 67.5%.

Vaccination coverage was low in Myanmar and Yala (median coverage of 75% and 67.5%, respectively) relative to other sites which had near-perfect coverage. The median percentage of deliveries attended by skilled birth attendants was also markedly lower in Bangladesh (60%) compared to other sites.

Country	Thailand			Laos	Cambodia	Myanmar	Bangladesh
Site (number of villages profiled)	Chiang Rai province (186)	Tak province (37)	Yala province (24)	Savannakhet province (194)	Battambang and Pailin provinces (81)	Karen state (35)	Chattogram division (130)
Key informants per village, n	1 (Village head or PHC staff member)	1 (VHW/VMW)	1 (VHW/VMW)	1 (Village head)	1 (Village head)	2 (Village head and VHW/VMW)	2–3 (Village head and VHW/VMW)
Demographic details							
Population per village, n	555 (422, 769)	902 (501, 1245)	345 (238, 621)	750 (486, 1135)	639 (417, 1127)	676 (340, 1021)	526 (240, 1366)
Households per village, n	180 (129, 234)	240 (122, 372)	101 (78, 147)	ND	169 (100, 275)	129 (64, 215)	121 (57, 267)
Main languages at site, n	10	4	2	4	1	8	8
Main religions at site, n	3	4	2	3	2	6	3
Health and socio-economic indicators							
Number of villages with a health facility within 30 min walk (%)	105 (56.5)	35 (94.6)	15 (62.5)	55 (28.4)	61 (75.3)	35 (100)	114 (87.7)
Longest travel time to closest health facility by motor vehicle if none within 30 min walk (min)	60	30	15	ND	90	NA	80
% adults with ≥5 years schooling*	75 (65, 100)	60 (50, 85)	60 (50, 70)	ND	100 (90, 100)	50 (70, 75)	70 (60, 80)
Male	75 (60, 90)	50 (50, 90)	50 (45, 55)		100 (75, 100)	60 (40, 70)	65 (50, 75)
Female	70 (55, 80)	60 (50, 90)	70 (65, 75)		100 (55, 100)	70 (55, 80)	65 (45, 80)
% attended deliveries [§]	100 (100, 100)	85 (80, 100)	100 (100, 100)	ND	100 (100, 100)	80 (47.5, 95)	60 (25, 85)
% fully-immunised children [†]	100 (100, 100)	100 (95, 100)	67.5 (58.8, 75)	ND	100 (100, 100)	75 (85, 95)	100 (100, 100)
% latrine coverage [‡]	97.3	83.1	92.3	ND	86.7	84.8	67.5

Table 3.3. Demographic and key health and socio-economic indicator data for rural villages in the South and Southeast Asian Community-based Trials Network by site.

Estimates are presented as medians (first quartile, third quartile) and n (%) unless otherwise indicated. *Completion of at least five years' schooling was used as an indicator of literacy given varying definitions of literacy between countries. [§]A delivery attended by a skilled birth attendant. [†]A child older than one year who has received the following vaccines: Bacille Calmette–Guérin; three doses of diphtheria, tetanus, and pertussis; three doses of measles, and polio. [‡]Percentage of the number of households across all villages at each site which have either flush toilets or latrines. NA, not applicable; ND, data not collected or not available due to local restrictions, particularly in Laos; PHC, primary health centre; VHW/VMW, village health worker/village malaria worker.

3.3.2 Access to health services

The percentage of villages with access to a health facility within 30 minutes' walk was highly variable, ranging from 28.4% in Laos to 100% in Myanmar. The travel times to the nearest health facility, for villages with no facility within 30 minutes' walk, ranged between 15–90 minutes by motor vehicle.

As might be expected, few villages at all sites had access to doctors; the percentage of villages which had a doctor on site or within 30 minutes' walk ranged from 4.2% in Yala to 20.0% in Myanmar (Figure 3.3a). By far the commonest types of health worker in the studied villages were primary health centre (PHC) workers/nurses and village health workers/village malaria workers (VHWs/VMWs). Interestingly, traditional healers were not found in most villages across all sites with the exception of Yala, where 70.8% of villages have them. All villages had access to a healthcare worker. Nevertheless, it should be borne in mind that many healthcare providers are informal, with little or no official training; these informal healthcare providers were found in 63.1% and 77.1% of villages in Bangladesh and Myanmar, respectively and do not include traditional healers or traditional birth attendants; however, in all of the villages where they were present, there was also at least one type of formal healthcare provider.

It should be of little surprise given the above findings that most facility-based healthcare in the profiled villages is delivered at PHCs (Figure 3.3b), and that where they are not, such as in Yala and Laos where there are few PHCs, the burden of primary healthcare delivery falls on VHWs/VMWs. This is most important in Laos, where 71.6% of villages have no healthcare facility, including pharmacies or medicine shops, within 30 minutes' walk. Notably also, in Myanmar 77.1% of villages were served by clinics set up by non-governmental organisations (NGOs) vs. 11.4% served by government PHCs. It is also important to note the relatively easy access to pharmacies or medicine shops at all sites except Chiang Rai and Laos, especially since medicines are generally available over the counter.

As shown also in Figure 3.3b, there are no secondary care facilities able to care for severely ill patients within 30 minutes' walk of any profiled village, with all easily accessible healthcare facilities being designed for the provision of basic primary care and/or diagnosis and treatment of uncomplicated malaria, in the case of malaria posts. It is, therefore, not unexpected that patients who perceive themselves as being severely unwell would generally primarily seek care from first-level referral hospitals i.e., those at the sub-district and district levels, with the exception of Yala, Cambodia, and Bangladesh (Figure 3.3c). At these three sites, the commonest facility to which severely unwell patients would present remains the PHC; this was a preferred option for emergency care in 37.5%, 77%, and 70% of villages, respectively. However, the large role of private sector facilities, such as private hospitals and clinics, in treating severely ill patients in Cambodia, Myanmar, and Yala should also be noted; at these sites, such facilities are a preferred option for emergency care in 65.0%, 31.4%, and 29.2% of villages, respectively.

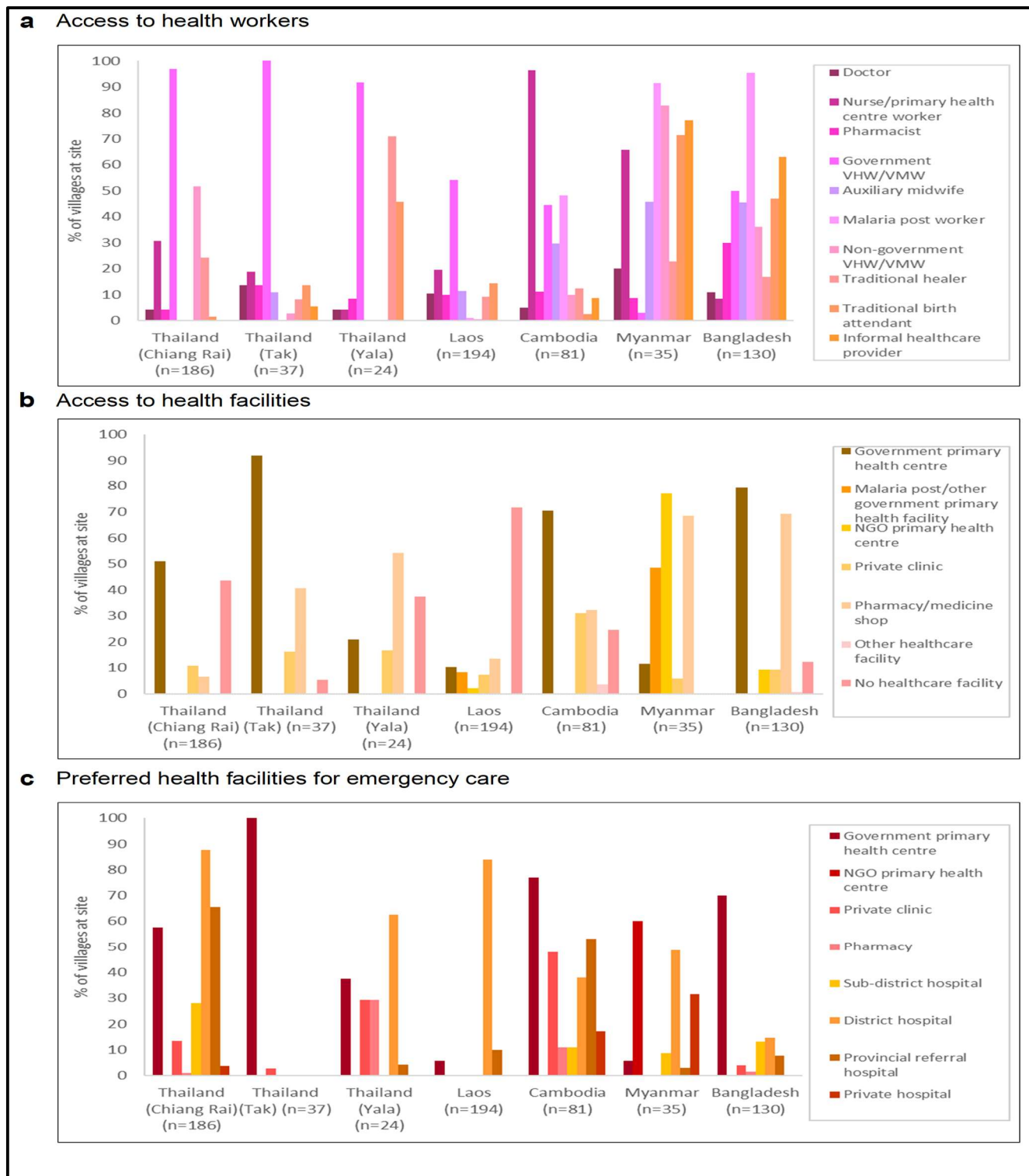


Figure 3.3. Percentages of villages in South and Southeast Asian Community-based Trials Network Rural Febrile Illness project study sites with access to different types of (a) healthcare worker and (b) healthcare facility.

Percentages of villages and the types of healthcare facilities at which patients perceived as being severely ill from those villages would seek care are shown in (c). Access was defined as having the healthcare worker or facility in the village or within 30 minutes' walk. NGO, non-governmental organisation; VHW/VMW, village health worker/village malaria worker.

3.3.3 Access to public utilities and education

3.3.3.1 *Water and sanitation*

Thai villages had the best access to improved drinking water sources, with the majority of villages having access to piped water available for at least most of the day (Table 3.2). Additionally, over half of the villages studied in the Thai provinces of Chiang Rai and Yala were able to obtain bottled water and/or filtered or distilled water via dispensers; in contrast, fewer than 10% of Cambodian and Lao villages were supplied with piped water, with the principal water sources being wells and boreholes (Figure 3.4a). Overall, however, a higher percentage of villages had access to improved than unimproved drinking water sources, and the majority of villages without piped water had their water sources located within the village (Figure 3.4a).

Unsurprisingly, the quality of sanitation facilities at each site mirrored the availability of piped water with the percentage of villages with access to flush toilets being the highest in Chiang Rai (94.6%), and the lowest in Cambodia (13.6%) (Figure 3.4b). Overall, most villages relied on improved pit latrines (Figure 3.4b). However, data on whether these were shared/public vs. private were not collected, although it is likely that at least some are shared facilities, especially in Bangladesh where 6.1% of villages were noted to have non-functioning latrines.

3.3.3.2 *Electricity and light sources, and mobile phone coverage*

With the exception of Myanmar, over 60% of villages at each site had access to mains power, with the highest penetration being in Yala (100%). Only 5.2% of villages at the Myanmar site were supplied with mains power; at this site, electricity was mainly obtained via generators or solar panels (Figure 3.5a). However, even in villages with mains power, supply was not always reliable, with the median number of hours per day ranging between six in Myanmar to 24 in Thailand (Table 3.2).

Regardless of source, electricity was generally available at the profiled villages even if not all households had reliable and affordable access to it, as evident by the continued use of firewood, charcoal, and candles (Figure 3.5a). The availability of electricity supports the use of mobile phones, evidenced by the widespread signal coverage across all sites (Table 3.2).

3.3.3.3 Educational facilities

Across all sites, the majority of villages had a primary school within 30 minutes' walk (Figure 3.5b), with an even higher percentage having any type of educational facility within this distance (Table 3.2). The site with the lowest access to educational facilities was Yala, where 62.5% of villages had a primary school within 30 minutes' walk (vs. 90% in Bangladesh). Furthermore, for villages in Yala with no school within this travel time, the median distance to the nearest school was longest compared to similar villages at all sites at 12.5 km (vs. ≤ 5 km at the other sites) (Table 3.2).

Country	Thailand			Laos	Cambodia	Myanmar	Bangladesh
Site (number of villages profiled)	Chiang Rai province (186)	Tak province (37)	Yala province (24)	Savannakhet province (194)	Battambang and Pailin provinces (81)	Karen state (35)	Chattogram division (130)
Access to public utilities							
Number of villages with water available year-round (%)	150 (80.6)	32 (86.5)	24 (100)	ND	55 (67.9)	22 (62.9)	128 (98.5)
Number of villages with piped water (%)	141 (75.8)	32 (86.5)	24 (100)	16 (8.2)	8 (9.9)	29 (82.9)	34 (26.2)
Hours/day piped water available*	24 (24, 24)	24 (24, 24)	15 (13, 16)	ND	24 (24, 24)	24 (12, 24)	20 (18, 24)
Number of villages without piped water but with intra-village water source (%)	40 (21.5)	3 (8.1)	NA	ND	65 (80.2)	4 (11.4)	95 (73.1)
Number of villages with mains power (%)	179 (96.2)	24 (64.9)	24 (100)	ND	63 (77.8)	2 (5.7)	115 (88.5)
Hours/day mains power available [§]	24 (24, 24)	24 (18, 24)	24 (24, 24)	ND	24 (24, 24)	6 (3.5, 15)	18 (17.5, 20)
Number of villages with mobile phone signal (%) [†]	186 (100)	26 (70.3)	20 (83.3)	194 (97.8)	81 (100)	35 (100)	128 (98.5)
Access to education							
Number of villages with a school within 30 min walk (%)	177 (95.2)	37 (100)	20 (83.3)	181 (93.2)	62 (76.5)	32 (91.4)	125 (96.2)
Distance to nearest school if not within 30 min walk, km	4.0 (2.0, 9.0)	NA	12.5 (9.3, 15.0)	4.0 (2.0, 5.0)	5.0 (2.9, 10.3)	3.3 (2.6, 6.7)	5.0 (4.0, 6.0)

Table 3.2. Access to public utilities and education for rural villages in the South and Southeast Asian Community-based Trials Network by site. The number of hours per day piped water and mains power are available, and distance to nearest school if not within 30 minutes' walk, are presented as median (first quartile, third quartile). *For villages with piped water. [§]For villages with mains power. [†]Defined as mobile phone signal present at least some of the time. NA, not applicable; ND, data not collected or available due to local restrictions, particularly in Laos.

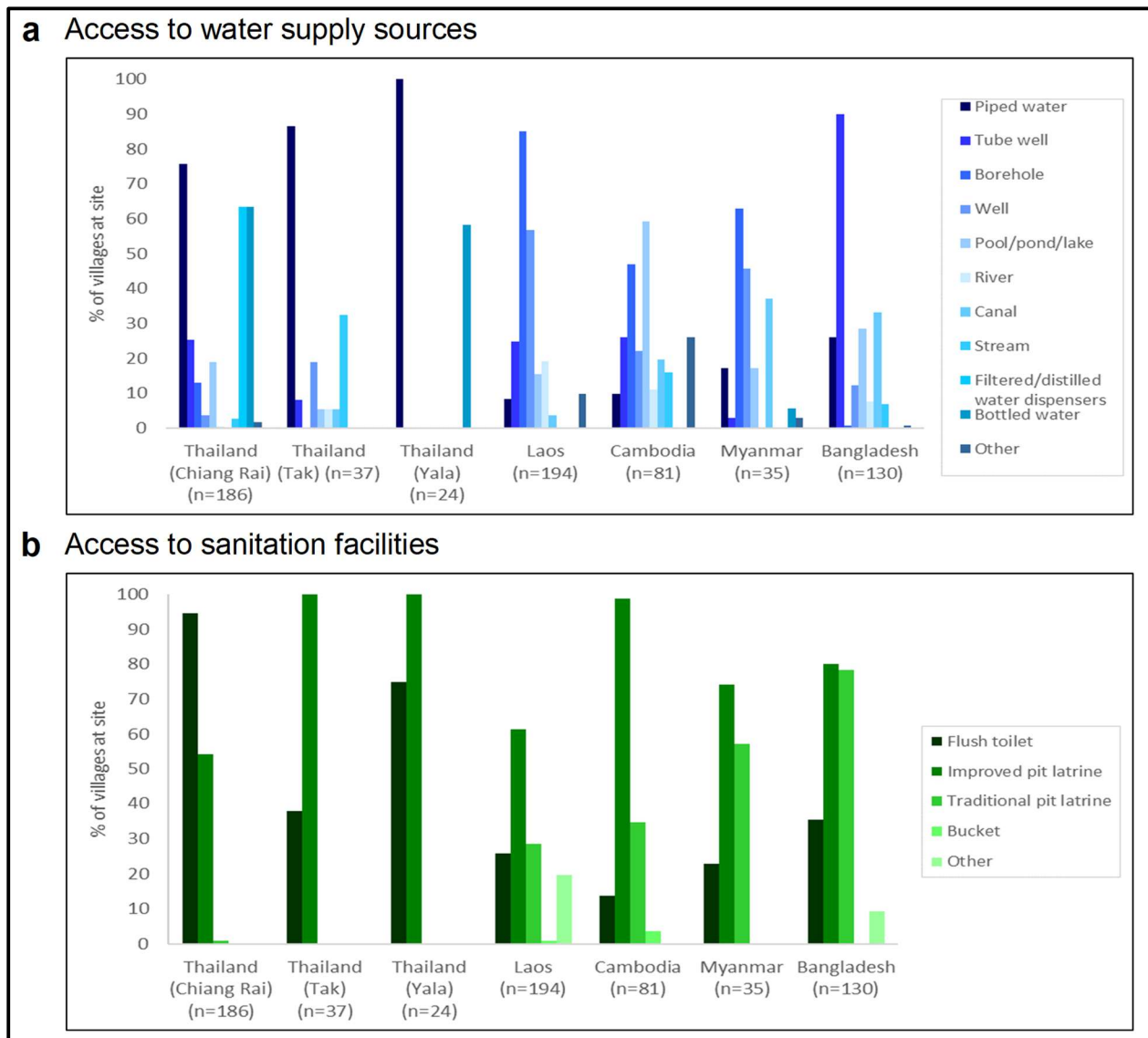


Figure 3.4. Percentages of villages in South and Southeast Asian Community-based Trials Network Rural Febrile Illness project study sites with access to different types of (a) water supply sources and (b) sanitation facilities. Access was defined as having the water source or sanitation facility in the village or within 30 minutes' walk.

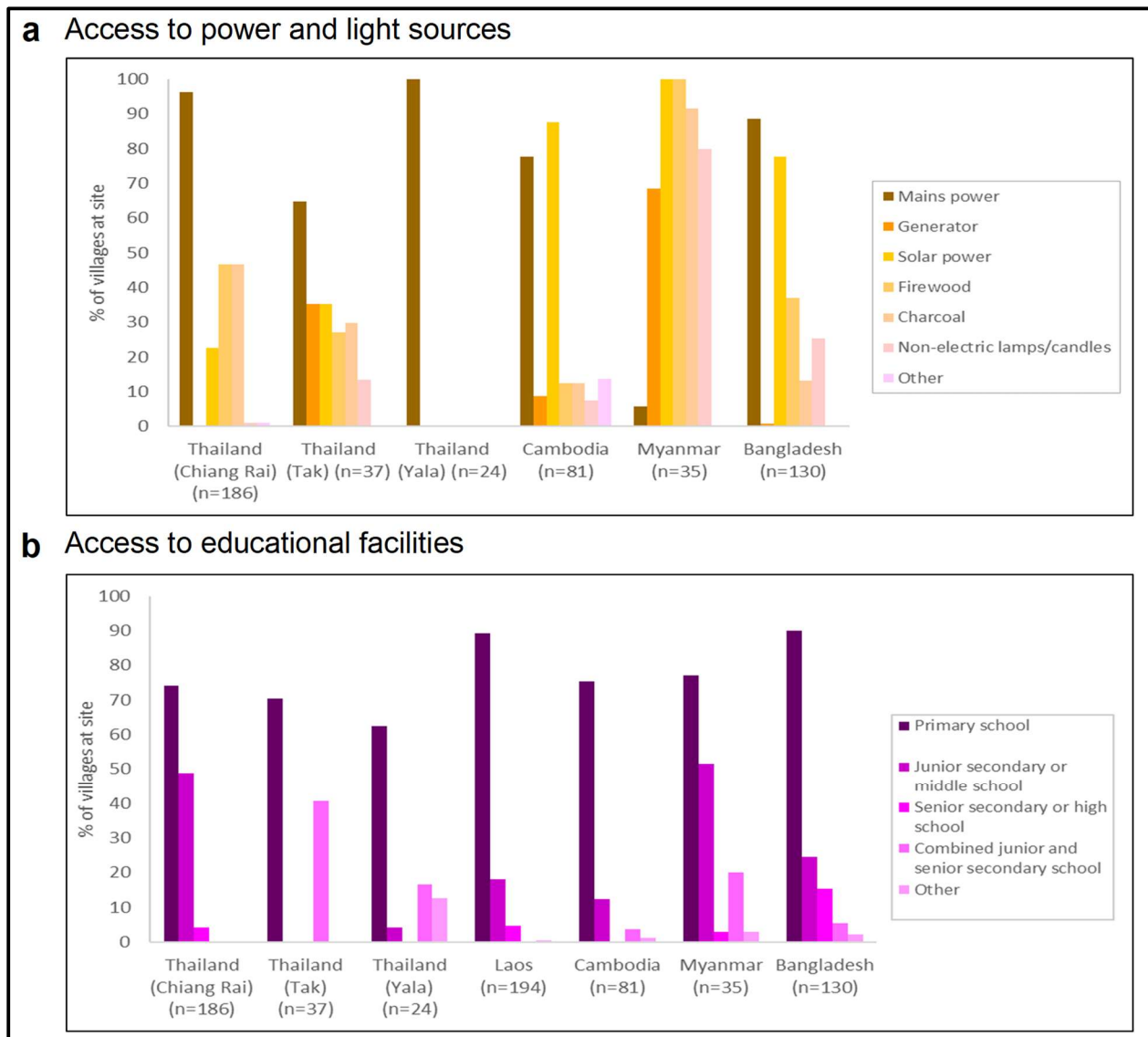


Figure 3.5. Percentages of villages in South and Southeast Asian Community-based Trials Network Rural Febrile Illness project study sites with access to different types of (a) power and light sources and (b) educational facilities. Access to power and light sources was defined as having the power and light source in the village, while access to educational facilities was defined as having the facility in the village or within 30 minutes' walk.

3.4 Discussion

3.4.1 Summary of main findings

This study profiled 687 villages located in five South and Southeast Asian low-income and middle-income countries (LMICs) at different stages of development, resulting in very different characteristics, especially in terms of access to services and public utilities. In line with this, there was considerable variation between sites in terms of health and socio-economic indicators.

Nevertheless, several common themes were evident, the first being the obvious ethno-cultural and linguistic diversity that exists even within villages at the same site. While health-seeking behaviour was not explored in this study, the influence of such diversity should be investigated as part of future work on this very important issue. The second is their reliance on PHCs (and analogous NGO primary health clinics), and VHWs/VMWs, as the backbone of primary healthcare provision. The latter are particularly common in Thailand, Laos, Bangladesh, and Cambodia where they have been a longstanding feature of village healthcare over the past decades. However, severely ill patients would generally travel out of their villages to seek care at first-level referral hospitals and private sector facilities in towns, bypassing village-level health services. Thirdly, while most villages were proximate to a primary school, the level of education was generally low. Fourthly, mobile phone coverage and availability of electricity was generally high.

3.4.2 Interpretation of main findings

The majority of the results are simple to interpret, but several key findings require further explanation. Firstly, the low vaccine coverage in Myanmar and Yala may partially be explained by these locations being conflict zones,^{80, 91} with an additional layer of mistrust of the government and, by extension, government programmes by the majority Malay ethnic group in

Yala.⁹¹ Furthermore, the low coverage of villages by public sector PHCs in Myanmar is due to the traditionally meagre government expenditure on healthcare,⁹² encouraging a parallel system of primary health clinics set up by NGOs to meet demand. This is especially so in Karen State where control by the central government has been patchy.⁹³ Lastly, while not all villages were supplied by electricity through power grids and, even in those that were, the number of hours per day that such supply is available is limited, mobile phone coverage was high across all sites. This is due to innovative solutions having been devised to overcome the lack of private household electricity supply, such as grocery shops installing shared solar-powered mobile phone charging points in villages in Myanmar.⁹⁴

Triangulation of the findings of this study with available recent reports of socio-economic and health indicators such as those from the Demographic and Health Survey (DHS) and Multiple Indicator Cluster Survey (MICS) programmes shows an overall broad degree of similarity, especially where public utilities, attended deliveries, immunisation, and educational attainment are concerned. This was particularly true for the Thai sites in Yala and Tak, and the site in Bangladesh, where provincial level data are available in the latest MICS report from 2023 and DHS report from 2022, respectively.^{95, 96} While this study was not able to collect much data for the Lao site, the 2023 MICS report for Savannakhet province corroborated much of the scant data obtained.⁹⁷ Extrapolating from this report, therefore, it is likely that immunisation coverage and educational attainment at this site are below the relevant national averages. One area of divergence was immunisation coverage and educational attainment at the Cambodian site, with the DHS 2021/2022 report providing much lower point estimates.⁹⁸ Given that the provincial-level figures from the DHS report cover both urban and rural areas, it is likely that this study overestimated these indicators, although this should be investigated further.

3.4.3 Strengths and weaknesses

The principal strength of this study is its focus on key health and socio-economic indicators, data on which public health and other policymakers, as well as researchers, can use for planning purposes. Furthermore, a pragmatic, low-cost, semi-desk-based methodology using key informants was chosen. This approach allowed reasonable estimates of the key indicators in the absence of easily accessible official information for all domains, in addition to the difficulties posed by the remote locations of many villages and travel restrictions for security reasons to some e.g., those in the Chattogram Hill Tracts in Bangladesh. It also has the benefit of allowing high-quality spatially granular data to be collected, permitting detailed comparisons to be made. The key informants were selected by staff of SEACTN country partner organisations to ensure a high degree of first-hand knowledge of the prevailing conditions in their respective villages, as is best practice.⁹⁹ This approach is well-suited to the objectives of this study, as it is appropriate if general, descriptive information is sufficient to guide decision-making, generate suggestions and recommendations, and assist in the design of more comprehensive quantitative research.¹⁰⁰ Key informant interviews are also appropriate for when quantitative data collected through other methods need to be interpreted,¹⁰⁰ which is exactly the situation with SEACTN where the data from the observational epidemiological study presented in the following chapter and similar others need to be viewed through a contextual prism.¹⁰¹

Nevertheless, while the results provide an idea of the characteristics of villages at the individual sites, they may not be generalisable to all rural villages within their respective countries. This is amply demonstrated by heterogeneity of the three Thai sites, despite all being located in remote areas bordering neighbouring countries; there are likely to be many more differences between these borderland villages and those in the more developed central plains. In the case of Cambodia, the relative ethno-linguistic homogeneity and high elementary educational attainment of the villages profiled for this study would not likely be found in villages

in the northeast of the country bordering Laos, where more languages are spoken and literacy rates lower.¹⁰² The selected villages at the Myanmar site had better road and telecommunication links than others due to the logistical and security considerations previously described. This is likely to have resulted in better access to water and sanitation, health services, and educational facilities, which may not be representative of the typical conditions elsewhere in Karen state or Myanmar in general. For example, there is an international hospital in Shwe Kokko close to several villages profiled at the Myanmar site, whereas no such facilities exist deeper in the interior of Karen state. Also, the higher immunisation coverage in these villages compared to the very low or negligible figures reported for villages elsewhere in Karen state,¹⁰³ is likely due to the ability of residents to access the more advanced health services in Thailand, including preventative care, as mentioned earlier.

Additionally, there are several well-known limitations of the key informant interview approach that should be borne in mind when interpreting the results of this study. Chief of these is the potential for bias since it was not possible to confirm the appropriateness of informant selection; for example, more qualified but less visible or prominent informants may not have been selected.¹⁰⁴ It is also possible that, due to their prominence, the socio-demographic strata from which key informants are drawn may not be similar to that of the majority of village dwellers, in particular those from the most marginalised groups, leading to a perhaps less than comprehensive understanding of their villages. This should be taken into account when interpreting the results, since their potentially differing perspectives may have caused them to overestimate their responses to questions on health and socio-economic indicators which require numerical answers. It is particularly important to consider this effect at the Myanmar site since, added to that of the relatively better access to services of the profiled villages at this site, it may have resulted in results which are less representative of more typical villages there. This notwithstanding, given that most of the data gathered related to demographic makeup and

availability and accessibility of physical facilities such as schools, public utilities, and healthcare services at each village it would be quite unlikely that highly divergent answers would be provided for these questions since it was expected that this would be common knowledge to most, if not all, adult villagers and certainly to the village head and healthcare workers servicing the village.

Another source of bias that should be considered is interviewer bias, although this was mitigated by using a data collection tool with questions to be read out verbatim by the interviewer, as well as having many questions with response options or which required numerical responses. However, the questions which required quantitative responses were in themselves a weakness, since key informant interviews are best suited to qualitative studies because they provide only a very restricted basis for quantification.¹⁰⁰ It is also difficult to verify the validity of the findings because only a very small number of informants were selected per village, certainly fewer than the ideal figure of 15–35,¹⁰⁴ which was deemed to be impracticable by all partner organisations. Hence, while most sites interviewed one per village and two interviewed two to three, this difference was inconsequential. Additionally, since the results shown in this report are intended to be a high-level overview and a large number of villages were included at each site, a not unreasonable assumption would be that the measures of central tendency presented would converge to a decently close approximation of the relevant true value for each site, as per the ‘wisdom of the crowd’ theorem. A final limitation of this study is that it while it may indicate the presence or absence of particular facilities or services, it gives no indication of their quality.¹⁰⁵

3.4.4 Areas for future research

There are two obvious priorities for further research. The first is to flesh out the findings with the results of other studies examining broadly similar themes, such as the SEACTN household health survey.¹⁰⁶ In addition, more detailed site-specific analyses triangulating the findings of

this study with geospatial epidemiological work analysing accessibility to health and other services will be extremely informative. Such efforts will allow further layers of contextual understanding to be built on the foundations established by this study.

Secondly, this study has uncovered the major public health and socio-economic issues important to each site, for example the low vaccination rates in Yala province, the low percentage of births attended by skilled attendants in Bangladesh, and the globally poor levels of educational attainment despite relatively easy physical access to primary schools. While this chapter presents high-level overviews of these problems, the granular, village-level data collected through this study can be leveraged for the purposes of micro-planning and further research, among others. Future studies should explore the reasons behind such problems in the light of the other contextual findings, with a view to developing potential interventions to solve these issues.

3.5 Conclusions

This study provides a rudimentary descriptive overview of the characteristics of under-served and under-studied villages in rural South and Southeast Asia, focusing on key health and socio-economic indicators and the availability and accessibility of amenities and public services essential to good health, such as water and sanitation. Notwithstanding its weaknesses, the results will go a long way to aiding the comprehensive interpretation of the findings of other studies conducted in these rural village settings by furnishing much-needed contextual information. As previously indicated, one such study in which such contextual understanding will be essential is that reported in the next chapter, which aims to define the epidemiology of acute fever in rural South and Southeast Asian primary care settings.

CHAPTER 4 | DEFINING THE EPIDEMIOLOGY OF ACUTE FEBRILE ILLNESS IN RURAL SOUTH AND SOUTHEAST ASIAN PRIMARY CARE

4.1 Introduction

As detailed in Chapter 2 ('Background'), acute febrile illness (AFI) is a common presenting symptom globally,¹ much more so in low-income and middle-income countries (LMICs), including those in South and Southeast Asia.⁵ In this region, rural primary care providers have traditionally viewed AFI as synonymous with malaria.¹⁰⁷⁻¹⁰⁹ Once the main cause of AFI, the incidence of malaria is now negligible in most of the region,¹² highlighting the conundrum of diagnosis and management of non-malarial febrile illness (NMFI) for which these providers are under-equipped and for which little diagnostic capacity is available outside major referral facilities.¹¹⁰

Compounding this problem is the dearth of high-quality epidemiological data upon which clinical guidelines and health policymaking can be based.^{14, 40} The little extant evidence is centred on hospital inpatients recruited in urban centres,⁴⁰ whereas despite increasing urbanisation, 50–85% of the population live rurally in villages at the peripheries of national health systems;^{106, 111} furthermore, low-income and lower-middle income countries are under-represented. In these understudied and underserved contexts, primary care providers are the mainstay of healthcare provision.

This descriptive observational study was devised to address the above knowledge gap. It is a major component of Work Package A (WP-A) of the South and Southeast Asian Community-based Trials Network (SEACTN) Rural Febrile Illness (RFI) project,⁵³ also described in Chapter 2, which aims to define the epidemiology of AFI-associated syndromes, their current

management, and patient outcomes. Given the systemic disparities and likely spatio-temporal differences in disease epidemiology between urban and rural areas,^{9, 111} gathering and synthesising baseline evidence relevant to rural areas will make a considerable difference towards improving the management of rural AFI at all levels spanning individuals to populations. Such an effort is a much-needed first step towards identifying key priorities and potential solutions, thus directing scarce resources towards the most pressing problems. The work described in this chapter will also lay the foundation for further epidemiological studies forming the remainder of SEACTN WP-A, including the estimation of incidences and attribution of microbiological diagnoses for each syndrome.

4.2 Methods

4.2.1 Setting

The study was conducted in seven rural sites across five countries in South and Southeast Asia. These sites are located in Bangladesh (Chattogram division), Cambodia (Battambang and Pailin provinces), Laos (Savannakhet province), Myanmar (Karen state), and Thailand (three sites in Chiang Rai, Tak, and Yala provinces). All sites, managed by local partners, are part of SEACTN, as described in Chapter 2, and consist of the three principal types of public sector primary care providers servicing villages in their respective catchment areas.

These three provider types are lay village malaria workers (VMWs) whose remit is the testing of febrile patients for malaria and treating those who test positive; lay village health workers (VHWs) who have undergone training in the rudiments of primary care; and primary health centres (PHCs) staffed by non-medically-qualified health workers of varying skill levels, although PHCs in certain sites such as Chiang Rai are overseen by doctors at first-referral hospitals.¹¹² VMWs may be based in villages or at malaria posts, as is common in Myanmar, and Tak and Yala provinces of Thailand.^{17, 113} The study sites and their local partner

organisations, as well as the number of villages and types of primary care provider at each site, are shown in Figure 4.1.

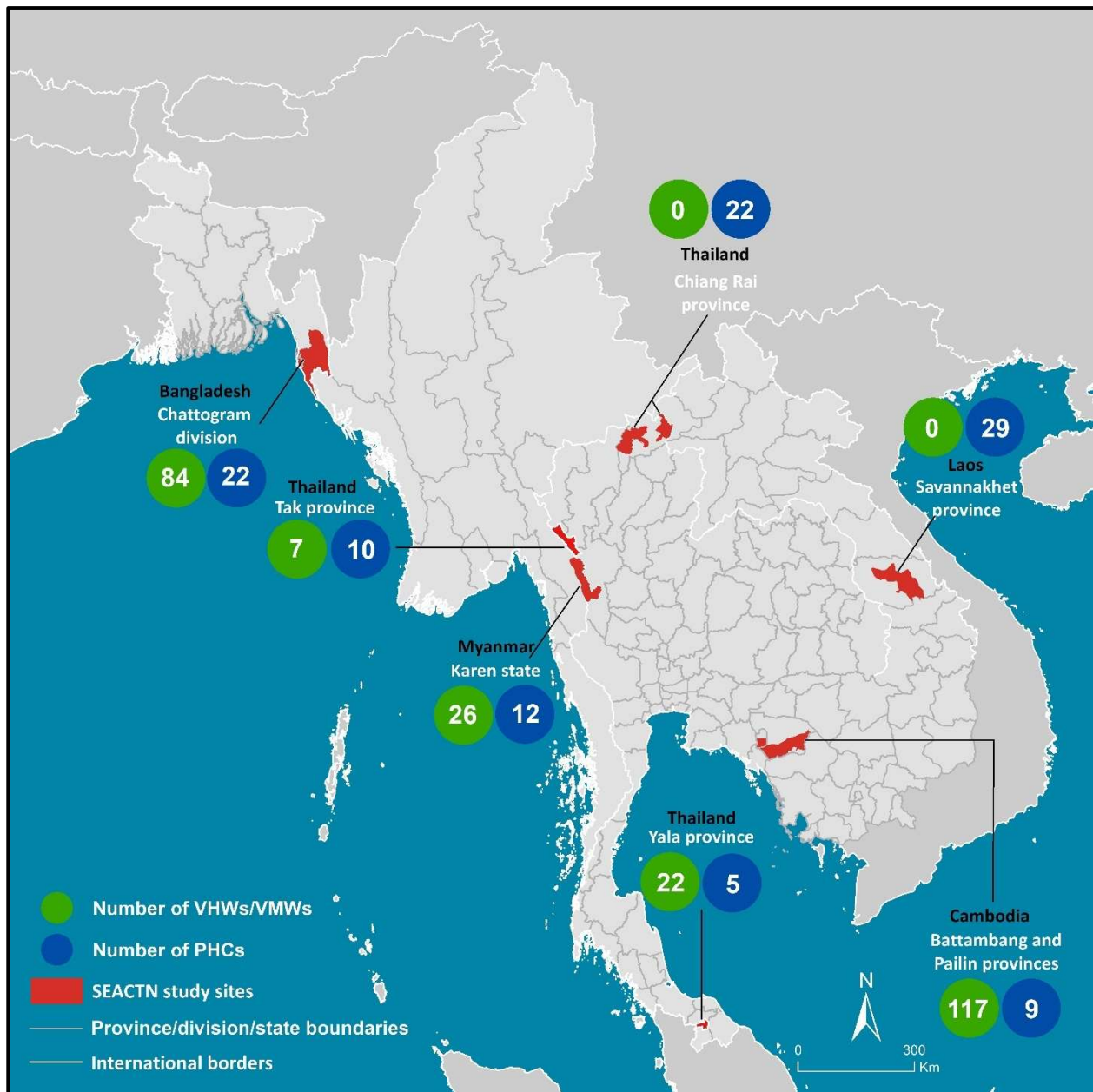


Figure 4.1. Study sites, and the types and numbers of primary care provider enrolling patients at each site. PHC, primary health centre; SEACTN, South and Southeast Asian Community-based Trials Network; VHW/VMW, village health worker/village malaria worker.

4.2.2 Study design

This was a prospective observational study which aimed to recruit 80,000–100,000 consecutive patients with AFI over a minimum of 12 months, with a minimum of 600 in each of three age groups (children <5 years, children 5 to 14 years, and adults ≥15 years) per site. The target number was based on pragmatic considerations, with the intention of capturing the highest number of cases to provide a comprehensive description of the regional epidemiology of rural AFI, subject to budgetary and logistical constraints. However, neonates (infants <28 days), while included in the target number for the children <5 years age group, were analysed separately given that they differ from older infants and children with respect to diagnosis, recommended management, and outcomes.

Patients of any age were eligible for enrolment if their presentation to the primary care provider was unscheduled and they had a documented fever or hypothermia (defined as an axillary temperature of ≥ 37.5 or $< 35.5^{\circ}\text{C}$, respectively) and/or gave a history of fever in the 24 hours prior to presentation, with a symptom duration ≤ 14 days. Hypothermia was included because it may be a feature of sepsis and is associated with poor prognosis in such patients.¹¹⁴ In addition, they (or their caregivers, in the case of minors) had to provide written informed consent and be willing and able to comply with the study protocol for the duration of their enrolment. Exclusion criteria were being under follow-up, or presentation due to accident, injury, trauma, or ≤ 3 days after routine immunisations.

Patients were followed up at 28 days post-presentation, with an allowance of up to 42 days given the relative inaccessibility of the study sites. At enrolment and follow-up, dried capillary blood spots (DBS) were collected for aetiological assays, except in neonates; however, the determination of causative organisms is not part of this thesis.

4.2.3 Data collection and study procedures

Recruitment and follow-up were undertaken by healthcare staff trained in the study methodology using standardised electronic case report forms translated into local languages and loaded on the CommCare app (Dimagi, Cambridge, USA) deployed on tablet devices. Case report form templates which formed the basis for the electronic versions can be found in Appendices 4.1 and 4.2.

Healthcare workers recruited patients as part of their usual workflow, which included body temperature measurement. Detailed clinical, epidemiological, and outcome data were collected according to the Standard Operating Procedures (SOPs) in Appendix 4.3, described in brief in the following sub-sections. Implausible values and missing data were minimised by programming the app with range checks, skip logic, and making answering certain questions compulsory to progress through the form. Data were transmitted in real time to servers at the Mahidol Oxford Tropical Medicine Research Unit (MORU) in Bangkok, Thailand at locations where mobile data connections were available, and at up to monthly intervals where they were not.

4.2.3.1 Patient characteristics

The age, gender, and principal reason for presentation of each enrolled patient was recorded. Enrolled females >12 years old were also asked for their pregnancy status. Participants were asked the duration of their symptoms and whether they had sought care prior to presentation and, if so, where.

4.2.3.2 Diagnosis and clinical management

Symptom data for each patient were collected based on pre-defined age group-specific symptom lists, which were constructed to include only common symptoms localisable to organ systems, as far as possible (Appendices 4.1 and 4.2). To ensure as comprehensive a

description of each patient's symptoms as possible, providers were required to answer 'yes' or 'no' for each symptom. Malaria rapid diagnostic tests (RDTs) in routine use at each site were also administered to each patient, other than in Chiang Rai where, in accordance with local policy, patients are not normally tested for malaria due to its established negligible incidence.⁵⁵

¹¹⁵ Physical examination findings were not recorded, as the majority of providers do not have sufficient training in this area and do not routinely examine patients. Testing for the COronaVirus Disease of 2019 (COVID-19) was not performed. This was because, while the study was conducted during the early years of the pandemic, it would not have been ethical to perform additional testing purely for research purposes but which may have resulted in further demand on already stretched health systems.

The following vital signs were also measured: pulse rate, respiratory rate, and level of consciousness on the AVPU (alert/responds to voice/responds to pain/unresponsive) scale. Patients enrolled at PHCs except in Cambodia also had oxygen saturation and blood pressure (in adults) measured using Lifebox-Smile Train hand-held pulse oximeters (Acare Technology, Taipei, Taiwan) at all sites other than Bangladesh, where Jumper JPD-500D fingertip pulse oximeters (Jumper Medical, Shenzhen, China) were used instead, and Omron HEM-7121 digital sphygmomanometers (Omron, Kyoto, Japan), respectively. Providers were also required to identify whether participants had any severely deranged vital signs or observed danger signs from pre-defined age group-specific lists based on guidelines including the World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) and Integrated Management of Adolescent and Adult Illness (IMAI), collectively termed 'danger signs' (Table 4.1).¹¹⁶⁻¹¹⁸ Additionally, the nutritional status of children aged 6 months to <5 years was assessed using mid-upper arm circumference (MUAC) measurement, with a MUAC <115 mm indicating severe acute malnutrition.¹¹⁹

Age group	Measured danger signs	Observed/reported danger signs
Neonates	• Documented temperature ≥ 37.5 or ≤ 35.5 °C • Fast breathing i.e., respiratory rate of ≥ 60 breaths per minute • SpO₂ <90% • Voice/pain/unresponsive on AVPU scale	• Difficulty breathing or turning blue • Yellowing of the eyes or skin • Convulsions • Unable to drink/feed/reduced suckling • Abnormally sleepy/moves only when stimulated
Children aged 29 days to <5 years	• Voice/pain/unresponsive on AVPU scale • SpO₂ <90% • Severely abnormal heart rate i.e., pulse of <80 or >160 beats per minute	• Convulsions • Unable to drink/feed • Unable to sit/stand/walk when previously able • Abnormally sleepy/lethargic • Vomits everything
Children aged 5 to <15 years	• Voice/pain/unresponsive on AVPU scale • Severely abnormal heart rate i.e., pulse of <70 or >150 beats per minute (5 to <12 years) or <50 or >130 beats per minute (12 to <15 years) • Fast breathing i.e., respiratory rate of ≥ 40 breaths per minute (5 to <12 years) or ≥ 30 breaths per minute (12 to <15 years) • SpO₂ <90%	• Convulsions • Unable to walk • Abnormally sleepy/lethargic/confused • Vomits everything • Unable to drink/feed
Adults aged ≥ 15 years	• Voice/pain/unresponsive on AVPU scale • Severely abnormal heart rate i.e., pulse of <40 or >140 beats per minute) • Fast breathing i.e., respiratory rate of ≥ 35 breaths per minute • SpO₂ <90% • Systolic blood pressure <90 mmHg	• Convulsions • Unable to walk • Abnormally sleepy/lethargic/confused • Vomits everything • Unable to drink/feed

Table 4.1. Measured and observed danger signs by age group. AVPU, Alert/Responds to Voice/Responds to Pain/Unresponsive; mmHg, millimetres of mercury; SpO₂, peripheral oxygen saturation.

Syndromic diagnoses were then assigned algorithmically for each patient based on their age, symptoms, vital signs, and, where applicable, malaria RDT result, as has previously been done in another AFI descriptive epidemiological study in Tanzania.¹²⁰ The diagnostic criteria underpinning the algorithms (Tables 4.2, 4.3, and 4.4) were developed through consensus by a five-person panel of medical specialists with expertise in adult and paediatric infectious diseases, internal medicine, respiratory medicine, and general practice and extensive experience working in resource-limited settings (Appendix 4.4). In accordance with previous studies from the region which found that multiple diagnoses were not uncommon,¹²¹⁻¹²⁵ and the WHO recommendation to treat syndromes separately in LMIC settings with high prevalences of infectious diseases,^{116, 117} up to three diagnoses were allowed per patient; any patient with more than one diagnosis was deemed to have co-infections. The limit of three diagnoses was chosen as a balance between the opposing principles of diagnostic parsimony and plenitude used in clinical practice.^{126, 127} To assess comparability of these algorithmic diagnoses with those made by PHC staff, the latter were asked to indicate their principal working diagnosis from a pre-defined list (Table 4.5). Diagnosing patients was already routinely done by PHC workers as part of standard patient care. They were not informed that the symptom and vital sign data collected would be used to generate diagnoses algorithmically. VMWs/VHWs were not required to do this, as they are not trained to diagnose.

PHC staff were asked to indicate whether each patient was prescribed antibiotics and, if so, which ones from a list of antibiotics available at each site. They were also asked to indicate if the patient was being referred for further healthcare and, if so, where. VHWs/VMWs were not required to do this, as they do not prescribe antibiotics.

4.2.3.3 Outcomes

The illness outcome for each patient was recorded at follow-up. Patients who were still alive were asked whether their symptoms had resolved. They were also asked if they had sought

care, obtained medication, or were hospitalised for at least one night since enrolment and, if so, where. Hospitalised patients were asked to estimate the approximate amount they spent in local currency, if able.

Syndromic diagnosis	Criteria
RESPIRATORY TRACT	
Pneumonia	Difficult breathing or turning blue AND (fast breathing OR SpO ₂ <93%)
GASTROINTESTINAL TRACT	
Gastroenteritis	Loose motions AND does not meet criteria for any other diagnosis
SKIN AND SOFT TISSUE	
Omphalitis	Redness around or discharge from umbilicus
Skin and soft tissue infection	Redness, discharge, or pustules on area of skin
NEUROLOGICAL	
Central nervous system disorder	Convulsions OR voice/pain/unresponsive on AVPU scale AND does not meet criteria for any other diagnosis
SYSTEMIC	
Malaria	Positive malaria RDT
Fever of unclear source	Any combination of symptoms and vital sign measurements not matching the above rules

Table 4.2. Algorithmic diagnostic criteria for syndromes affecting neonates. Fast breathing is defined as a respiratory rate of ≥ 60 breaths per minute. If malaria is present, this supersedes all other diagnoses except for omphalitis and skin and soft tissue infection, in which case both diagnoses should be assigned. AVPU, Alert/Responds to Voice/Responds to Pain/Unresponsive; SpO₂, peripheral oxygen saturation; RDT, rapid diagnostic test.

Syndromic diagnosis	Criteria
UPPER RESPIRATORY TRACT	
Rhinitis, pharyngitis, or tonsillitis	Runny nose, nasal congestion, or sore throat
Bronchitis	Cough OR difficulty breathing AND NO fast breathing
LOWER RESPIRATORY TRACT	
Bronchiolitis or pneumonia	(Cough OR difficulty breathing) AND (fast breathing OR SpO ₂ <93%) AND age ≤2 years
Pneumonia	(Cough OR difficulty breathing) AND (fast breathing OR SpO ₂ <93%) AND age >2 years
EAR, NOSE, AND THROAT	
Mastoiditis or otitis	Ear pain or discharge, swelling behind the ear or pulling at the ear
DENTAL	
Suspected dental abscess	Tooth pain (not normal teething pains)
URINARY TRACT	
Urinary tract infection	Pain/crying on urination or avoiding urination AND age >2 years
GASTROINTESTINAL TRACT	
Gastroenteritis	(Loose or frequent motions AND NO blood in stools) AND does not meet criteria for any other diagnosis
Dysentery	(Loose or frequent motions AND blood in stools) AND does not meet criteria for any other diagnosis
SKIN AND SOFT TISSUE	
Skin and soft tissue infection	Redness, discharge, or pustules on area of skin
BONE AND JOINT	
Septic arthritis	Visible swelling or redness of one or more joints
NEUROLOGICAL	
Central nervous system disorder	Convulsions OR voice/pain/unresponsive on AVPU scale AND does not meet criteria for any other diagnosis
SYSTEMIC	
Malaria	Positive malaria RDT
Possible rickettsiosis	Eschar
Fever of unclear source	Any combination not matching the above rules

Table 4.3. Syndromic diagnostic criteria for children aged 29 days to <5 years. Fast breathing is defined as a respiratory rate of ≥60 breaths per minute (age 29 days to <2 months), ≥50 (age 2 to <12 months) or ≥40 (age 12 months to <5 years). If more than one respiratory tract infection is possible, the most severe will be assigned in this order: (Bronchiolitis or pneumonia OR Pneumonia) > Bronchitis > Rhinitis, pharyngitis, or tonsillitis. Up to three syndromic diagnoses can be assigned. AVPU, Alert/Responds to Voice/Responds to Pain/Unresponsive; SpO₂, peripheral oxygen saturation; RDT, rapid diagnostic test.

Syndromic diagnosis	Criteria
UPPER RESPIRATORY TRACT	
Rhinitis, pharyngitis, or tonsillitis	Runny nose, nasal congestion, or sore throat OR loss of smell or taste
Bronchitis	(Cough OR wheeze or noisy breathing OR shortness of breath or difficult breathing) AND NO fast breathing
LOWER RESPIRATORY TRACT	
Pneumonia	(Cough OR shortness of breath or difficult breathing) AND (fast breathing OR SpO ₂ <93%)
EAR, NOSE, AND THROAT	
Mastoiditis or otitis	Ear pain or discharge, swelling behind the ear or pulling at the ear
DENTAL	
Suspected dental abscess	Tooth pain
URINARY TRACT	
Urinary tract infection	Frequent urination or pain on urination
GASTROINTESTINAL TRACT	
Gastroenteritis	(Loose or frequent motions AND NO blood in stools) AND does not meet criteria for any other diagnosis
Dysentery	(Loose or frequent motions AND blood in stools) AND does not meet criteria for any other diagnosis
SKIN AND SOFT TISSUE	
Skin and soft tissue infection	Redness, discharge, or pustules on area of skin
BONE AND JOINT	
Septic arthritis	Visible swelling or redness of one or more joints
NEUROLOGICAL	
Central nervous system disorder	Convulsions OR voice/pain/unresponsive on AVPU scale AND does not meet criteria for any other diagnosis
SYSTEMIC	
Malaria	Positive malaria RDT
Possible rickettsiosis	Eschar
Fever of unclear source	Any combination not matching the above rules

Table 4.4. Syndromic diagnostic criteria for children aged ≥5 to <15 years and adults aged ≥15 years.

Fast breathing is defined as a respiratory rate of ≥40 breaths per minute (age 5 to <12 years), ≥30 (age 12 to <15 years) or ≥35 (age ≥15 years). If more than one respiratory tract infection is possible, the most severe will be assigned in this order: (Bronchiolitis or pneumonia OR Pneumonia) > Bronchitis > Rhinitis, pharyngitis, or tonsillitis. Up to three syndromic diagnoses can be assigned. AVPU, Alert/Responds to Voice/Responds to Pain/Unresponsive; SpO₂, peripheral oxygen saturation; RDT, rapid diagnostic test.

Primary health centre worker diagnosis	Algorithmic diagnosis
Ear infection	Mastoiditis or otitis
Toothache / tooth infection	Suspected dental abscess
Upper respiratory tract infection	Rhinitis, pharyngitis, or tonsillitis Bronchitis
Lower respiratory tract infection	Pneumonia Bronchiolitis or pneumonia
Urinary tract infection Sexually-transmitted infection	Urinary tract infection
Skin and soft tissue infection	Skin and soft tissue infection Omphalitis
Bone or joint infection	Septic arthritis
Brain or nervous system infection	Central nervous system disorder
Diarrhoeal illness Other gastro-intestinal tract infection	Gastroenteritis Dysentery
Eye infection	Fever of unclear source Rhinitis, pharyngitis, or tonsillitis
Malaria	Malaria
Fever of unclear source / Fever not otherwise specified / Other	Fever of unknown source Possible rickettsiosis
>1 diagnosis including malaria	>1 diagnosis including malaria
>1 diagnosis not including malaria	>1 diagnosis not including malaria

Table 4.5. Algorithmic diagnoses and their required corresponding primary health centre worker diagnosis for the latter to be assessed as acceptable compared to the algorithmic diagnosis. The diagnostic criteria for the algorithmic diagnoses are shown in Tables 4.2, 4.3, and 4.4.

4.3 Results

A total of 84,260 patients were enrolled, distributed approximately equally between patients recruited at PHCs (43,181/84,260, 51.2%) and patients recruited by VHWs/VMWs (41,079/84,260, 48.8%). Despite the disruptions caused by the COronaVirus Disease of 2019 (COVID-19) pandemic all sites were able to enrol patients for at least 12 months (Table 4.6). Participant flow through the study is shown in Figure 4.2.

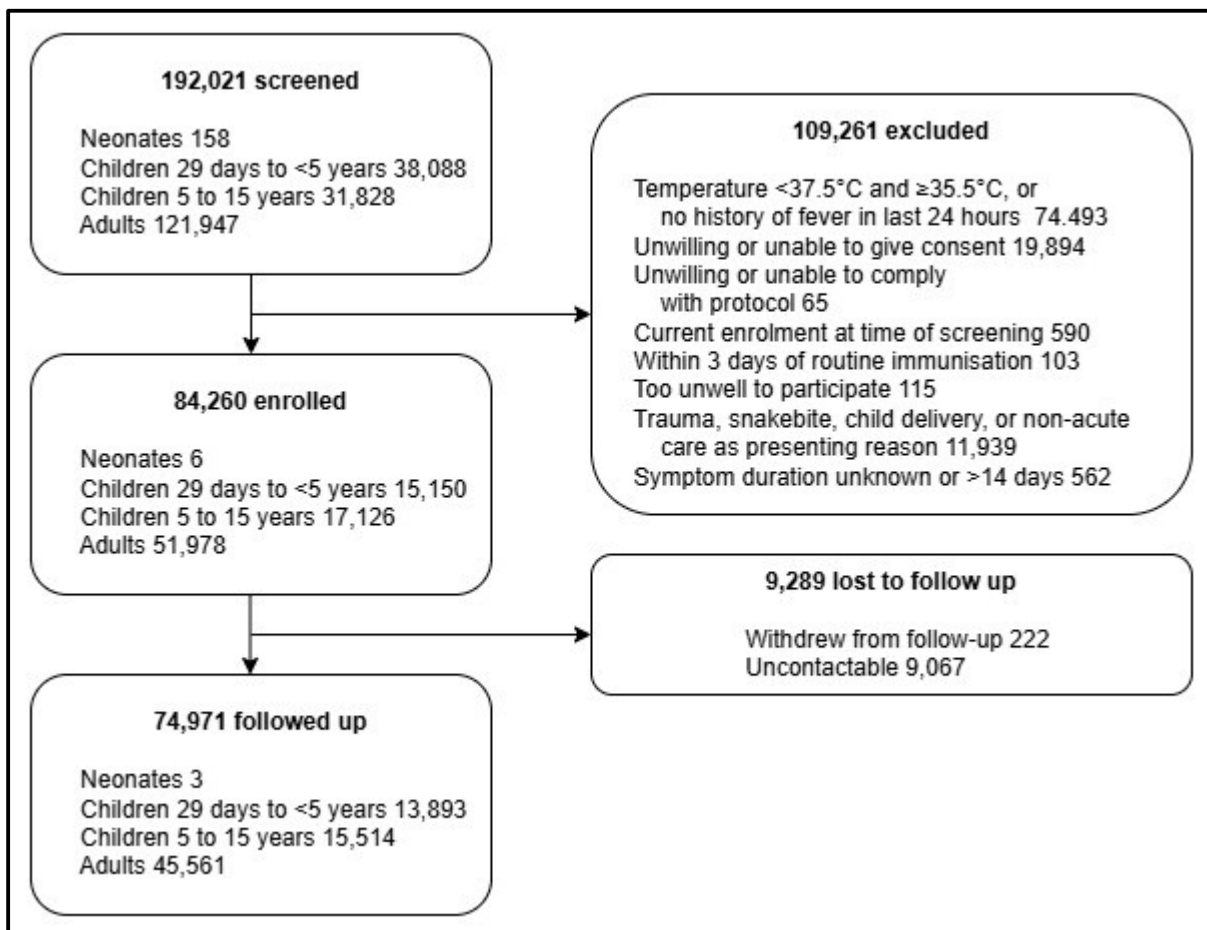


Figure 4.2. Study flowchart.

	Chattogram division, Bangladesh	Battambang and Pailin provinces, Cambodia	Savannakhet province, Laos	Karen state, Myanmar	Chiang Rai province, Thailand	Tak province, Thailand	Yala province, Thailand
Recruitment period (months)	Mar 2022 – Oct 2023 (19)	Feb 2022 – Sep 2023 (19)	Jul 2021 – Apr 2023 (21)	Jan 2022 – Nov 2023 (22)	Nov 2021 – Oct 2023 (23)	Apr 2022 – Apr 2023 (12)	Apr 2022 – May 2023 (13)
Neonates							
Screened	0	0	84	0	0	0	0
Too unwell	1	14	0	18	39	0	0
Recruited	1	4	0	1	0	0	0
Followed up	1	1	NA	1	NA	NA	NA
Children 29 days to <5 years							
Screened	0	0	18,451	0	9	0	0
Too unwell	775	263	4	5,481	11,683	360	785
Recruited	762	261	9,420	2,041	1,522	360	784
Followed up	741	128	8,584	1,972	1,463	230	775
Children 5 to <15 years							
Screened	2	1	6,311	1	7	0	0
Too unwell	3,393	1,624	0	7,730	9,869	1,204	1,022
Recruited	3,330	1,606	4,535	3,906	1,525	1,202	1,022
Followed up	3,273	1,070	4,224	3,785	1,446	783	933
Adults ≥15 years							
Screened	6	4	25,764	7	65	0	0
Too unwell	15,292	9,234	9	30,559	30,216	2,117	5,566
Recruited	14,930	9,043	11,019	6,892	2,427	2,109	5,558
Followed up	14,652	5,697	10,220	6,516	2,330	1,175	4,971

Table 4.6. Participant recruitment and follow-up by age group and site. NA, not applicable.

Over 40% of screened patients were enrolled, although there were site-specific differences in terms of the percentages of patients screened for eligibility who were subsequently recruited (Table 4.6). This is reflective of the diversity of primary care providers through which patient recruitment into the study was performed. For instance, the Thai sites in Tak and Yala provinces comprised predominantly of malaria posts are much more likely to encounter primarily febrile patients meeting eligibility criteria than their counterpart in Chiang Rai which is comprised entirely of PHCs, since PHCs see a wider range of acute and non-acute presentations. Additionally, in 2021 the Laos site, which is also solely comprised of PHCs, screened all patients, including those with scheduled appointments, for eligibility. Inability to obtain patient or caregiver consent was also an issue in Laos, Myanmar, and Chiang Rai, primarily driven by the cultural beliefs surrounding blood sampling.

Notwithstanding the differences between the types of primary care provider described above, fever was still the most common reason for care-seeking given by patients who presented acutely, dwarfing all other reasons even in PHC settings (Table 4.7).

	Chattogram division, Bangladesh	Battambang and Pailin provinces, Cambodia	Savannakhet province, Laos	Karen state, Myanmar	Chiang Rai province, Thailand	Tak province, Thailand	Yala province, Thailand	All sites
Acute presentations in study enrolment period, n	19,464	11,135	32,549	17,921	18,775	3,681	7,373	110,898
Reason for acute presentation, n (%)								
Fever	19,446 (99.9)	11,061 (99.3)	27,787 (85.4)	15,728 (99.9)	16,742 (89.2)	3,680 (99.9)	7,369 (99.9)	101,813 (91.8)
Other acute illness	12 (0.06)	72 (0.06)	2,363 (7.3)	138 (0.8)	66 (0.4)	1 (0.03)	4 (0.05)	2,656 (2.4)
Trauma or injury	4 (0.02)	2 (0.02)	1,981 (6.1)	2,001 (11.2)	1,961 (10.4)	0 (0)	0 (0)	5,949 (5.4)
Snakebite	1 (0.005)	0 (0)	4 (0.01)	6 (0.03)	4 (0.02)	0 (0)	0 (0)	15 (0.01)
Child delivery	1 (0.005)	0 (0)	414 (1.3)	48 (0.3)	2 (0.01)	0 (0)	0 (0)	465 (0.4)

Table 4.7. Reasons for acute presentation during study enrolment period by site and overall.

4.3.1 Characteristics of enrolled patients

Table 4.8 summarises the characteristics of enrolled patients. Adults were the largest age group at all sites, constituting 51,978/84,260 (61.7%) of all enrolled patients. Conversely, only 6 neonates (0.01%) were recruited. Enrolled patients were mainly young people, with the median age across all sites being 20 years and even lower in Laos, Myanmar, and Chiang Rai and Tak. Overall, the ratio of males and females was approximately equal, although females far outnumbered males in Bangladesh. Despite the large number of enrolled females of childbearing age, pregnant women made up only 1,296/84,260 (1.5%) of all patients; however this may be an under-estimate as pregnancy status was determined by self-report rather than formal testing given cultural sensitivities. Rates of child malnutrition were generally low, except in Laos and Yala where 18.0% and 48.7% of children between 6 and 59 months old were severely acutely malnourished.

There were very few severely unwell patients. Across all sites, only 115/185,943 (0.06%) of patients were judged to be too unwell to participate, predominantly adults from Chiang Rai (65/115, or 56.5%) (Figure 4.2 and Table 4.6). Of those recruited, only 4,477/84,260 (5.3%) had at least one danger sign indicating that hospital referral should be recommended. Bangladesh and Myanmar had the highest percentages of participants with danger signs, with 2,138/19,023 (11.2%) and 960/12,840 (7.5%), respectively; at the other sites, participants with danger signs did not exceed 5%.

Patients also tended to present early, with a median illness duration of two days. This was generally the case across sites and age groups as well. This predisposition towards early care-seeking meant that only 9,571/84,260 (11.4%) of patients had sought care elsewhere before being enrolled. Self-medication from pharmacies and drug stores was the most common form of prior care-seeking, although it was also not uncommon for patients who had sought prior care before presenting to a PHC to have been seen at a hospital (Figures 4.3 and 4.4), given

that there is little gate-keeping and patients are free to seek care from any provider.⁶⁴⁻⁶⁸ This may also explain the very small number of severely unwell patients seen, as these patients would likely have gone directly to hospital rather than present to a primary care provider.

	Chattogram division, Bangladesh	Battambang and Pailin provinces, Cambodia	Savannakhet province, Laos*	Karen state, Myanmar	Chiang Rai province, Thailand*	Tak province, Thailand	Yala province, Thailand	All sites
Number enrolled, n	19,023	10,914	24,974	12,840	5,474	3,671	7,364	84,260
Enrolling provider, n (%)								
VHW/VMW	15,329 (80.6)	9,481 (86.9)	NA	7,375 (57.4)	NA	3,386 (92.2)	5,508 (74.8)	41,079 (48.8)
PHC	3,684 (19.4)	1,433 (13.1)	24,974 (100)	5,465 (42.6)	5,474 (100)	285 (7.8)	1,856 (25.2)	43,181 (51.2)
Median age, years (Q1, Q3)	25 (17, 37)	32 (19, 47)	10 (3, 28)	16 (7, 28)	11 (4, 42)	18 (9, 34)	32 (15, 49)	21 (8, 36)
Gender, n (%)								
Male	5,895 (31.0)	4,835 (44.3)	12,340 (49.4)	7,194 (56.0)	2,469 (45.1)	2,035 (55.4)	2,810 (38.2)	37,578 (44.6)
Female	13,127 (69.0)	6,072 (55.6)	12,633 (50.6)	5,640 (43.9)	3,005 (54.9)	1,634 (44.5)	4,540 (61.2)	46,651 (55.4)
Other	1 (0.01)	7 (0.06)	1 (0)	6 (0.05)	0 (0)	2 (0.05)	14 (0.2)	31 (0.04)
Danger signs present, n (%)	2,138 (11.2)	212 (1.9)	606 (2.4)	960 (7.5)	268 (4.9)	21 (0.6)	272 (3.7)	4,477 (5.3)
Pregnant females, n (%)	300 (1.6)	536 (4.9)	180 (0.7)	165 (1.3)	7 (0.1)	34 (0.9)	74 (1.0)	1,296 (1.5)
Severely malnourished young children, n (%)**	41/742 (5.5)	21/260 (8.1)	1,614/8,989 (18.0)	105/1,930 (5.4)	28/1,462 (1.9)	4/357 (1.1)	380/780 (48.7)	2,193/14,520 (15.1)
Median symptom duration, days (Q1, Q3)								
Neonate	2 (2, 2)	3 (2, 4)	NA	2 (2, 2)	NA	NA	NA	2 (2, 3)
Young child	3 (3, 5)	2 (2, 3)	2 (1, 2)	2 (2, 3)	2 (1, 3)	3 (2, 3)	2 (1, 2)	2 (1, 3)
Older child	3 (3, 5)	3 (2, 3)	2 (1, 3)	2 (2, 3)	2 (1, 3)	2 (2, 3)	2 (2, 3)	2 (2, 3)
Adult	4 (3, 5)	2 (2, 3)	2 (1, 3)	2 (2, 3)	2 (1, 3)	3 (2, 3)	2 (2, 3)	3 (2, 3)
Prior care-seeking, n (%)†	6,906 (36.3)	1,198 (11.0)	379 (1.5)	556 (4.3)	31 (0.6)	339 (9.2)	162 (2.2)	9,571 (11.4)

Table 4.8. Demographic and other key participant details by site and overall. NA, not applicable; PHC, primary health centre; Q1, first quartile; Q3, third quartile; VHW, village health worker; VMW, village malaria worker. *These sites recruited exclusively at primary health centres. **Defined as a mid-upper arm circumference of <115 mm in children aged 6–59 months. †Further details of healthcare providers from where care was sought prior to recruitment by village health workers/village malaria workers and primary health centres are shown in Figures 4.3 and 4.4, respectively.

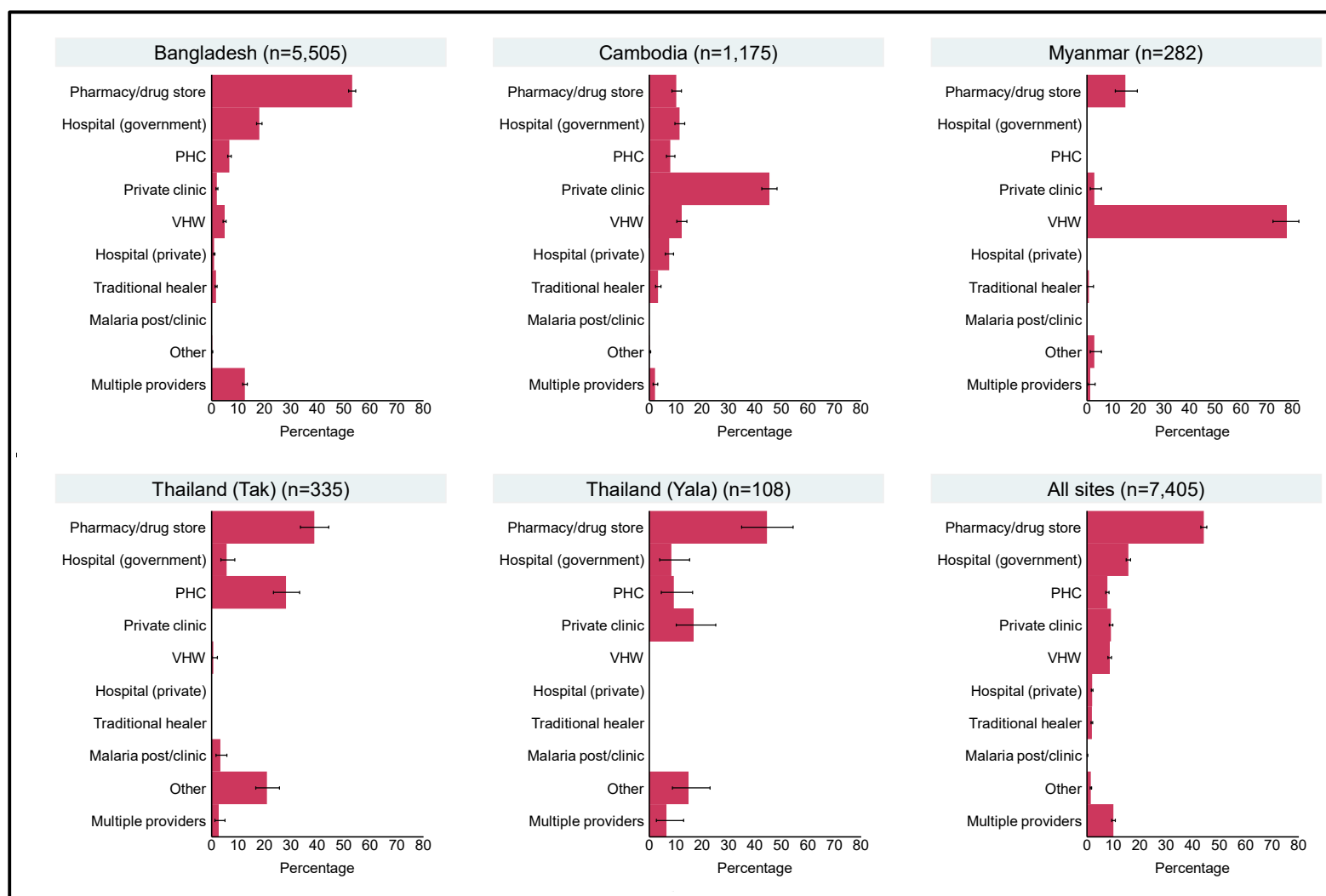


Figure 4.3. Frequencies of healthcare providers from which patients enrolled by village health workers/village malaria workers sought care prior to the time of enrolment by site and overall. Error bars represent 95% confidence intervals. The Laos and Thailand (Chiang Rai) sites are not shown as they enrolled patients exclusively in primary health centres. PHC, primary health centre; VHW, village health worker.

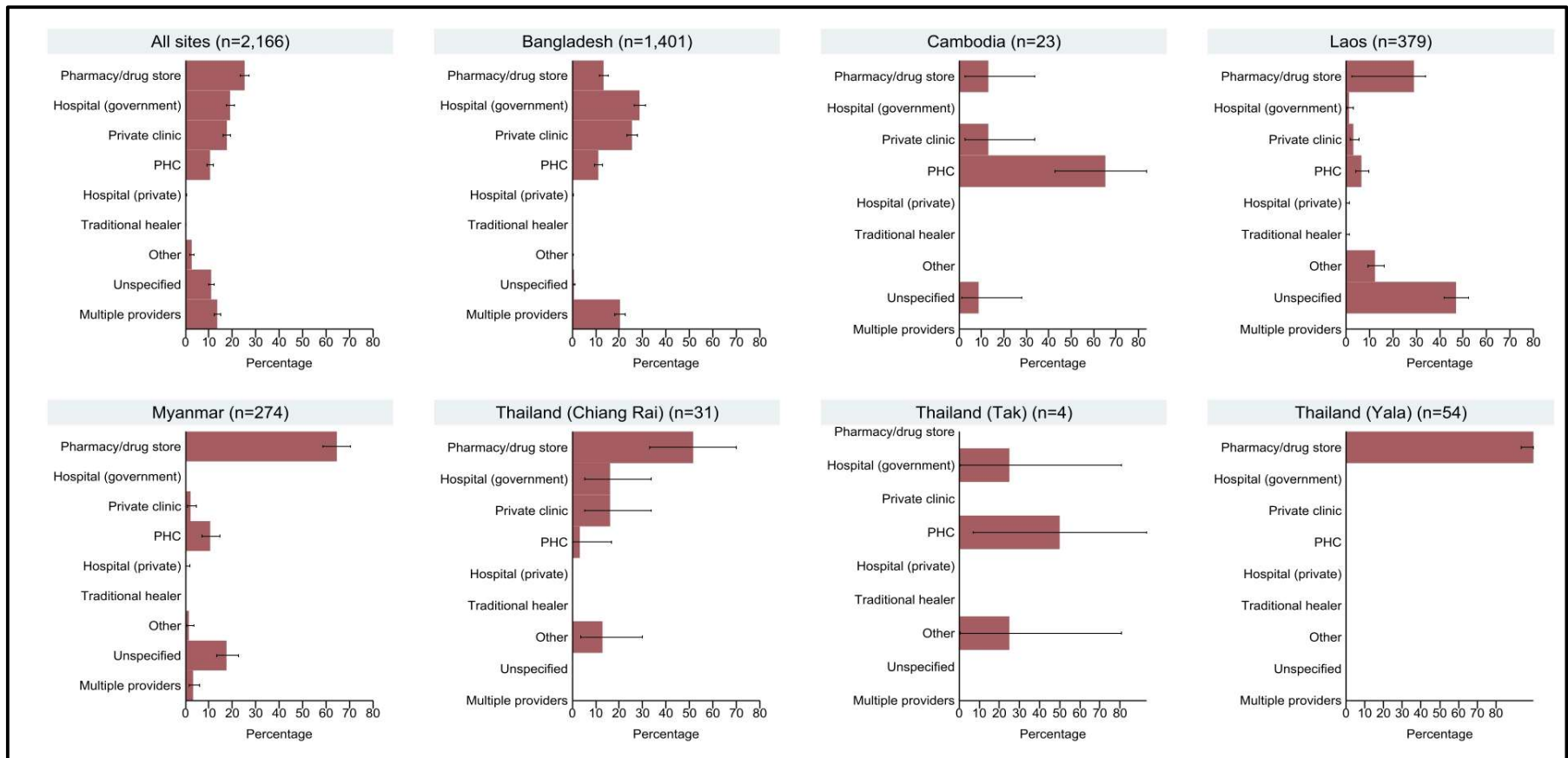


Figure 4.4. Frequencies of healthcare providers from which patients enrolled by primary health centres sought care prior to the time of enrolment by site and overall. Error bars represent 95% confidence intervals. PHC, primary health centre; VHW, village health worker.

4.3.2 Diagnoses and presenting syndromes

4.3.2.1 *Non-malarial febrile illnesses*

Upper respiratory tract infection (URTI), comprising the diagnoses of 'rhinitis, pharyngitis, or tonsillitis' or 'bronchitis' was the commonest NMFI and also the commonest presenting syndrome overall; 48,281/84,260 (57.3%) of all enrolled patients were determined to have presented with rhinitis, pharyngitis, or tonsillitis and 3,110/84,260 (3.7%) with bronchitis based on the algorithmic diagnosis rules previously described in the Methods. Rhinitis, pharyngitis, or tonsillitis was also the most common diagnosis across all age groups when all sites were collectively considered (Figures 4.5, 4.6, and 4.7).

Fever of unclear source was the second most common diagnosis, comprising 25,977/84,260 (30.8%) of all recruited patients. In Cambodia, Myanmar, and Tak, patients with fever of unclear source constituted the majority of participants. Together, therefore, URTI and fever of unclear source accounted for over 91.8% of enrolled patients overall, and between 73.4 and 99.2% of participants at each site.

With regard to the remaining diagnoses, those affecting only single organ systems, such as urinary tract infection (UTI), were relatively uncommon. In total, these made up 2,100/84,260 (2.5%) of all diagnoses. With the exception of gastroenteritis and dysentery, which comprised 523/24,974 (2.1%) and 125/5,474 (2.3%) of patients enrolled in Laos and Chiang Rai, respectively, the other single organ system diagnoses each comprised 1% or less of the total participants at each site and in each age group except neonates (Figures 4.5, 4.6, and 4.7). Of the six neonates enrolled, four (66.7%) had fever of unclear source, while one (16.7%) each had pneumonia and central nervous system disorder.

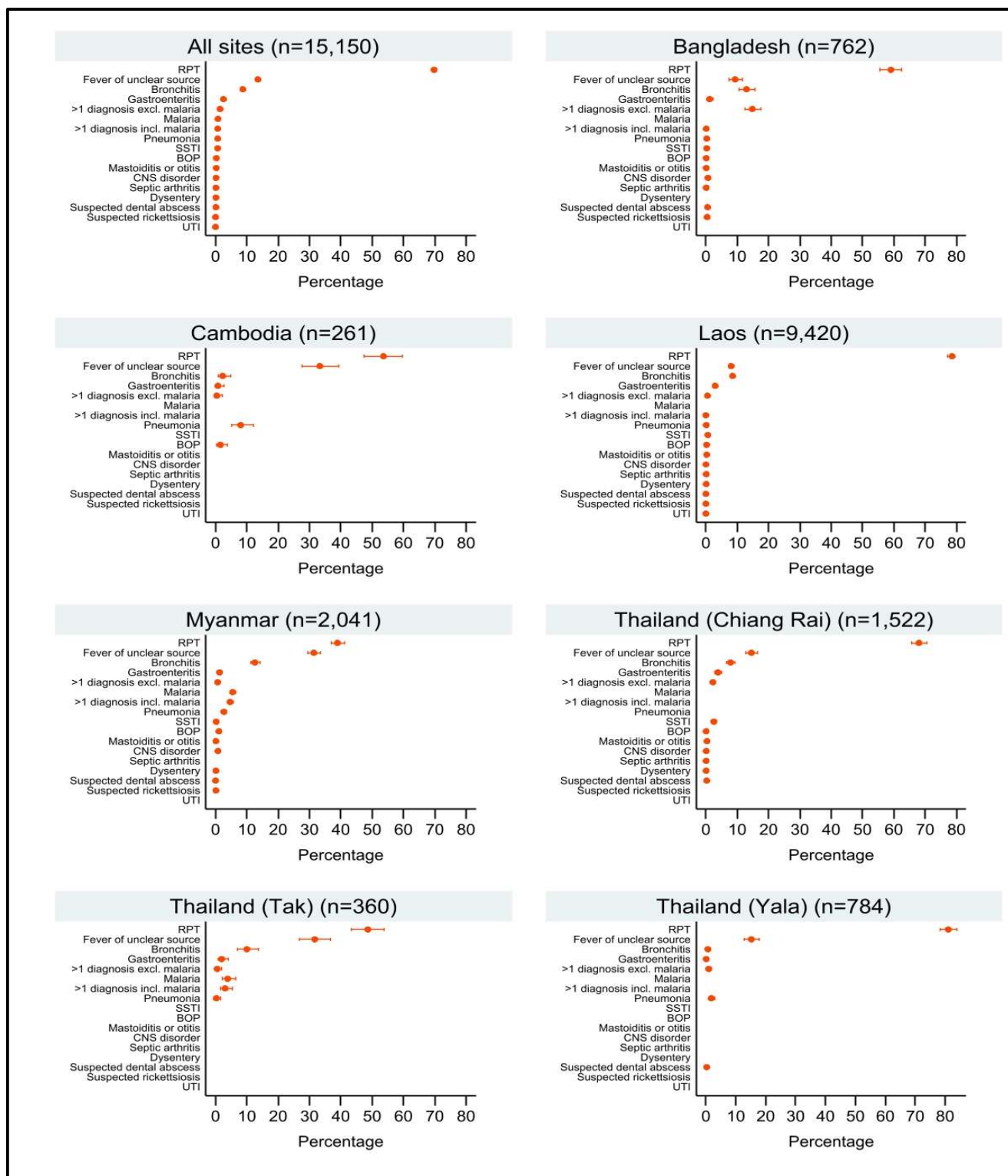


Figure 4.5. Syndromic diagnoses associated with acute febrile illness in children aged 29 days to <5 years by site and overall. Error bars represent 95% confidence intervals. BOP, bronchiolitis or pneumonia; CNS, central nervous system; RPT, rhinitis, pharyngitis, or tonsillitis; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

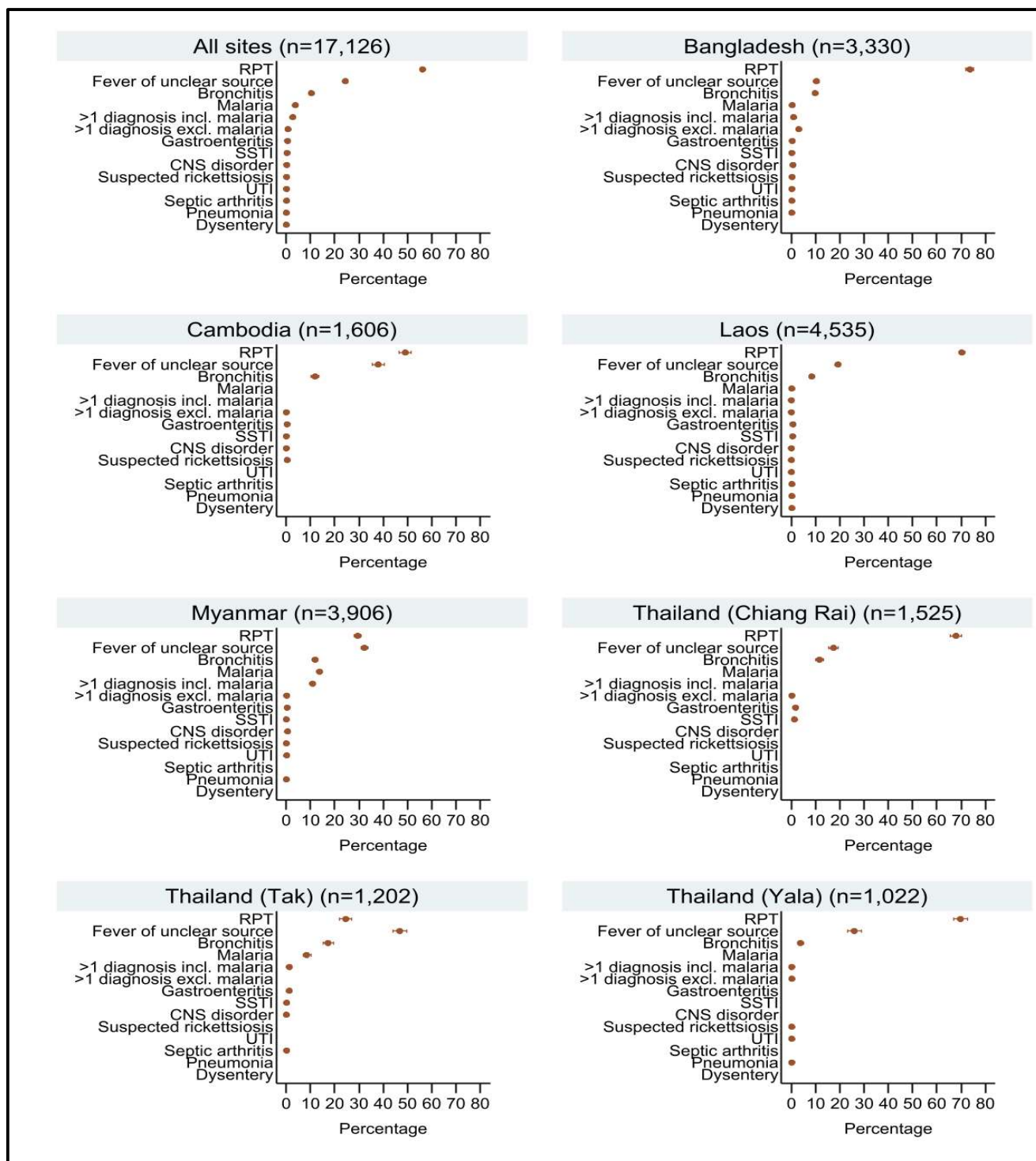


Figure 4.6. Syndromic diagnoses associated with acute febrile illness in children aged 5 to <15 years by site and overall. Error bars represent 95% confidence intervals. CNS, central nervous system; RPT, rhinitis, pharyngitis, or tonsillitis; SSSI, skin and soft tissue infection; UTI, urinary tract infection.

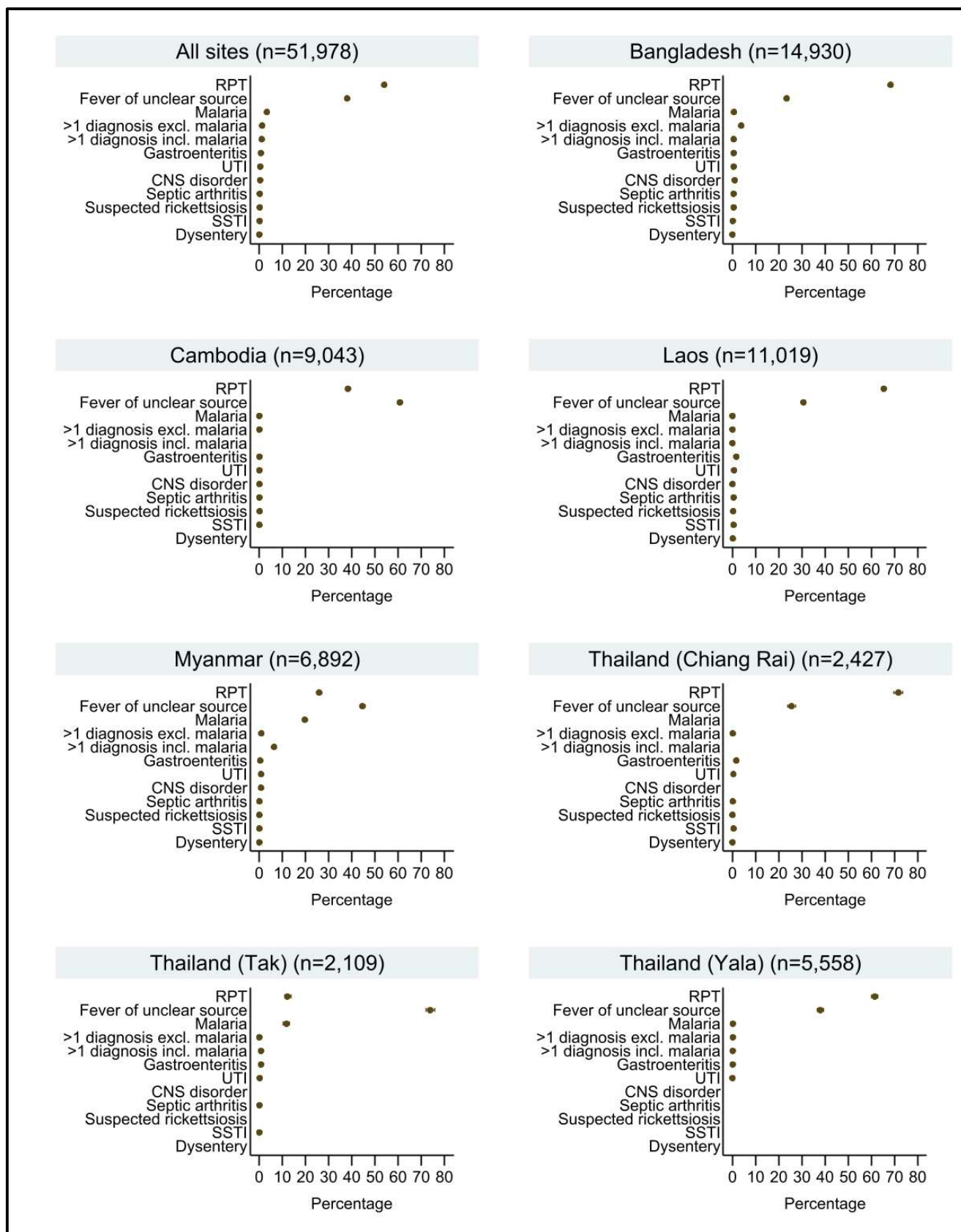


Figure 4.7. Syndromic diagnoses associated with acute febrile illness in adults aged ≥ 15 years by site and overall. Error bars represent 95% confidence intervals. CNS, central nervous system; RPT, rhinitis, pharyngitis, or tonsillitis; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

4.3.2.2 Malaria and malarial co-infections

The number of participants with malaria, as confirmed by a positive RDT, was very low overall (2,503/84,260, 3.0%), with the vast majority of tests returning negative results (Table 4.9). There were also 1,132/84,260 (1.3%) patients with malarial co-infections, defined as malaria plus any other diagnosis. However, note that while the term ‘malarial co-infection’ is used in this report, in practice it was not possible to differentiate between true co-infections occurring concurrently with malaria and syndromes affecting single organ systems caused by malaria, since malarial symptoms may mimic those of other diseases and asymptomatic malaria is not uncommon even in low-transmission areas.^{128, 129}

Importantly, the Myanmar site had a much higher percentage of patients with malaria (2,007/12,840, 15.6%) and malarial co-infections (963/12,840, 7.5%) compared with almost all other sites where these figures were negligible, the exception being Tak in Thailand which borders Myanmar (Figures 4.5, 4.6, and 4.7). In Tak, 364/3,671 (9.9%) of patients had malaria and 44/3,671 (1.2%) had malarial co-infections.

Malaria was predominantly caused by non-falciparum species of the *Plasmodium* parasite (Table 4.9). While exact identification to species level of non-falciparum parasites was not possible in Myanmar where the bulk of malaria infections were seen due to the type of RDT used, it is likely that these were mostly *P. vivax* in keeping with the findings from the other sites as well as the current evidence on malaria epidemiology in that country and the wider Greater Mekong Sub-region, where this species is now the most common cause of malaria.^{12, 130}

	Chattogram division, Bangladesh	Battambang and Pailin provinces, Cambodia	Savannakhet province, Laos	Karen state, Myanmar*	Chiang Rai province, Thailand**	Tak province, Thailand	Yala province, Thailand	All sites
Number of malaria RDTs performed, n	18,481	10,465	24,972	12,412	8	2,971	6,933	76,212
Number of positive RDTs, n (%)	222 (1.2)	2 (0.02)	17 (0.07)	2,970 (23.9)	0 (0)	408 (13.7)	16 (0.2)	3,635 (4.8)
<i>Plasmodium</i> species (n, %)								
<i>P. falciparum</i>	97 (43.7)	0 (0)	4 (23.5)	61 (2.1)	NA	3 (0.7)	0 (0)	165 (4.5)
<i>P. vivax</i>	118 (53.2)	2 (100)	7 (41.2)	NA		397 (97.3)	15 (93.8)	539 (14.8)
<i>P. ovale</i>	0 (0)	0 (0)	0 (0)	NA		1 (0.3)	0 (0)	1 (0.03)
Non-falciparum, unspecified	6 (2.7)	0 (0)	3 (17.7)	2,848 (95.9)		7 (1.7)	1 (6.3)	2,865 (78.8)
Mixed infection	1 (0.5)	0 (0)	1 (5.9)	59 (2.0)		0 (0)	0 (0)	61 (1.7)
Not recorded	0 (0)	0 (0)	2 (11.8)	2 (0.07)		0 (0)	0 (0)	4 (0.1)

Table 4.9. Malaria rapid diagnostic test results by site and overall. *Plasmodium* species results use the number of positive RDTs as the denominator, and the results reported for *P. falciparum*, *P. vivax*, and *P. ovale* indicate that only that species was detected. *The RDTs used at the Myanmar site were unable to differentiate between non-falciparum species of *Plasmodium* parasite. **Unlike the other sites, in line with local policy malaria RDTs are only performed in Chiang Rai if the index of suspicion is high, given the established minimal incidence of malaria at this site. NA, not applicable; RDT, rapid diagnostic test.

4.3.2.3 Non-malarial co-infections

Patients with non-malarial co-infections comprised just 1.2% (995/84,260) of the total number enrolled. Interestingly, however, the relative frequency of non-malarial co-infections was much higher in Bangladesh (784/19,023, 4.1%) compared to all other sites where the relative frequency of this diagnosis was <1%. This finding was also seen when participants were stratified by site and age group, and was most marked in Bangladeshi children <5 years old. In this group of patients, 113/762 (14.8%) had more than one non-malarial diagnosis (Figures 4.5, 4.6, and 4.7).

4.3.2.4 Diagnostic agreement

As can be seen in Table 4.10, the degree of agreement between diagnoses generated by the algorithmic diagnosis rules and those made by PHC staff ranged from a low 25.8% in Bangladesh to a relatively high 79.0% in Yala. Four sites had degrees of agreement exceeding 70% (Cambodia, Laos, Chiang Rai, and Yala). It should, however, be emphasised that the PHC workers were expected only to identify the organ system affected e.g., 'ear infection', rather than specify an exact working diagnosis e.g., 'mastoiditis'. Nevertheless, these findings are a useful addition to the current scant evidence for the diagnostic skillsets available in rural PHC settings.

	Chattogram division, Bangladesh	Battambang and Pailin provinces, Cambodia	Savannakhet province, Laos	Karen state, Myanmar	Chiang Rai province, Thailand	Tak province, Thailand	Yala province, Thailand	All sites
CLINICAL MANAGEMENT								
Diagnostic agreement, n (%)*	954/3,694 (25.8)	1,082/1,433 (75.5)	17,796/24,974 (71.3)	3,131/5,465 (57.3)	3,843/5,474 (70.2)	111//285 (39.0)	1,466/1,856 (79.0)	28,383/43,181 (65.7)
Antibiotic prescription, n (%)*	597/3,964 (16.2)	217/1,191 (18.2)	4,356/15,746 (27.7)	2,064/4,296 (48.0)	178/4,429 (4.0)	1/164 (0.6)	8/1,615 (0.5)	7,421/31,135 (23.8)
Referral to hospital, n (%)	916/19,023 (4.8)	209/10,914 (1.9)	52/24,974 (0.1)	3/12,840 (0.02)	3/5,474 (0.05)	12/3,671 (0.3)	11/7,364 (0.1)	1,206/84,260 (1.4)
Danger sign(s)	80/916 (8.7)	5/209 (2.4)	6/52 (11.5)	1/3 (33.3)	NA	2/12 (16.7)	2/11 (18.2)	96/1,206 (8.0)
No danger signs	836/916 (91.3)	204/209 (97.6)	46/52 (88.5)	2/3 (66.7)	3/3 (100)	10/12 (83.3)	9/11 (81.8)	1,110/1,206 (92.0)
Referral to other providers, n (%)**	698/19,023 (3.7)	487/10,914 (4.5)	698/24,974 (3.0)	119/12,840 (0.9)	0/5,474 (0)	34/3,671 (0.9)	306/7,364 (4.2)	1,647/84,260 (2.0)
Danger sign(s)	120/698 (17.2)	6/487 (1.2)	120/698 (17.2)	3/119 (2.5)	NA	1/34 (2.9)	0/306 (0)	131/1,647 (8.0)
No danger signs	578/698 (82.8)	481/487 (98.8)	578/698 (82.8)	118/119 (92.5)	NA	33/34 (97.1)	306/306 (100)	1,516/1,647 (92.0)
Referral to hospital if danger sign(s) present, n (%)	80/2,138 (3.7)	5/212 (2.4)	6/606 (1.0)	1/960 (0.1)	0/268 (0)	2/21 (9.5)	2/272 (0.7)	96/4,477 (2.1)
Referral to any provider if danger signs present, n (%)	200/2,138 (9.4)	11/212 (5.2)	7/606 (1.2)	4/960 (0.4)	0/268 (0)	3/21 (14.3)	2/272 (0.7)	227/4,477 (5.1)
FOLLOW-UP, CARE-SEEKING, AND OUTCOME								
Number who completed follow- up, n (%)	18,667/19,023 (98.1)	6,896/10,914 (63.2)	23,028/24,974 (92.2)	12,274/12,840 (95.6)	5,239/5,474 (95.7)	2,188/3,671 (59.6)	6,679/7,364 (90.7)	74,971/84,260 (89.0)

Sought care during follow up, n (%)†	7,829/18,659 (42.0)	1,135/6,892 (16.5)	41/22,018 (0.2)	91/12,177 (0.7)	81/5,238 (1.5)	547/2,187 (25.0)	70/6,678 (1.0)	9,794/73,849 (13.3)
Received oral medication during follow up, n (%)	7,512/7,829 (96.0)	237/1,135 (20.9)	32/41 (78.1)	85/91 (93.4)	74/81 (91.4)	215/547 (39.3)	61/70 (87.1)	8,216/9,794 (83.9)
Hospital admission during follow up, n (%)	24/7,829 (0.3)	5/1,135 (0.4)	15/41 (36.6)	20/91 (22.0)	10/81 (12.3)	14/547 (2.6)	2/70 (2.9)	90/9,794 (0.9)
Median length of hospital stay, days (Q1, Q3)	3 (2, 6)	3 (3, 4)	2 (1, 4)	4 (3, 5)	4 (3, 7)	3 (3, 4)	12 (3, 20)	3 (2, 5)
Outcome, n (%)								
Recovery	17,688/18,663 (94.8)	1,709/6,892 (24.8)	21,871/23,017 (95.0)	11,954/12,268 (97.4)	4,997/5,238 (95.4)	2,165/2,187 (99.0)	6,439/6,678 (96.4)	66,823/74,943 (89.2)
Non-recovery	975/18,663 (5.2)	5,183/6,892 (75.2)	1,146/23,017 (0.5)	314/12,268 (1.8)	241/5,238 (4.6)	22/2,187 (1.0)	239/6,678 (3.6)	8,120/74,943 (10.8)
Unchanged	576/975 (59.3)	738/5,183 (14.2)	10/1,146 (0.9)	3/314 (1.0)	1/241 (0.1)	4/22 (18.8)	53/239 (22.2)	1,385/8,120 (17.1)
Better	382/975 (39.3)	4,393/5,183 (84.8)	138/1,146 (12.0)	216/314 (68.8)	238/241 (98.8)	17/22 (77.3)	185/239 (77.4)	5,569/8,120 (68.6)
Worse	13/975 (1.3)	52/5,183 (1.0)	1/1,146 (0.1)	4/314 (1.3)	2/241 (0.8)	1/22 (4.6)	1/239 (0.4)	74/8,120 (0.9)
Unknown	4/975 (0.4)	0/5,183 (0)	997/1,146 (87.0)	91/314 (29.0)	0/241 (0)	0/22 (0)	0/239 (0)	1,092/8,120 (13.5)
Death	4/18,667 (0.02)	4/6,896 (0.06)	11/23,028 (0.04)	6/12,274 (0.05)	1/5,239 (0.02)	1/2,188 (0.05)	1/6,679 (0.01)	28/74,971 (0.04)

Table 4.10. Clinical management, care-seeking during follow up, and outcome by site and overall. Diagnostic agreement was assessed as shown in Table 4.5 by comparing the diagnosis entered by the primary health centre worker and that assigned algorithmically based on symptom and vital sign data. Non-recovery was defined as persistence of symptoms, which were either unchanged, better, or worse with reference to the date of enrolment. NA, not applicable; SD, standard deviation; 95% CI, 95% confidence interval. *PHC patients only; commencement of data collection on antibiotic prescription varied between sites. **Further details of healthcare providers to where referrals were made are shown in Figure 4.9. †Further details of healthcare providers from where care was sought during follow up are shown in Figures 4.10 and 4.11. ‡Only one patient provided cost data.

4.3.3 Clinical management

4.3.3.1 Antimicrobial prescribing

Of the 31,135 patients recruited at PHCs for whom antibiotic prescribing data were collected, 7,421 (23.8%) received antimicrobials. The prescription rate ranged from 0.5% in Yala to 48.0% in Myanmar (Table 4.10). Notably, PHCs at sites in Thailand had much lower prescription rates compared to their counterparts in other countries.

β -lactams were the most commonly prescribed antibiotic class, with amoxicillin being the most commonly prescribed agent. Consistent with the relative frequency of URTIs, the bulk of antibiotic prescribing was for this syndrome (Figure 4.8).

Unlike antibiotic prescribing, prescription of antimalarials was much better targeted, in keeping with the established emphasis of vertical malaria programmes on testing for, and treating, the disease. Unsurprisingly, most antimalarial prescribing occurred in Myanmar to patients with positive malaria RDT test results, given that almost all malaria infections were concentrated at this site, as previously described. Chloroquine was the most commonly prescribed antimalarial (556/595, or 93.5% of antimalarial prescriptions overall), although given the high rate of chloroquine resistance was not likely to have been useful in Myanmar where it was mostly prescribed.

4.3.3.2 Referral

Across all sites, 2,853/84,260 (3.4%) of enrolled patients were referred elsewhere for further healthcare on the day of recruitment. Of these, 1,206/2,853 (42.3%) of participants were referred to hospital and the remainder to other healthcare providers.

Overall, the overwhelming majority of patients with danger signs were not referred to hospital (4,381/4,477, 97.9%) or to any healthcare provider (4,250/4,477, 94.9%). This was true

at every site (Table 4.10). Referral rates of severely unwell patients to any healthcare provider ranged from 0% in Chiang Rai to 14.3% in Yala (Table 4.10). Notably, despite automatic prompting by the app when danger signs were encountered, their sensitivity and specificity for hospital referral were 8.0% and 94.7%, respectively; 1,110/1,206 (92.0%) of hospital referrals did not have danger signs.

Non-hospital referral destinations were mainly to PHCs and pharmacies or drug stores (Figure 4.9). The former is not surprising, given that almost half the patients enrolled were seen by VHWs/VMWs, for whom PHCs are the first referral point for patients deemed well enough not to require assessment in hospital. As VHWs/VMWs do not dispense medications and the types of drugs, including antimicrobials, available at PHCs are limited, it is also unsurprising that many patients are instructed to obtain medicines in the private market.

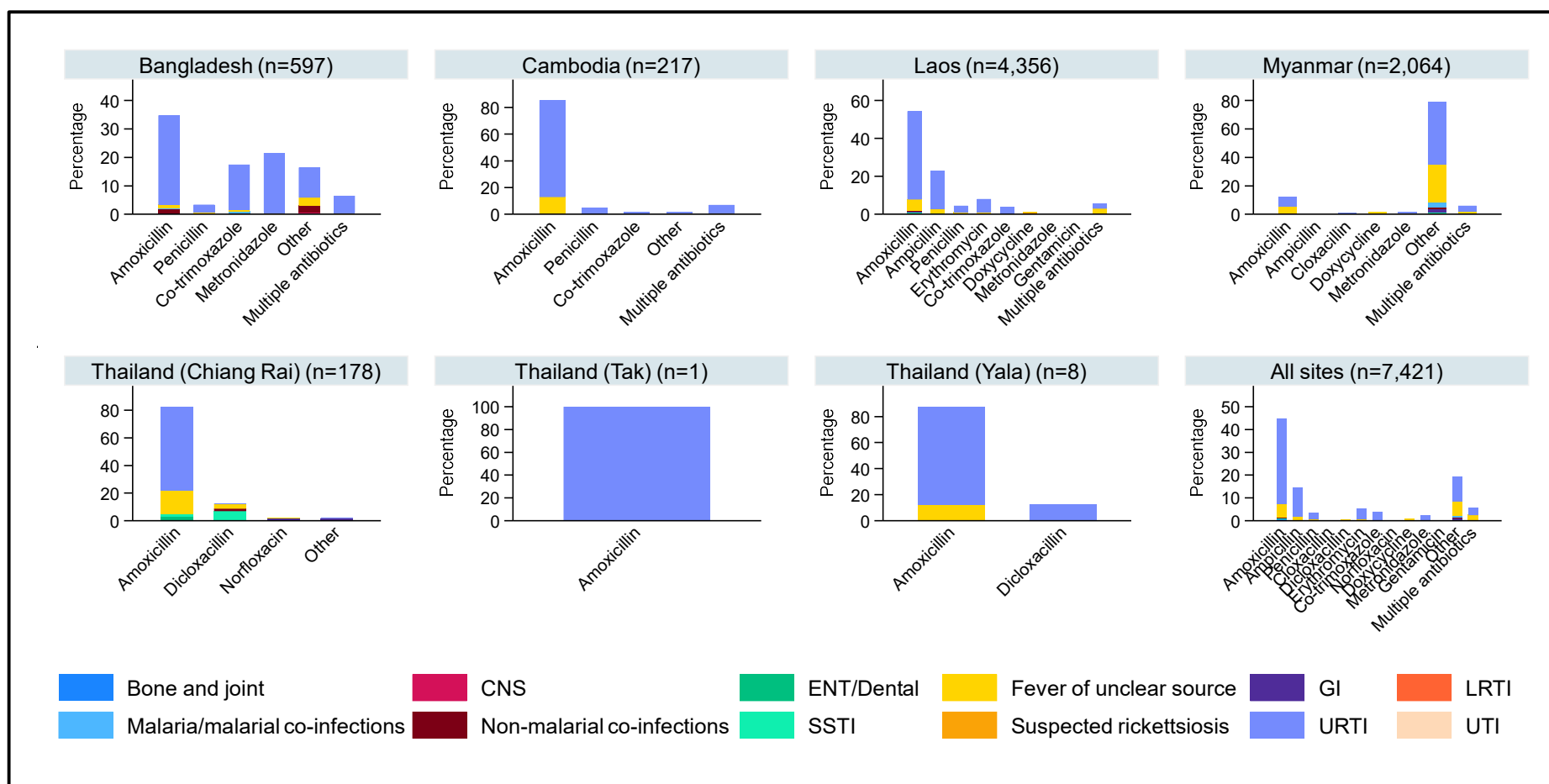


Figure 4.8. Antibiotics prescribed and their corresponding algorithmic syndromic diagnosis groups by site and overall. CNS, central nervous system; ENT, ear, nose, and throat; GI, gastrointestinal; LRTI, lower respiratory tract infection; SSTI, skin and soft tissue infection; URTI, upper respiratory tract infection; UTI, urinary tract infection.

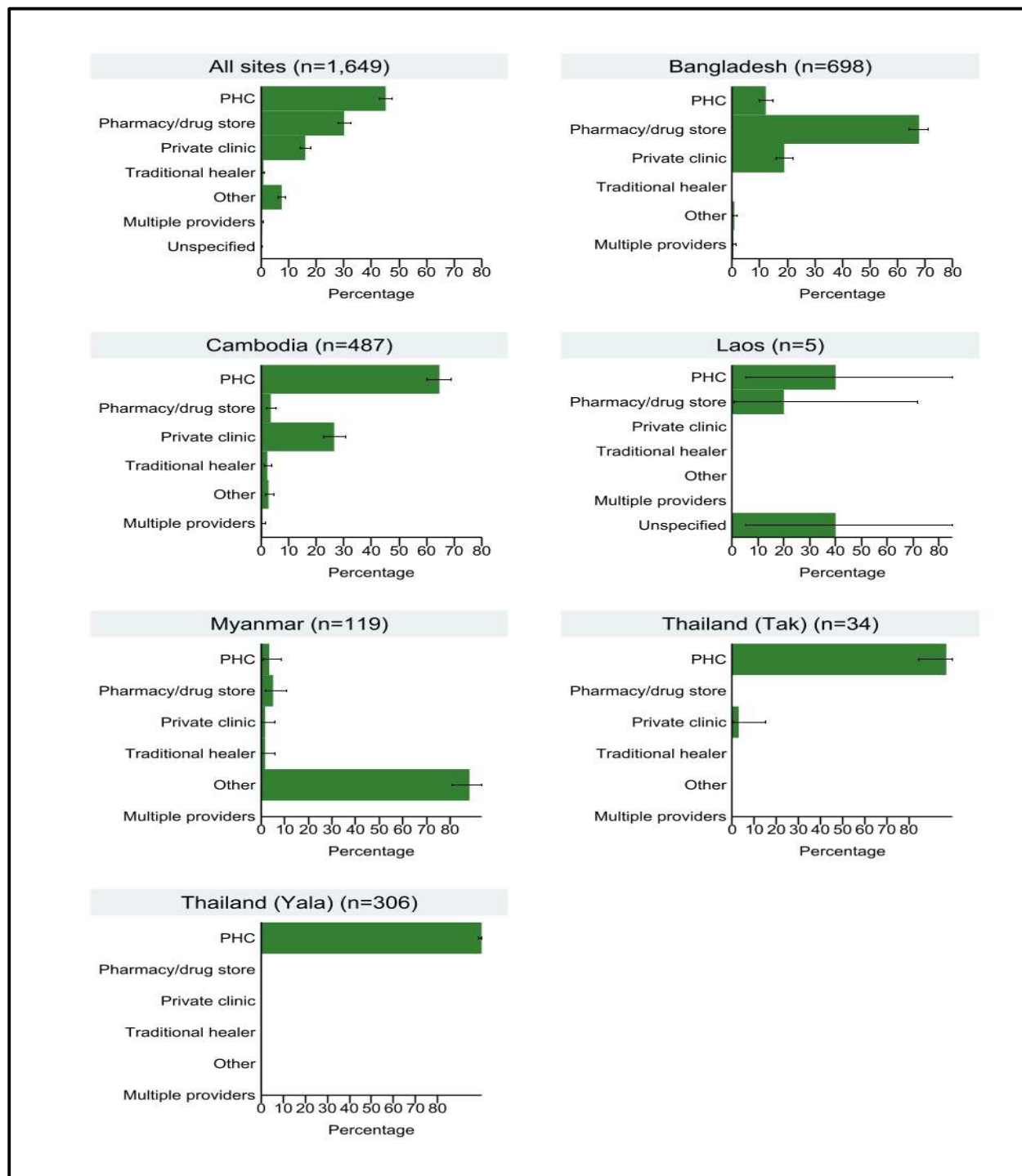


Figure 4.9. Non-hospital healthcare providers to which patients were referred at the time of enrolment by site and overall. Error bars represent 95% confidence intervals. No referrals to non-hospital healthcare providers were made at the Thailand (Chiang Rai) site. PHC, primary health centre.

4.3.4 Follow up and outcomes

In total, 74,971/84,260 (89.0%) of enrolled patients were successfully followed up, as shown in Figure 4.2. Follow-up rates at all sites exceeded 90% except in Cambodia and Tak, which together contributed 5,501/9,289 (59.2%) of losses to follow-up, mainly in adults (Tables 4.6 and 4.10). This is likely due to there being a considerable number of itinerant agricultural labourers at these sites who work away from their home villages for long stretches at a time.

4.3.4.1 Care-seeking

Of the 74,971 patients who completed follow up, 9,794 (13.1%) sought further care following recruitment. Care-seeking was most frequent in Bangladesh and Tak, where the percentages of patients who had sought further care were 42.0% and 25.0%, respectively (Table 4.10). Patients most frequently sought further care from pharmacies or drug stores (Figures 4.10 and 4.11), which corroborates the results reported in Chapter 3 ('Demographic, health, and socio-economic status profiles of villages in rural South and Southeast Asia') on the availability and accessibility of health services for rural village dwellers. Given this finding, that 8,216/9,794 (83.9%) received some form of oral medication during the follow up period is not unexpected, with this figure exceeding 90% in some sites (Table 4.10).

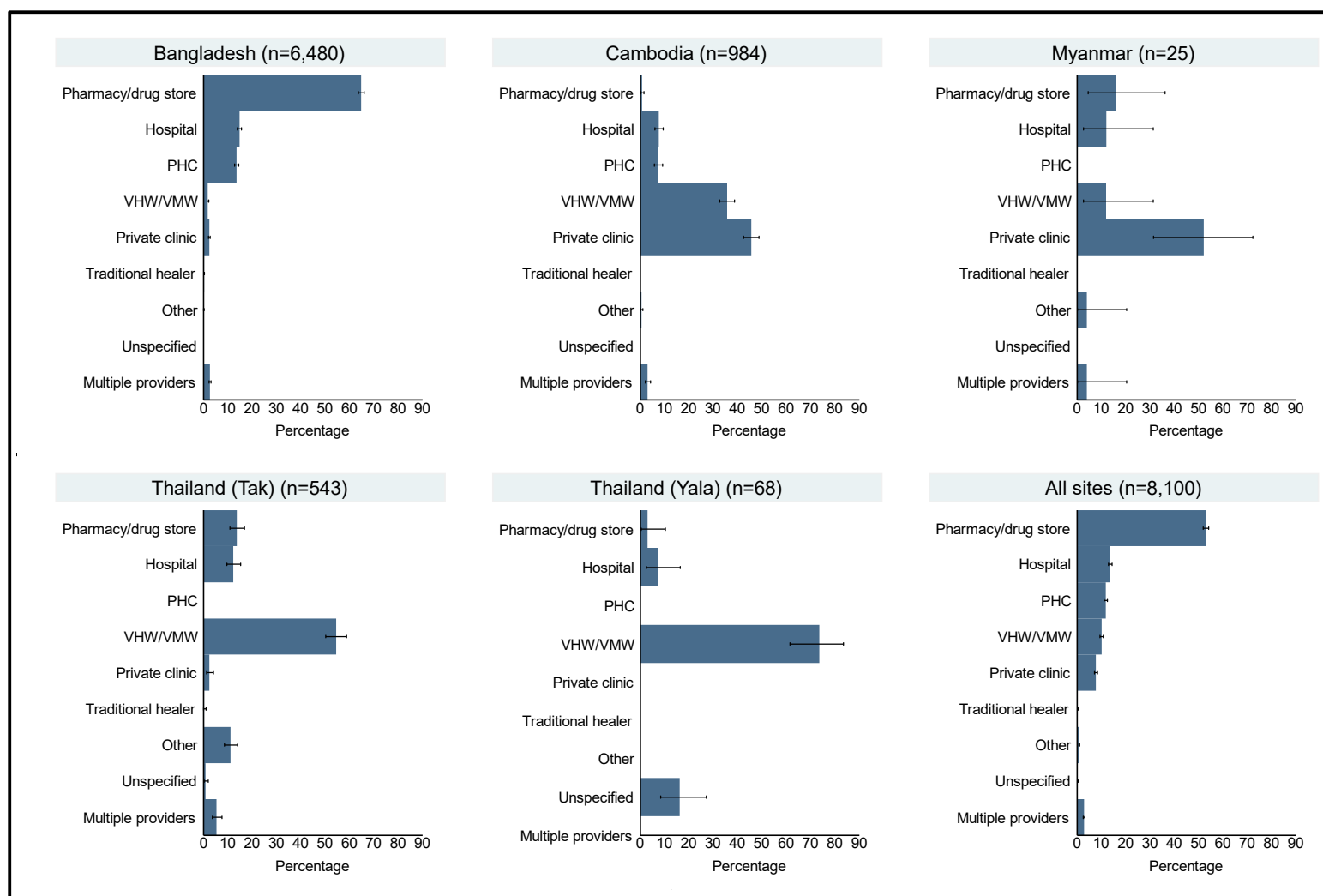


Figure 4.10. Frequencies of healthcare providers from which patients enrolled by village health workers/village malaria workers sought care following enrolment by site and overall. Error bars represent 95% confidence intervals. The Laos and Thailand (Chiang Rai) sites are not shown as they enrolled patients exclusively in primary health centres. PHC, primary health centre; VHW/VMW, village health worker/village malaria worker.

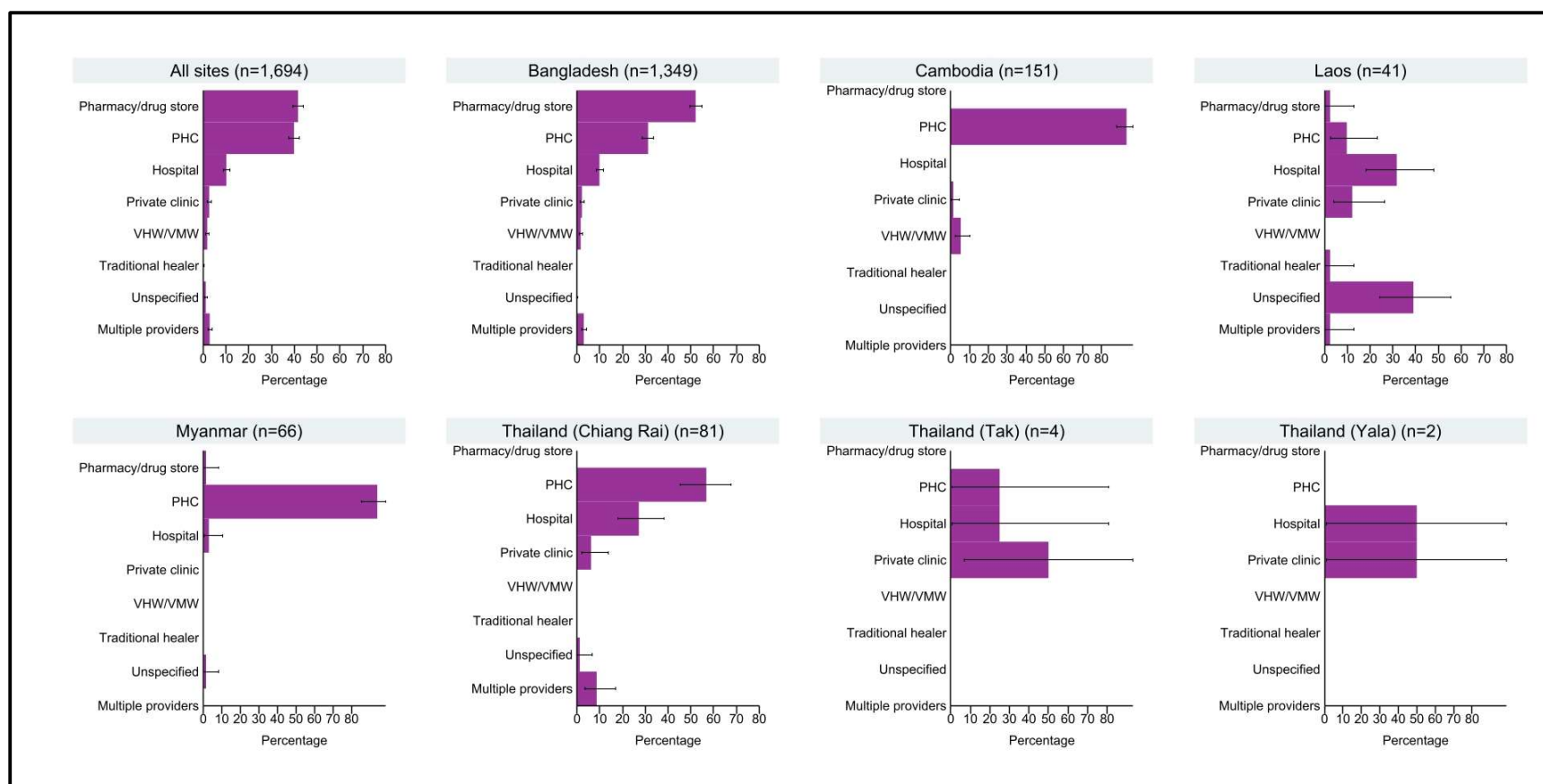


Figure 4.11. Frequencies of healthcare providers from which patients enrolled by primary health centres sought care following enrolment by site and overall. Error bars represent 95% confidence intervals. PHC, primary health centre; VHW/VMW, village health worker/village malaria worker.

4.3.4.2 Survival

The bulk of followed up patients whose vital status was able to be ascertained survived their presenting illness (74,943/74,971, 99.9%). To further minimise bias in estimating the mortality rate, VHWs/VMWs servicing the villages where participants who were lost to follow up and had not explicitly withdrawn from the study lived were tasked with determining whether these patients were still alive. In this manner, a further 1,747 of 9,289 (18.8%) patients who were lost to follow up were able to have their survival status ascertained. Only three of these patients were determined to have died, but inability to establish their dates of death meant that whether they had died during the follow up period could not be determined. Additionally, because the follow up window had closed, data on symptom resolution was not collected from survivors.

Of the 28 patients who died, seven (26.0%) had danger signs at presentation but only one (3.6%) was referred to hospital. Consistent with this, most deaths occurred at home (23/28, 82.1%). The majority of deceased patients were adults, with the median age of death being 48 years (interquartile range 21–65 years). The commonest diagnosis at presentation in participants who died was fever of unclear source (19/28, 66.7%), although interestingly 7/28 (25.0%) had URTI.

4.3.4.3 Symptom resolution

Data on symptom resolution were collected from 73,851 survivors. At follow up, 66,823/74,943 (89.2%) had recovered fully from their presenting illness. The percentage of participants who reported full resolution of their symptoms when followed up was $\geq 94\%$ at all sites except Cambodia, where only 24.8% reported full recovery. At this site, only 47/5,183 (0.9%) of participants who reported that their symptoms had not resolved had exhibited danger signs at presentation. The most common diagnoses in this sub-group of patients were fever of unclear source (2,746/5,183, 53.0%) and URTI (2,374/5,183, 45.8%), which together accounted for 98.8% of all patients who reported unresolved symptoms at follow up.

4.3.4.4 Hospitalisation

Overall, 1,118/74,971 (1.5%) participants who were successfully followed up were referred to hospital. However, of these only 2 (0.2%) referrals resulted in a hospital admission of any duration, indicating that the vast majority of those referred either did not go to hospital or, if they did go, were not admitted following initial assessment in secondary care. The former may reflect the inaccessibility of hospitals at certain sites, as reported in Chapter 3.

Nevertheless, a further 88/74,971 (0.1%) participants who were not initially referred to hospital were admitted during their follow-up period. In total, 90/74,971 (0.1%) of patients who completed follow-up were admitted to hospital, all of whom survived. The median length of stay was short at 3 days (interquartile range 2–5 days), with 36/89 (40.4%) of all admissions lasting >3 days. Hospital admission rates did not vary much by site (Table 4.10).

Thirty patients who were admitted to hospital were able to provide estimates of the monetary cost of admission to themselves and their families in local currency. The median daily cost of hospital admission by site in 2023 US dollars is shown in Table 4.10. However, it should be noted that these were only crude estimates obtained in an unstructured way from a small proportion of hospitalised patients.

4.4 Discussion

4.4.1 Summary of main findings

Similar to primary care settings elsewhere, the most common AFI syndrome in rural South and Southeast Asian primary care is URTI (61.0% of enrolled patients);¹³¹ the second most common diagnosis, fever of unclear source, accounted for a further 30.8%. The percentage of co-infections was not trivial at 2.5%. Malaria comprised a negligible fraction of AFI cases in the region, except in Myanmar where it comprised 15.6% of AFI. Non-falciparum malaria was predominant and primarily treated with chloroquine.

On the whole, a considerable percentage of PHC staff were able to identify the organ system affected by a particular syndrome, except in Bangladesh where only 25.8% were able to do so. Despite this, antibiotic prescribing was poorly targeted, with the exception of sites in Thailand, with the bulk of antibiotics directed towards URTIs. Hospital referrals were also poorly targeted, with the majority of patients with danger signs not being referred at initial presentation i.e., the sensitivity of danger signs for hospital referral was low. Only 0.1% of referrals to hospital resulted in admission, further supporting the assertion that many patients not requiring admission were referred, although the reasons influencing admission decisions were not explored. Nevertheless, the mortality rate was low at 0.04% with the vast majority of patients recovering fully, although this is likely to be an under-estimate given selection bias (since patients who are less severely unwell are more likely to be enrolled) and loss to follow up (since patients lost to follow up are not included in calculating the mortality rate). In any case, mortality would not surpass 9.0% since survival status was able to be ascertained for 91.0% of enrolled patients, and is likely to be much lower since approximately half the patients whose survival was not determined presented with URTIs, which are almost always self-limiting.¹³²

Finally, an important finding is the important role pharmacies and drug stores play in primary healthcare provision as, compared to other types of healthcare facility, they are the most frequently visited by patients before and after presenting to formal primary care providers.

4.4.2 Interpretation of main findings

This is the first study to describe richly the epidemiology of AFI in the main primary care settings of rural South and Southeast Asia. A further novel aspect of this research is the departure from the methodology of previous research on AFI in this region, which has prioritised microbial aetiology;^{27, 44, 121-123, 125, 133, 134} however, syndromic diagnoses are, arguably, are more important in terms of relevance to a semi-skilled primary healthcare worker with no access to laboratory diagnostics. This hypothesis has been borne out by the finding that the bulk of patients had

URTIs, which are almost always viral and for which determining an exact cause is not generally essential.¹³² The results do, however, indicate that development of aetiological diagnostic capacity would be most useful for fevers of unclear source, ideally with multiplex point-of-care RDTs given the plethora of causes for this syndrome.^{41, 124, 135} They also support the assertion that there is wide scope to improve healthcare worker skillsets, at least where diagnosis, antibiotic prescription, and care escalation are concerned.

That a not inconsequential percentage of patients had co-infections accords with the results of previous fever studies in the region,¹²¹⁻¹²⁵ lending further weight for managing each syndrome separately as is currently recommended by the WHO in tropical LMIC settings.^{116, 117}

The poorly-delineated forested border region encompassing the sites in Tak province in Thailand and Karen state in Myanmar is a known focus of high malaria incidence,^{115, 136} explaining the relatively high percentages of malaria cases in these sites. Malaria eradication in Myanmar is hampered by under-investment in public health combined with longstanding civil unrest, with remoteness and uncontrolled cross-border movements additional obstacles in Karen state.

With regard to the low sensitivity of danger signs for hospital referral, that the vast majority of patients recorded as exhibiting one or more of these had good outcomes indicates that health workers may have overcalled these in many cases, especially the more subjective observed ones. More robust training in identification of the severely ill patient is, thus, necessary.

Two other findings require further elaboration. The first is that the very low antibiotic prescription rates at Thai PHCs can be attributed to the success of the wide-ranging, multifaceted 'Antibiotics Smart Use' programme which has been in place since 2007.¹³⁷ This programme comprises a suite of interventions to promote antimicrobial stewardship at every

level of the health system, including PHCs; in the first year of the programme alone, antibiotic prescriptions at PHCs declined between 39% and 46%.¹³⁸ One factor contributing to this success at the rural PHC level is the forging of strong partnerships with health volunteers, local administrators, and village leaders who then advocate for better antimicrobial use in their communities.¹³⁷ Furthermore, since the programme includes strengthening clinical diagnostic capacity, patients diagnosed with infections requiring treatment with antibiotics outside the limited range stocked by PHCs can be directed elsewhere instead rather than receive inappropriate empirical treatment.

The second is that the high percentage of Cambodian patients with unresolved symptoms is likely a gross over-estimate because the clinical significance of the unresolved symptoms was not established and patients at this site may have a greater propensity to report the presence of any lingering symptom. For example, therefore, given nearly half of these patients had URTI, it is possible that post-infective cough or fatigue may have featured prominently as reported unresolved symptoms. Additionally, relatively very few in this sub-group had severe illness at presentation, as indicated by the presence of danger signs. The probability of disability caused by severe illness and manifesting as unresolved symptoms would, therefore, likely be small.

Finally, discussion of the impact of the COVID-19 pandemic on the results of this study is warranted. As the providers that participated constitute the backbone of primary care provision in the study settings, it is quite likely that patients with COVID-19 were among those enrolled. This is supported by the majority of enrolled patients having a diagnosis of URTI although, as explained previously, testing for the causative coronavirus was not done for ethical reasons, hence the proportion attributable to COVID-19 was not able to be quantified. Whether the pandemic may have caused changes to circulating respiratory viruses in the study settings is also not known since the study did not set out to establish aetiology beyond that possible

through assays on the dried blood spots collected, which do not include respiratory viruses. In any case, there is little to no baseline surveillance data from these relatively inaccessible sites to enable comparison.

It is also worthwhile mentioning that unless there was a specific plan in place at individual PHCs to have a separate workstream for patients presenting with respiratory symptoms for infection control reasons, who would then not be enrolled, all patients presenting to PHCs who met the inclusion criteria were eligible for recruitment. It was not known how many PHCs instituted such measures and when, given the dynamic state of affairs and restrictions on travel to study sites until 2022. This, along with informal screening likely having happened in many of the sites as discussed in the next section, means that the numbers of patients presenting with fever may have been overestimated and some who met inclusion criteria but were seen as part of a separate acute respiratory illness workflow may not have been enrolled. As the study did not aim to assess health-seeking behaviour, it was also not possible to evaluate the effects of the COVID-19 pandemic on this.

4.4.3 Strengths and weaknesses

A key strength of this study is the large-scale consecutive enrolment of patients from providers representative of the principal settings where rural primary care is delivered in the study sites, which in themselves represent key countries in the South and Southeast Asian region with high potential to improve rural primary care. Additionally, to ensure that seasonal variation in clinical syndromes was adequately captured, patients were recruited for at least 12 months at each site. Over 88% of participants were followed up, mitigating selection bias from loss to follow-up; furthermore, survival status was ascertained for 18.8% of those lost to follow-up.

A further strength is the focus on syndromes as previously described, thus ensuring the clinical and health policy relevance of the results while avoiding the cost and logistical issues

associated with collection, storage, and transportation of biological samples other than DBS from remote areas, as these are more stable than other sample types such as nasopharyngeal swabs and venous blood.¹³⁹ This approach was supported by the lessons learnt from previous rigorous studies of AFI worldwide which showed that the yield of laboratory aetiological investigations was generally low, often not exceeding 50%.^{16, 48, 140} Collecting data on clinical management and patient outcomes in addition to epidemiological data also provides further solid evidence to assist the design of interventions to improve practice. Additionally, data collection was performed in real time using a mobile app with inbuilt logic to maximise data quality, a novel approach which demonstrates the feasibility of electronic data collection and potential digital health interventions in low-resource settings.

Given the observational nature of the study, its chief weakness is selection bias stemming from several sources e.g., patients who are more unwell are likely to have bypassed study facilities and gone straight to hospital or private sector facilities as indicated by the results of the village profiling study reported in Chapter 3, artificially lowering the frequency of adverse outcomes. In addition, some patients meeting eligibility criteria may not have been recruited if healthcare workers were busy, and withholding of consent was not inconsiderable at some sites. Furthermore, it is likely that informal or undocumented screening occurred, the degree of which is not uniform across sites. This is because busy healthcare workers may not be particularly motivated to enter in information for someone whom they know will not be enrolled. It was also not possible to ensure that healthcare workers took sufficient care at all times to obtain symptom and vital sign data, thus misclassification in terms of clinical syndromes may also have occurred. Finally, while the findings provide a clear epidemiological overview of AFI in rural areas of this region, sufficiently detailed data on health-seeking behaviour for AFI was not collected as has been done elsewhere,^{39, 141} precluding accurate estimation of incidence rates. Nevertheless, the frequencies of the reported syndromes are likely reflective of their relative

incidences, since patients were recruited from the main types of primary care providers at each site.

4.4.4 Areas for future research

Work is currently underway to perform wide-ranging aetiological investigations on a representative sample of the DBS collected from enrolled patients in an attempt to attribute causative organisms to syndromes. This will add a further layer of completeness to the epidemiological picture painted by this study, notwithstanding the predominance of URTI and the limitations imposed by performing microbiological analyses on DBS. Further epidemiological studies should focus on patient groups under-represented in this study, such as pregnant women and neonates, and include hospital outpatient departments to capture primary care presentations in more severely ill patients.

Aside from this, the most obvious and urgent focus for future work is the trialling and evaluation of interventions to improve AFI management by VHWs/VMWs and PHCs, which could include adapting tools to aid clinical decision-making currently used in other settings, and developing novel interventions such as point-of-care diagnostics and electronic clinical decision support algorithms. These should prioritise diagnosis formulation, antimicrobial stewardship, and identification of the severely ill patient as key objectives, since these are the aspects of clinical management shown in this study to be sub-optimal. Such efforts will help maintain trust in VHWs/VMWs and PHCs,¹⁸ combat antimicrobial resistance,¹⁴² and optimise stretched secondary care resources, respectively, and should include work to understand healthcare worker behaviours, which will smoothen the change management process when new interventions are rolled out.¹⁴³ One such electronic clinical decision support algorithm, designed to run as an app on mobile devices, has been developed based on the findings reported in this chapter as part of the work for this thesis, and is currently being evaluated through a cluster-

randomised trial in 30 Cambodian PHCs. A description of the algorithm development process and trial protocol can be found in Chapter 7.

In parallel, patient beliefs and expectations should also be investigated more fully, for example studying health-seeking behaviours to understand why care is preferentially sought from certain types of facilities or providers over others for AFI and factors influencing compliance with hospital referral decisions. It will also be crucial to define patient understanding of antibiotics and their expectations of healthcare workers with regard to antibiotic prescribing, as well as explore ways to involve pharmacies and drug stores in antimicrobial stewardship.

Surveillance should be another theme of future research since this region is the cradle of emerging infectious diseases,¹⁴⁴ especially respiratory infections which, as shown in this chapter, make up the bulk of primary care presentations for AFI. Countries adjacent to Myanmar must also be vigilant against chloroquine-resistant malaria,¹⁴⁵ which may threaten the success of malaria control programmes in South and Southeast Asia if it crosses the porous borders Myanmar shares with its neighbours.

4.5 Conclusions

In the VHW/VMW and PHC settings which are the mainstay of primary care provision in rural South and Southeast Asia, patients with AFI do not generally present with severe illness and have good clinical outcomes. However, there is much scope to improve the diagnostic and clinical decision-making capacity of rural primary healthcare providers working at the peripheries of often weak health systems. Opportunities, therefore, abound for interventions to improve primary care management of AFI, some well-established in other contexts and others novel. However, before any of these interventions can be rolled out at scale, they must be thoroughly evaluated from a multi-disciplinary perspective, including through clinical and cost effectiveness

lenses. Evaluations of three potential interventions form the remainder of this thesis, building upon the findings of this chapter.

CHAPTER 5 | EVALUATION OF PULSE OXIMETRY IN THE PRIMARY CARE MANAGEMENT OF ACUTE FEBRILE ILLNESS

This chapter draws upon work published in:

1. **Chew R**, Zhang M, Chandna A, Lubell Y. The impact of pulse oximetry on diagnosis, management and outcomes of acute febrile illness in low-income and middle-income countries: a systematic review. *BMJ Glob Health*. 2021;6(11):e007282.
2. **Chew R**, Greer RC, Tasak N, Day NPJ, Lubell Y. Modelling the cost-effectiveness of pulse oximetry in primary care management of acute respiratory infection in rural northern Thailand. *Trop Med Int Health*. 2022;27(10):881-890.

5.1 Introduction

As shown by the findings of the observational study reported in the preceding chapter, acute respiratory infection (ARI), in particular upper respiratory tract infection (URTI), is the commonest presenting syndrome in patients with acute febrile illness (AFI) in rural South and Southeast Asia. In patients with ARI, hypoxaemia is a predictor of severe disease,¹⁴⁶ but is poorly detected by clinical examination.¹⁴⁷ Pulse oximetry is the optimal method of detecting hypoxaemia by measuring peripheral oxygen saturation (SpO₂) and is commonly used in high-income countries (HICs) for this purpose in all age groups, leading to SpO₂ being dubbed the ‘fifth vital sign’.^{148, 149} As part of its Integrated Management of Childhood Illness (IMCI) strategy in low-income and middle-income countries (LMICs), the World Health Organization (WHO) currently recommends the use of pulse oximetry to determine the presence of hypoxaemia and guide administration of oxygen therapy in children <5 years.^{150, 151}

Despite this, pulse oximetry is not widely adopted as part of the clinical assessment of patients with ARI in LMICs, including those in South and Southeast Asia, in contrast to HICs.¹⁵² While cost and training impositions are major reasons for this, there are numerous others, such as weaknesses in policy and leadership, poor change management strategies targeted at generally overworked and under-resourced workforces, and difficulty accessing repairs or replacements for malfunctioning devices.^{153, 154} Pulse oximetry is especially rarely used in LMIC primary care settings which, as described in Chapter 2 ('Background'), are the mainstay of healthcare delivery in areas where access to healthcare is limited and skilled staff are scarce. This skill shortage indicates a gap that could be filled by pulse oximetry functioning as a clinical decision support aid to optimise patient management, which may yield potential benefits such as reducing inappropriate antibiotic prescribing for URTIs that are almost always viral and do not require antimicrobial therapy.^{132, 155}

Two further important points bear mentioning. Firstly, acute fever is a common feature of sepsis, but fever is a non-specific sign present in both severe and mild illness.¹⁵⁶ Secondly, hypoxaemia is increasingly recognised as a clinical feature of sepsis due to non-respiratory infections such as malaria,¹⁵⁷⁻¹⁵⁹ and it is common for patients to have overlapping clinical signs and symptoms of ARI and non-respiratory infections concurrently.¹⁶⁰ Therefore, incorporation of SpO₂ measurement into guidelines based principally on clinical examination, such as the WHO IMCI algorithms, may further assist healthcare workers in low-resource settings identify severely ill patients and formulate management plans with a greater degree of confidence and accuracy.

Efforts are underway to increase access to pulse oximetry in LMICs, aided partly by the availability of durable low-cost oximeters and galvanised by the WHO recommendation to use them in hospitals and primary health centres,¹⁵¹ with the COroNaVirus Disease of 2019 (COVID-19) pandemic providing extra impetus. However, there is little high-quality evidence of their utility in these settings,¹⁶¹ with even the WHO acknowledging this in spite of their support for increased uptake of pulse oximetry.^{150, 151} It is important to note that the contexts in which health

services are provided in LMICs differ considerably from those in HICs, for instance in terms of staff-to-patient ratios, staff levels of training, and health facility infrastructure. In the better-resourced health systems of HICs the potential benefits of an intervention will often be more fully realised than in LMICs where sub-optimal contextual aspects might diminish effectiveness or even feasibility. Therefore, the benefits of pulse oximetry, especially in refining diagnosis and treatment,^{162, 163} seen in HICs may not be fully generalizable to LMICs, given the absence of some or all the necessary mediators, such as reliable supplemental oxygen and trained staff, in the latter.

The WHO recommendations are approximately a decade old. As such, a two-pronged approach of a methodologically sound examination of the contemporary evidence regarding the utility of pulse oximetry in the management of AFI and associated syndromes such as ARI, along with the generation of new evidence, is highly necessary to address this important issue. Such research is the focus of this chapter, at the end of which conclusions relevant to rural South and Southeast Asian primary care will be drawn, in line with the theme of this thesis.

5.2 Systematic review of the evidence

To begin, an assessment of available evidence regarding the impact of pulse oximetry on diagnosis, clinical management, and outcomes of patients with AFI in LMICs was conducted in the form of a systematic review. The review was not limited to primary care settings or to South and Southeast Asia, since valuable lessons may be learnt from experiences in other contexts.

5.2.1 Methods

5.2.1.1 Protocol and registration

This systematic review was performed according to a pre-specified protocol, which was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number CRD42021257241).¹⁶⁴ The results are reported here in

accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines.¹⁶⁵ The completed PRISMA 2020 checklist can be found in Appendix 5.1.

5.2.1.2 Eligibility criteria

Observational and interventional studies conducted in LMICs designed with one group where pulse oximetry was used and at least one comparator group where pulse oximetry was not used were eligible for inclusion. The target population was adults, children, and neonates presenting with acute febrile illness, or syndromes associated with AFI such as pneumonia or malaria, to a healthcare worker or facility of any type or level. Modelling studies, studies in which the participants were patients undergoing peri-operative care, or studies in which pulse oximetry was used for asymptomatic screening were excluded. The outcomes of interest were diagnosis, management (including, but not limited to, further investigation, treatment, and onward referral), and patient outcomes (including, but not limited to, morbidity and mortality) of AFI or a clinical syndrome associated with AFI such as, but not limited to, pneumonia, malaria, or urinary tract infection.

5.2.1.3 Search strategy

The following databases were searched on 29 June 2021 with no restriction on language or date of publication: PubMed, Excerpta Medica dataBASE (EMBASE), Commonwealth Agricultural Bureaux International (CABI) Global Health, Global Index Medicus, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science. The search strings used for each of these databases are shown in Table 5.1. The websites of the WHO, the International Committee of the Red Cross, and Médecins Sans Frontières were also searched to identify relevant grey literature.

To ensure that the list of included studies was as comprehensive as possible, the reference lists of any relevant systematic reviews returned from the above searches, as well as

the Database of Abstracts of Reviews of Effects (DARE) were searched to identify further studies. In addition, backward and forward snowballing using the Google Scholar citation tracking facility was applied to included studies, and publication lists of first and last authors of included studies as per Google Scholar were also scrutinised. Finally, a Technical Advisory Panel who peer-reviewed this search strategy was assembled, the members of which are listed in Appendix 5.2. Advisors were also asked to identify obvious omissions in the list of included articles, suggest additional authors whose publication lists were examined, and suggest key practitioners who were approached for further studies, including grey literature. These key practitioners are listed in Appendix 5.3.

PubMed

"Oximetry"[MeSH] OR "pulse oximet*"[Title/Abstract]

AND

"fever"[MeSH] OR fever[Title/Abstract] OR febrile[Title/Abstract] OR pyrexia[Title/Abstract] OR "communicable diseases"[MeSH] OR "sepsis"[MeSH] OR "systemic inflammatory response syndrome"[MeSH] OR "pneumonia"[MeSH] OR "systemic inflammatory response syndrome"[Title/Abstract] OR SIRS[Title/Abstract] OR septic[Title/Abstract] OR infect*[Title/Abstract] OR respiratory[Title/Abstract] OR pneumonia[Title/Abstract]

AND

"Developing Countries"[MeSH] OR "Asia"[MeSH] OR "Africa"[MeSH] OR "Latin America"[MeSH] OR "South America" [MeSH] OR Asia[Title/Abstract] OR Africa[Title/Abstract] OR "South America"[Title/Abstract] OR "Latin America"[Title/Abstract] OR "Oceania"[Title/Abstract] OR "Australasia"[Title/Abstract] OR "Pacific"[Title/Abstract] OR "low income"[Title/Abstract] OR "middle income"[Title/Abstract] OR "low and middle income" OR "developing countr*"[Title/Abstract] OR "low resource"[Title/Abstract] OR "resource limited"[Title/Abstract]

CABI Global Health

pulse oximetry.mp.

AND

(sepsis or septic or fever or pyrexia or febrile or pneumonia or infectio* or SIRS or systemic inflammatory response syndrome or respiratory).mp.

Global Index Medicus

(mh:(oximetry)) OR (tw:("pulse oximet*"))

AND

(mh:(fever)) OR (mh:(sepsis)) OR (mh:(pneumonia)) OR (mh:("communicable diseases")) OR (mh:("systemic inflammatory response syndrome")) OR (tw:(fever)) OR (tw:(pyrexia)) OR (tw:(febrile))

OR (tw:("systemic inflammatory response syndrome")) OR (tw:(SIRS)) OR (tw:(septic)) OR (tw:(infect*)) OR (tw:(respiratory)) OR (tw:(pneumonia))

DARE

Pulse oximet* [All fields]

CINAHL

MM pulse oximetry OR MM pulse oximeter OR AB pulse oximet*

AND

MM sepsis OR MM fever OR MM pyrexia OR MM pneumonia OR MM systemic inflammatory response syndrome OR MM infectious disease OR MM infection OR AB (sepsis or septic) OR AB infect* OR AB pneumonia OR AB (fever or febrile or pyrexia) OR AB (sirs or systemic inflammatory response syndrome) OR AB respiratory

AND

MM Imic or low income countries or middle income countries or developing countries OR AB asia OR AB africa OR AB (south america or latin america or central america) OR AB pacific OR AB oceania OR AB australasia OR AB low resource

EMBASE

Exp pulse oximetry/ or "pulse oximet*".mp.

AND

fever.mp. or exp fever/ or pyrexia.mp. or sepsis.mp. or exp sepsis/ or pneumonia.mp. or exp pneumonia/ or respiratory.mp. or exp systemic inflammatory response syndrome/ or exp infection/ or infection.mp.

AND

Exp middle income country/ or exp developing country/ or Imic.mp. or asia.mp. or exp Asia/ or exp Africa/ or africa.mp. or latin america.mp. or exp "South and Central America"/ or oceania.mp. or exp Pacific islands/ or australasia.mp.

CENTRAL
#1: MeSH descriptor: [oximetry] explode all trees
#2: MeSH descriptor: [fever] explode all trees
#3: MeSH descriptor: [pyrexia] explode all trees
#4: MeSH descriptor: [sepsis] explode all trees
#5: MeSH descriptor: [pneumonia] explode all trees
#6: MeSH descriptor: [communicable diseases] explode all trees
#7: MeSH descriptor: [systemic inflammatory response syndrome] explode all trees
#8: (fever OR febrile OR pyrexia OR "systemic inflammatory response syndrome" OR SIRS OR septic OR infect* OR respiratory OR pneumonia):ti,ab,kw
#9: #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10: #1 AND #9

Table 5.1. Search strings used to retrieve articles from online databases for screening. CABI, Commonwealth Agricultural Bureaux International; CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; DARE, Database of Abstracts of Reviews of Effects; EMBASE, Excerpta Medica dataBASE. All databases were last accessed on 29 June 2021.

5.2.1.4 Study selection

The titles and abstracts of the studies returned by database, website, snowball, and hand searches, as well as recommendations arising from Technical Advisory Panel input, were independently screened by two reviewers, applying the aforementioned inclusion and exclusion criteria. If there was ambiguity about whether a study should be included from the title and abstract alone, the full text of the study was obtained for further assessment. Full texts of all studies identified through title and abstract screening were read to produce a final list of included studies and reasons for rejection recorded. The list of studies rejected at this stage and reasons for rejection can be found in Appendix 5.4. Disagreement between reviewers was resolved by discussion in the first instance. A third reviewer, whose decision was final, was asked to adjudicate if required.

5.2.1.5 Data extraction

Relevant data from each included study was extracted independently by one reviewer into a Microsoft Excel spreadsheet based on the fields in the Cochrane data collection form for intervention reviews for RCTs and non-RCTs.¹⁶⁶ The accuracy of the extracted data for each study was checked by a second reviewer, and any discrepancies resolved by discussion. The data extraction template can be found in Appendix 5.5.

5.2.1.6 Data analysis and synthesis of results

Meta-analysis of data to produce pooled odds and risk ratios was precluded by the small number and heterogeneity of included studies, as well as the paucity of randomised studies.¹⁶⁷ Pertinent data from each study were, therefore, tabulated and a narrative synthesis to draw conclusions performed, taking into consideration differences in study design and setting.

5.2.1.7 Quality assessment

The Cochrane Risk of Bias 2 tool for Cluster Randomised Trials (RoB 2 CRT) was used to assess risk of bias for cluster-randomised trials,¹⁶⁸ and the Cochrane Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) tool was used to assess risk of bias for non-randomised studies.¹⁶⁹ No individually-randomised trials were among the included studies but, had there been, the Cochrane Risk of Bias 2 tool would have been used to assess risk of bias in such studies.¹⁷⁰ Each study was independently assessed by two reviewers, with disagreements resolved through discussion in the first instance. A third reviewer, whose decision was final, was asked to adjudicate if required. Risk of bias for cluster-randomised trials was categorised as either ‘low’, ‘some concerns’, or ‘high’ as per RoB 2 CRT, while risk of bias for non-randomised studies was categorised as either ‘low’, ‘moderate’, ‘serious’, or ‘critical’ as per ROBINS-I.

5.2.2 Results

A total of 4,898 studies were considered for inclusion. Ten were ultimately selected, as per the PRISMA flow diagram in Figure 5.1. All selected studies enrolled children aged <15 years. Six studies included, but not exclusively, patients <2 months old;¹⁷¹⁻¹⁷⁶ another enrolled only those in this age group.¹⁷⁷ Seven studies included patients aged 2 months to ≤5 years,^{171-176, 178-180} and only two included children >5 years and adolescents.^{174, 176} Only two studies were randomised trials,^{174, 179} and only two, including one of these randomised trials, evaluated the use of pulse oximetry in non-respiratory infections;^{171, 174} the clinical syndrome of interest in the remainder was community-acquired pneumonia or acute lower respiratory tract infection (ALRI).¹⁷²⁻¹⁸⁰ In three studies pulse oximetry was used as part of a set of interventions, all of which included varying improvements to oxygen provision.^{173, 174, 176}

Three studies were conducted in Papua New Guinea,^{172, 173, 176} one in Peru,¹⁷⁸ and six in sub-Saharan Africa.^{171, 175, 177, 179, 180} Five studies were conducted in rural primary care settings,^{171, 175, 177, 179, 180} three in rural hospitals,^{172, 173, 176} and two in urban hospitals.^{174, 178} All

studies used $p < 0.05$ as the threshold for statistical significance, except for Madico et al. where statistical significance was not assessed.¹⁷⁸

5.2.2.1 Quality of included studies

The risk of bias assessment for each study is shown in Figure 5.2(a) (for cluster-randomised trials) and Figure 5.2(b) (for non-randomised studies), which were produced using the *robvis* tool.¹⁸¹ With four exceptions,^{174, 177-179} all studies were at serious risk of bias. Four of the eight non-randomised studies were at serious risk of bias due to confounding solely or in combination with other domains,^{171-173, 175} while one was at serious risk of bias due to missing data,¹⁷⁵ and another due to selection bias.¹⁸⁰ The risk of bias of both cluster-randomised trials was moderate.^{174, 179}

Notably, two studies did not supply appropriately-sized probes and reported considerable staff difficulty using pulse oximeters.^{177, 180} This contributed to inaccurate or non-recording of SpO₂.

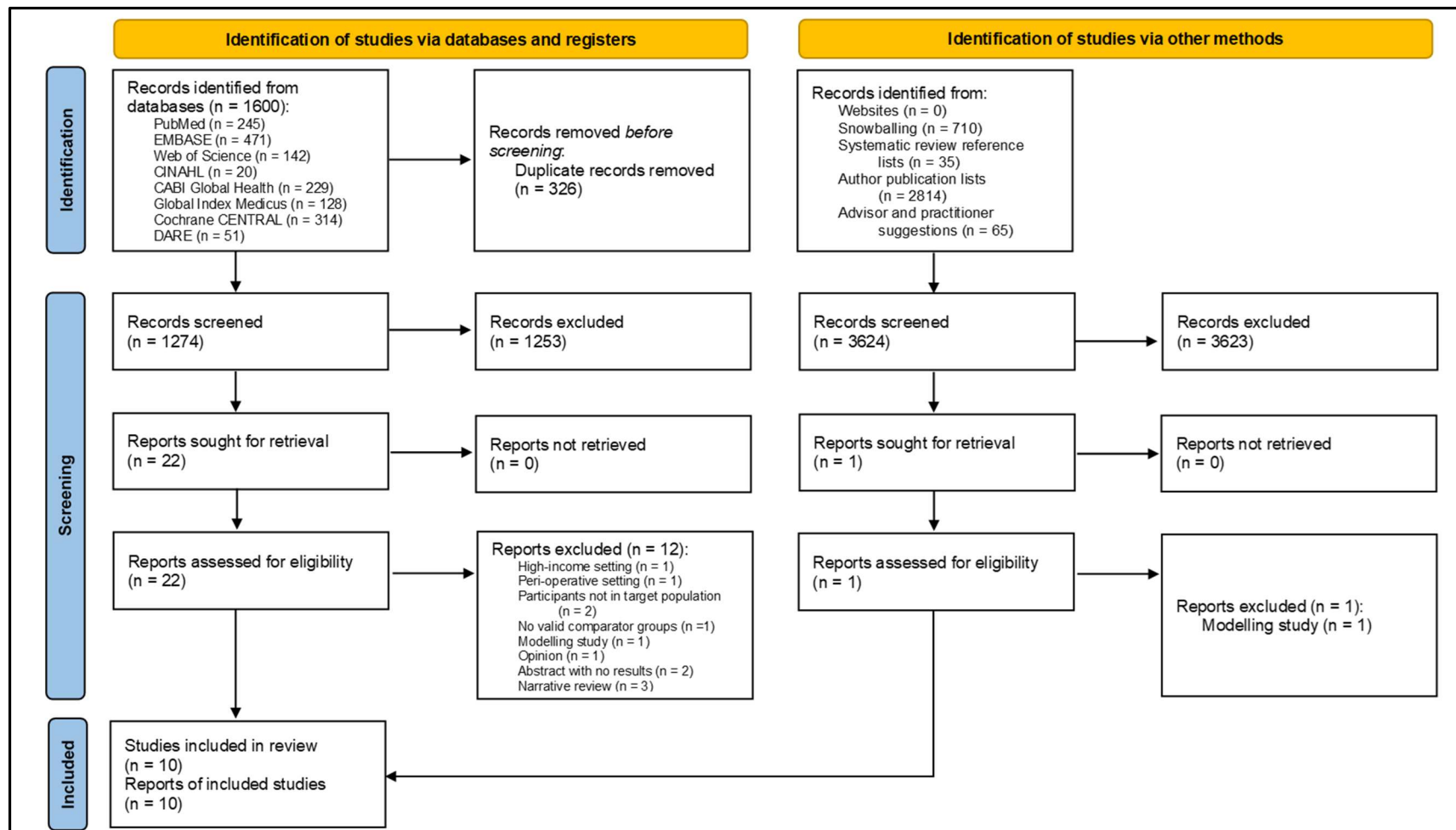


Figure 5.1. Systematic review Preferred Reporting Items for Systematic Review and Meta-Analysis 2020 (PRISMA 2020) flow diagram. A distinction is made between ‘studies included in review’ and ‘reports of included studies’ because during the review process it may not have been possible to retrieve reports for all studies.

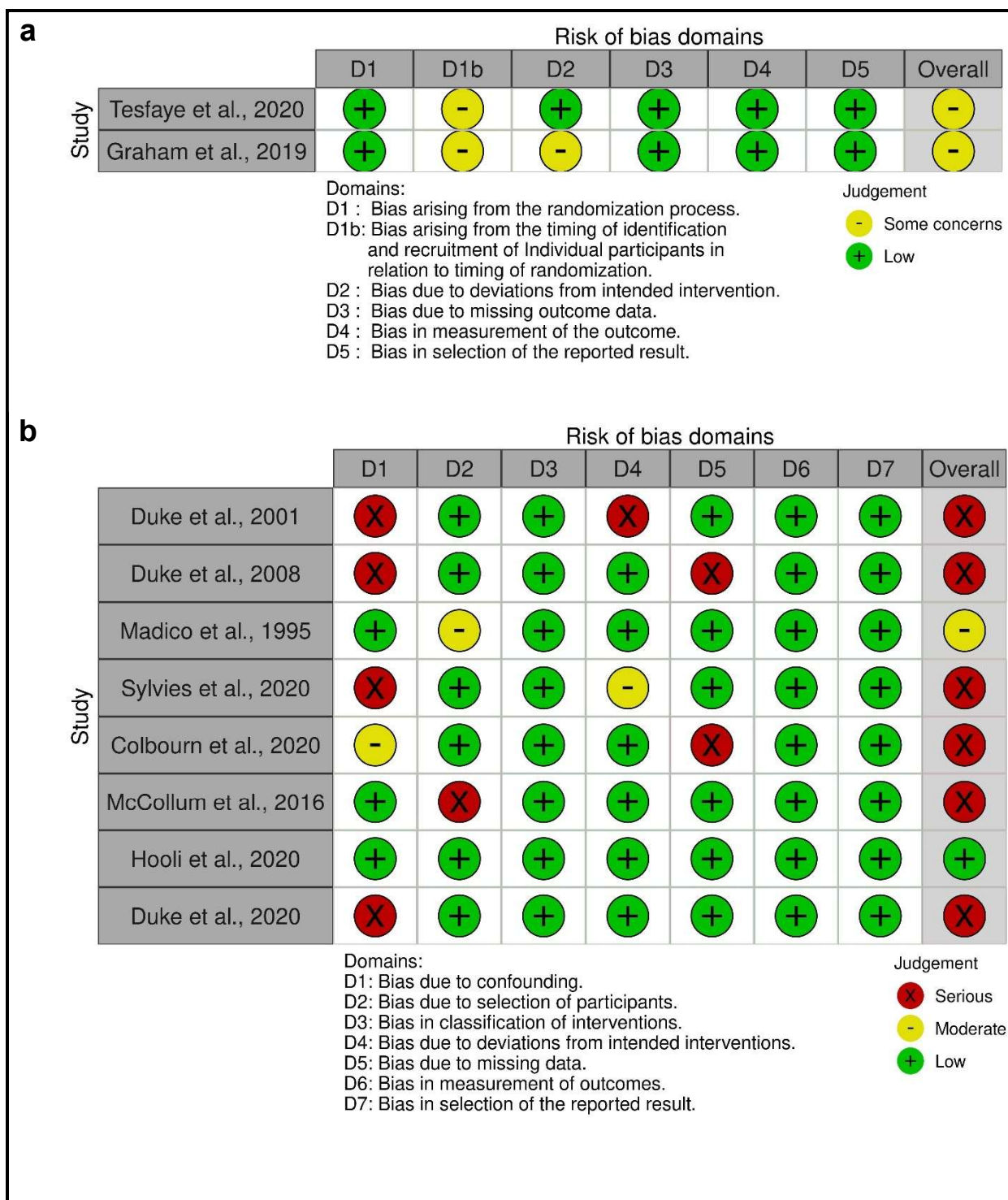


Figure 5.2. Risk of bias assessments of (a) included cluster-randomised trials, performed using the Cochrane Risk of Bias 2 tool for cluster-randomised trials (RoB 2 CRT) and (b) included non-randomised studies, performed using the Cochrane Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) tool.

5.2.2.2 Impact of pulse oximetry on diagnosis

Two studies assessed the diagnostic impact of pulse oximetry, the principal findings of which are described below and their characteristics in Table 5.2. The strength of the evidence presented in this section is moderate.

In a small single-hospital prospective cohort study, Madico et al. found that the yield of pulse oximetry alone for the diagnosis of acute lower respiratory tract infection in children aged 2-60 months presenting to a Peruvian urban paediatric emergency department was comparable with that of the 1990 WHO diagnostic guideline at approximately 80%,¹⁸² using third-party independent clinical diagnosis as a proxy reference standard. The third-party independent clinical diagnosis was made without pulse oximetry. When both pulse oximetry and guideline were used together, near-perfect (94%) concordance with clinical diagnosis was achieved.¹⁷⁸

The diagnostic utility of pulse oximetry in a rural primary care setting was also demonstrated by Tesfaye et al., who conducted a cluster-randomised trial in 24 primary health centres in Ethiopia. There was a significant five-fold increase in the adjusted odds of diagnosing severe pneumonia in similarly-aged symptomatic children when pulse oximetry with cut-off SpO₂ <90% was used in conjunction with the 2014 WHO IMCI guideline, compared with guideline alone [adjusted odds ratio (aOR) 5.4, 95% confidence interval (CI) 2.0–14.3].¹⁷⁹

Study	Study design	Syndrome	Intervention and comparison groups	Outcome measure	Participants	Age range	Setting	Country (continent)	Reported effect
Madico, 1995 ¹⁷⁸	Prospective cohort study	ALRI	PO vs. WHO algorithm ¹⁸² vs. PO + WHO algorithm vs. Clinical diagnosis*	Independent third-party clinical diagnosis of ALRI made without pulse oximetry	269 children with ARI	2-60 months	Single urban hospital paediatric emergency department	Peru (South America)	125/160 (78.1%) diagnosed in PO group vs. 130/160 (81.3%) in WHO algorithm group vs. 150/160 (93.8%) in PO + WHO algorithm group
Tesfaye, 2020 ¹⁷⁹	Parallel cluster-randomised trial	Pneumonia	PO + IMCI vs. IMCI ^{116§}	Clinical diagnosis of severe pneumonia	1804 children with cough or difficulty breathing <14 days	2-59 months	24 rural primary health centres	Ethiopia (Africa)	148/928 (15.9%; 95% CI 4.7-27.2%) diagnosed in PO + IMCI group vs. 34/876 (3.9%; 95% CI 1.2-6.6%) in IMCI group, p<0.001 Adjusted OR 5.4 (95% CI 2.0–14.3), p=0.001

Table 5.2. Impact of pulse oximetry on diagnosis of acute febrile illness or associated syndromes. ALRI, acute lower respiratory tract infection (pneumonic and non-pneumonic); ARI, acute respiratory infection; IMCI, World Health Organization Integrated Management of Childhood Illness guideline 2014; OR, odds ratio; PO, pulse oximetry; 95% CI, 95% confidence interval. Hypoxaemia was defined as peripheral oxygen saturation (SpO₂) <90% unless indicated otherwise.

*Hypoxaemia defined as SpO₂ <96.6%. §Intervention group included a staff training component on the use of pulse oximetry.

5.2.2.3 Impact of pulse oximetry on clinical management

Four studies assessed the impact of pulse oximetry on clinical management (Table 5.3). The strength of the evidence presented in this section is low-moderate.

Three of these studies examined the effect of pulse oximetry in addition to various contemporaneous clinical guidelines on referral to hospital from primary care for severe pneumonia. All were conducted in sub-Saharan Africa and demonstrated increased referral rates in older children when pulse oximetry was used.^{177, 179, 180} However, compliance with referral decisions was inconsistent.^{179, 180}

In keeping with their finding of significantly increased odds of diagnosing severe pneumonia with the combined use of pulse oximetry and 2014 IMCI guideline, Tesfaye et al. also reported that the proportion of children referred to hospital for severe pneumonia in the intervention group was nearly twice that in the comparator group. Importantly, only approximately half the children referred in the intervention group and three-quarters of those in the comparator group actually presented to hospital.¹⁷⁹

In a rural Malawian primary care setting comparable to that in Ethiopia where the study by Tesfaye was conducted, McCollum et al. also showed that pulse oximetry had the potential to reduce missed referrals to hospital in a large cohort of similarly-aged children with pneumonia. Between 5 and 42% of children with severe disease would not have been deemed eligible for referral in the absence of pulse oximetry, depending on the sensitivity of the guideline used and whether the children were seen at health centres or mobile village clinics. The SpO₂ cut-off was <90%; had the cut-off been <93% to include children with moderate hypoxaemia, the percentage of missed eligible referrals would have been in the range 20 to 62%. However, like in the study by Tesfaye et al., even with pulse oximetry only 48% of patients eligible for referral were actually referred, indicating that factors other than clinical assessment play a role in clinician and caregiver decision-making.¹⁸⁰

Hooli et al. applied the same methodology and SpO₂ cut-off of <90% as McCollum et al. to 261 neonates and infants <2 months in the same Malawian settings, and found that both national and IMCI guidelines missed less than 1% of cases who should have been referred in the absence of pulse oximetry.^{116, 183} When the cut-off was increased to <93%, the national Malawian guideline missed just under 2% whilst the WHO IMCI guideline missed approximately 1%.¹⁷⁷

Lastly, Sylvies et al. conducted an uncontrolled before-and-after study comparing antibiotic prescription rates for non-malarial febrile illness in children <5 years in five Malawian mobile rural health clinics. Pulse oximetry used together with the IMCI guideline was compared with three comparators: IMCI guideline, 2016 national guideline, and 2019 national guideline. Antibiotic prescription rates were reduced by approximately half in the pulse oximetry plus IMCI group compared to the others. When compared to IMCI alone, the addition of pulse oximetry increased the odds of reducing antibiotic prescription over seven-fold, despite only 30% of children in the intervention group having had SpO₂ measured (odds ratio for reduced antibiotic prescription 7.3, 95% CI 4.8–11.4).¹⁷¹ However, it should be noted that this was not a randomised controlled trial.

Study	Study design	Syndrome	Intervention and comparison groups	Outcome measure	Participants	Age range	Setting	Country (continent)	Reported effect
McCollum, 2016 ¹⁸⁰	Retrospective secondary analysis of prospective cohort study data	Pneumonia	PO + IMCI vs. PO + Malawi guideline 2000 vs. IMCI ¹¹⁶ vs. Malawi guideline 2000 ^{183§}	Missed eligibility for referral to hospital	14092 children with pneumonia	2-59 months	18 rural health centres and 38 village clinics	Malawi (Africa)	At rural health centres, IMCI resulted in 390/938 (41.5%) missed eligible referrals and Malawi guideline 2000 in 143/1761 (8.1%) if PO not used At village clinics, both IMCI and Malawi guideline 2000 resulted in 52/990 (5.3%) missed eligible referrals if PO not used
Hooli, 2020 ¹⁷⁷	Retrospective secondary analysis of prospective cohort study data	Pneumonia	PO + IMCI vs. PO + Malawi guideline 2000 vs. IMCI ¹¹⁶ vs. Malawi guideline 2000 ^{183§}	Missed eligibility for referral to hospital	261 infants with cough and/or shortness of breath	<2 months	18 rural health centres	Malawi (Africa)	IMCI resulted in 1/238 (0.4%) missed referral if PO not used, and Malawi guideline 2000 1/236 (0.4%) If hypoxaemia was defined as SpO₂ <93%, IMCI resulted in 2/238 (0.8%) missed referral if PO not used, and Malawi guideline 2000 4/236 (1.7%)
Tesfaye, 2020 ¹⁷⁹	Parallel cluster randomised trial	Pneumonia	PO + IMCI vs. IMCI ^{116§}	Referral to hospital	1804 children with cough or difficulty breathing <14 days	2-59 months	24 rural primary health centres	Ethiopia (Africa)	116/148 (78.4%, 95% CI 67.6–89.2) referred in PO + IMCI group vs. 15/34 (44.1%, 95% CI 6.9–81.3) in IMCI group, p=0.496.

Sylvies, 2020 ¹⁷¹	Uncontrolled before-and-after study	Non-malarial fever	PO + IMCI vs. IMCI ¹¹⁶ vs. Malawi guideline 2019 vs. Malawi guideline 2016*§	Antibiotic prescription	3504 children with non-malarial fever	0-59 months	Five mobile rural health clinics	Malawi (Africa)	336/795 (42.2%) prescribed antibiotics in PO + IMCI group vs. 150/178 (84.2%) in IMCI group vs. 485/571 (84.9%) in Malawi guideline 2019 group vs. 1461/1960 (74.5%) in Malawi guideline 2016 group, p<0.001 OR for reduced antibiotic prescription in PO + IMCI group vs. IMCI group 7.3 (95% CI 4.8-11.4); vs. Malawi guideline 2019 group 7.9 (95% CI 6.1–10.5); vs. Malawi guideline 2016 group 4.0 (95% CI 3.3–4.7)

Table 5.3. Impact of pulse oximetry on management of acute febrile illness or associated syndromes. IMCI, World Health Organization Integrated Management of Childhood Illness guideline 2014; OR, odds ratio; PO, pulse oximetry; 95% CI, 95% confidence interval. All interventions incorporating pulse oximetry included a staff training component. Hypoxaemia was defined as peripheral oxygen saturation (SpO₂) <90% unless indicated otherwise. *Hypoxaemia defined as SpO₂ <95%.

§Intervention groups with pulse oximetry included a staff training component on the use of pulse oximetry.

5.2.2.4 Impact of pulse oximetry on patient outcomes

Six studies assessed the impact of pulse oximetry on patient outcomes (Table 5.4). The strength of the evidence presented in this section is low.

Five studies used mortality as their outcome measure, which was measured at different time points in the patient journey. Pulse oximetry was trialled as a component of intervention sets of varying sophistication across the different study settings.¹⁷²⁻¹⁷⁶ Effect sizes ranged from negligible to considerable, and appeared to be largely influenced by study context and setting as well as the level of system-wide support included in the intervention.

Duke and collaborators performed a series of uncontrolled before-and-after studies in various rural Papua New Guinean hospital settings, commencing with a study in a highland hospital comparing the use of pulse oximetry vs. clinical signs to guide supplemental oxygen administration in children <5 years with severe or very severe pneumonia. Hypoxaemia was defined as SpO₂ <85% due to the altitude of the hospital. Thirty-day mortality was reduced by 35% following the use of pulse oximetry, but this was not statistically significant [relative risk (RR) 0.65, 95% CI 0.41–1.02].¹⁷² Building on this finding, they conducted a much larger study involving similarly-aged children admitted with pneumonia of any severity to five dissimilar hospitals. Overall, pulse oximetry as a component of an improved oxygen system significantly reduced the in-hospital mortality rate by over a third compared with standard care (RR 0.65, 95% CI 0.52–0.78), but significant mortality rate reductions were seen in only two out of the five hospitals.¹⁷³ Their most recent study, conducted across 36 hospitals, also showed a significant 59% reduction in in-hospital pneumonia mortality in neonates and older children, with pulse oximetry being introduced as part of an oxygen system supported by continuous electricity supply and quality improvement processes compared with standard care (incidence rate ratio 0.41, 95% CI 0.24–0.71). Again, this improved outcome was seen in most, but not all, hospitals, with the variability related to facility baseline rates of pneumonia admissions, baseline quality of

clinical care, and sustainability of the intervention.¹⁷⁶ It is also important to note that the mortality reductions associated with the introduction of pulse oximetry were realised in the context of substantial improvements to the hard and soft infrastructure of the health facilities.

A stepped-wedge cluster randomised trial by Graham et al. in 12 urban Nigerian hospitals with a two-stage intervention comprising first of pulse oximetry, followed by its incorporation into an improved oxygen system similar to the one in the study by Duke et al. (2020),¹⁷⁶ was helpful in addressing the question of the contribution of pulse oximetry alone in reducing child and neonatal mortality. Augmentation of standard care with pulse oximetry significantly reduced in-hospital mortality from paediatric acute lower respiratory tract infection by 67% in a pre-specified subgroup analysis of 3,828 children aged between 28 days and 14 years (aOR 0.33, 95% CI 0.12–0.92). However, the improved oxygen system had no significant additional impact on this outcome (aOR 1.42, 95% CI 0.60–3.36). Neither pulse oximetry nor the improved oxygen system had any significant impact on the severity-adjusted odds of mortality from paediatric malaria, paediatric acute febrile encephalopathy, and neonatal sepsis.¹⁷⁴

Colbourn et al. undertook a prospective data linkage study assessing the potential impact of pulse oximetry on mortality from community-acquired pneumonia in children <5 years in a rural Malawian primary care setting. Supplementation of clinical sign-based guidelines with pulse oximetry would have identified an additional death (1/16, 6%) from mobile rural village clinics missed by guidelines alone but no additional deaths from rural health centres, further indicating a possible role for pulse oximetry in identifying children at high risk of deterioration in the community. Hypoxaemia was defined as SpO₂ <90%, but increasing the threshold to <93% did not identify any additional deaths at either mobile village clinic or rural health centre level. However, these results should be interpreted with caution as only 6% of mobile village clinic episodes and 11% of rural health centre episodes were linked to mortality data.¹⁷⁵

Finally, Tesfaye et al. examined the effect of pulse oximetry on treatment failure of severe pneumonia at 14 days, finding no significant difference between the intervention and

comparator groups (absolute difference -3.6%, 95% CI -17–10.7%). The authors state that this finding may be due to the substantial proportion of children in both groups who were referred to hospital but did not go, primarily due to lack of transport.¹⁷⁹

5.2.3 Discussion

5.2.3.1 Summary of main findings

This systematic review highlights the potential benefits of pulse oximetry in the assessment of acute febrile illness by healthcare staff of various skill levels working in diverse LMIC primary and secondary care settings, but also the paucity of high-quality studies addressing diagnostic, clinical management, and patient outcome endpoints. There is moderately strong evidence for the use of pulse oximetry to aid the diagnosis of pneumonia in children and referral to hospital of those with severe respiratory illnesses.^{178, 179} In contrast, there was an absence of studies examining its benefit in other syndromes associated with AFI, with only one study at serious risk of bias reporting a reduction in empirical antibiotic prescription.^{171, 174} Several studies, mainly in hospital settings, reported a mortality benefit, but all save one were compromised by confounding (in particular secular trends) or other biases,¹⁷⁴ indicating a disconnect between the certainty of evidence for a diagnostic and prognostic benefit of pulse oximetry. The generalisability of the included results beyond paediatric patients is poor, because no studies recruited adults and, although six studies enrolled patients <2 months, only one focused exclusively on neonates and very young infants.¹⁷⁷ Moreover, no studies were conducted in Asia where the burden of infectious diseases remains disproportionately high,¹⁸⁴ and where most recent emerging respiratory infections of public health importance have originated.^{185, 186} It is critical to note that the bulk of studies reporting beneficial effects of pulse oximetry used it as part of a bundle of linked interventions, underscoring the importance of a systems approach.

Study	Study design	Syndrome	Intervention and comparison groups	Outcome measure	Participants	Age range	Setting	Country (continent)	Reported effect
Duke, 2001 ¹⁷²	Uncontrolled before-and-after study	Community-acquired pneumonia	PO vs. clinical signs*	30-day mortality	961 children with severe or very severe pneumonia	>28 days and <5 years	Single rural hospital at high altitude	Papua New Guinea (Australasia)	Mortality rate in PO group 46/703 (6.5%) vs. 26/258 (10%) in clinical signs group RR 0.65 (95% CI 0.41–1.02, p=0.07)
Duke, 2008 ¹⁷³	Uncontrolled before-and-after study	Community-acquired pneumonia	PO + improved oxygen system vs. Standard care [§]	In-hospital mortality	11291 children with pneumonia	>1 month and <5 years	Five rural hospitals	Papua New Guinea (Australasia)	Mortality in intervention group 133/4130 (3.22%, 95% CI 2.7–3.8%) vs. 356/7161 (4.97%, 95% CI 4.5–5.5) in comparison group RR 0.65 (95% CI 0.52–0.78), p<0.0001
Graham, 2019 ¹⁷⁴	Stepped-wedge cluster RCT	ALRI, malaria, AFE, neonatal sepsis	PO + improved oxygen system vs. PO + standard care vs. Standard care [§]	Mortality (in-hospital or discharged expected to die)	3828 children with ALRI, 6113 children with AFE, 11092 children with malaria, and 7515 neonates with sepsis**	0 days to <15 years	Nine general and three paediatric/maternity urban hospitals	Nigeria (Africa)	ALRI: aOR for PO + standard care vs. Standard care 0.33 (95% CI 0.12–0.92), p=0.035; for PO + improved oxygen package vs. PO + standard care 1.42 (95% CI 0.60–3.36), p=0.427 Malaria, AFE, and neonatal sepsis: Neither PO + improved oxygen system nor PO +

									standard care significantly affected aORs for mortality from these conditions vs. standard care
Colbourn, 2020 ¹⁷⁵	Prospective data linkage study	Community-acquired pneumonia	PO + Malawi guideline 2000 vs. Malawi guideline 2000 ^{[183]§}	30-day mortality	13814 children with pneumonia	0-59 months	Mobile rural village clinics run by 38 community health workers and 18 rural health centres	Malawi (Africa)	PO would have identified 1/16 (6%) additional death at mobile rural village clinic level compared to Malawi guideline 2000 regardless of whether hypoxaemia was defined as SpO₂ <90% or <93% PO would not have identified any additional deaths at rural health centre level compared to Malawi guideline 2000 regardless of whether hypoxaemia was defined as SpO₂ <90% or <93%
Duke, 2020 ¹⁷⁶	Uncontrolled before-and-after study	Community-acquired pneumonia	PO + improved oxygen system + QI vs. Standard care [§]	In-hospital mortality	18933 neonates and children with pneumonia**	0-13 years	36 rural hospitals	Papua New Guinea (Australasia)	IR for deaths per 100 pneumonia admissions in intervention group 1.17 (95% CI 0.48-1.86) vs. 2.83 (95% CI 1.98-4.06) IRR 0.41 (95% CI 0.24-0.71, p<0.005)

Tesfaye, 2020 ¹⁷⁹	Parallel cluster RCT	Community-acquired pneumonia	PO + IMCI vs. IMCI ^{116§}	Treatment failure at 14 days***	1804 children with cough or difficulty breathing <14 days	2-59 months	24 rural primary health centres	Ethiopia (Africa)	132/928 (14.2%, 95% CI 6.0-22.4) failed treatment in the PO + IMCI group vs. 93/876 (10.6%, 95% CI 5.2–16.1) in the IMCI group, p=0.622

Table 5.4. Impact of pulse oximetry on outcomes of acute febrile illness or associated syndromes. AFE, acute febrile encephalopathy; ALRI, acute lower respiratory infection; aOR, adjusted odds ratio; IMCI, World Health Organization Integrated Management of Childhood Illness 2014; IR, incidence rate; IRR, incidence rate ratio; PO, pulse oximetry; QI, quality improvement; RR, risk ratio; 95% CI, 95% confidence interval. Hypoxaemia was defined as peripheral oxygen saturation (SpO₂) <90% unless indicated otherwise. *Hypoxaemia defined as SpO₂ <85%. **Pre-specified subgroup analysis. ***Defined as the development or persistence of general danger signs, persistence of fever, persistence of tachypnoea, chest wall indrawing, presence of persistent cough, recurrence of fever, withdrawal from the trial, or death. §Intervention groups with pulse oximetry included a staff training component.

5.2.3.2 Interpretation of main findings

Notwithstanding the weak nature of the evidence, several generalisable inferences relevant to clinical practice and health policy can be made. Firstly, given the likely value of pulse oximetry in identifying the severely ill febrile child,¹⁷⁹ its protocol-driven use in secondary care settings where oxygen is available may reduce morbidity and mortality in this cohort through targeting of oxygen and nursing resources.^{172-174, 176} However, any such resource re-allocation must not detract from the care of less ill patients whose capacity to benefit may be adversely affected, thus negating any potential overall benefit.

Secondly, while pulse oximetry may assist primary and other acute care clinicians in identifying and managing severe disease, uncovering the considerable hidden burden of severe pneumonia has implications for health service provision and hospital resourcing to avoid overstressing secondary healthcare facilities.¹⁷⁹ This is particularly relevant in settings where AFI is commonly attributed to other causes, such as malaria.¹⁸⁷ The current evidence shows that this is countered by the low uptake of hospital referral decisions, which is common in resource-limited settings but predisposes to excess morbidity and mortality. Therefore, pulse oximetry must be supplemented by efforts to increase the uptake of hospital referral recommendations or, alternatively, to increase the availability of oxygen, parenteral antibiotics, and close observation in rural health centres. Barriers to accessing higher-level care – not just infrastructural but also psychosocial, such as competing priorities and perceived staff incompetence – may erode the benefits of pulse oximetry in terms of patient outcomes, as was demonstrated by Tesfaye et al.¹⁷⁹ The observations relevant to these two conclusions strongly underline the importance of taking a system-wide view if pulse oximetry is to be implemented, especially in health systems which may not be robust.

Thirdly, customising pulse oximetry to the setting in which it is to be used is of utmost importance, since contextual factors directly impact on feasibility. For example, pulse oximetry

will play different roles in primary vs. higher level health facilities; in the former, it may aid gatekeeping by identifying those who can be managed in the community. However, in primary care settings the prevalence of hypoxaemia will be low, necessitating measures to minimise the risk of false positives. The resource limitations present in LMICs inevitably add a further layer of complexity to these considerations. Regardless, the utility of pulse oximetry is likely to be optimal in settings with a rigorous quality assurance programme and that actively invest in staff upskilling to ensure the sustainability of the intervention, especially in settings with low staff numbers per facility.^{173, 174, 176} Staff should be given appropriate and ongoing training not just in the mechanics of pulse oximetry but also in its use in syndromic diagnosis and clinical management, thus building patient and caregiver trust in their clinical decision-making;^{171, 174, 176, 177, 180, 188, 189} larger-scale benefits, such as better antibiotic stewardship may follow.¹⁷¹

Fourthly, pulse oximetry should not be rolled out in isolation if its full potential to improve the care of acutely febrile patients in LMICs is to be realised. Rather, it must be part of a systems approach incorporating reliable access to supplemental oxygen as well as strengthening of health infrastructure, sustainable provision of context-appropriate equipment and staff training, and continuous and comprehensive quality improvement. As such, pulse oximetry should not be seen as a simple but rather a complex intervention, with appropriate planning required to ensure all relevant components of the health system interact smoothly. Such efforts should be based on first principles of implementation science and findings from the wider evidence base, drawing on experiences of rolling out other complex interventions.^{190, 191}

5.2.3.3 Strengths and weaknesses

Whilst this review is the first to appraise pulse oximetry in the assessment of patients with AFI residing in resource-limited settings, it has several weaknesses. The greatest of these limitations is the heterogeneity in study design, interventions, and endpoints, which renders robust statistical comparison of effect sizes in the already small number of studies impossible.¹⁶⁷

Secondly, study quality was generally poor, and the populations and syndromes to which the findings are applicable limited. Thirdly, while the search strategy was constructed to be as comprehensive as possible, such as through making the primary focus of the review AFI rather than specific infective syndromes, snowballing, and reaching out to major global health practitioners for grey literature, it is possible that not all relevant studies were included. However, a systematic review of articles published up to 2015 examining the effect of pulse oximetry on paediatric mortality, morbidity, length of stay, and treatment and management changes in both HICs and LMICs identified only one study included in this review; the other four studies evaluated in the earlier review were not included as they were conducted in HICs.¹⁶¹ This fact, in addition to the larger number of databases searched, indicates a low probability of the search strategy missing important studies. Furthermore, framing this review around AFI has the advantage of identifying studies applicable to healthcare workers in LMICs who may have limited diagnostic skills but who are expected to manage patients presenting with this non-specific symptom. Finally, while systematic reviews like this one are useful in synthesising evidence from sources with diverse methodologies and contexts, critical features and procedural details of the intervention of interest are not able to be described at length. Along with the need to consider the broader evidence base, as mentioned earlier, this limitation necessitates approaches such as Intervention Component Analysis or similar frameworks when translating the evidence presented here into practice.¹⁹²

5.2.3.4 Areas for future research

This review has identified several key issues which future research on this topic must address to increase confidence in the above conclusions and make them more generalisable. The first is the determination of age- and altitude-appropriate SpO₂ thresholds below which escalation of care should be considered. This is particularly important in neonates and very young infants in whom moderate hypoxaemia has been shown to be associated with increased mortality,¹⁴⁶ but

for whom no recommendation exists in the IMCI guidance widely used in LMICs.¹¹⁶ Given the already low bar for escalation to higher level care in this patient group based on clinical assessment alone, lowering the oxygen saturation threshold for referral to <93% may not result in over-referral as much as it would for older children but the value added by pulse oximetry may also be reduced.¹⁷⁷ This is important from a cost-effectiveness viewpoint, as optimal peripheral oxygen saturation measurement in neonates and very young infants requires extra investment in the form of neonatal probes. A similar lacuna also exists for patients who reside at high altitude, as their usual peripheral oxygen saturations may fall below the widely accepted cut-off for severe hypoxaemia of 90%.^{193, 194} Related to these issues is the need to establish the accuracy of contemporary pulse oximeters in darker-skinned patients across a range of ages, disease states, and oxygen saturations, given the conflicting findings in the literature on this issue.¹⁹⁵⁻¹⁹⁷

The second is the development of algorithmic diagnostic and prognostic tools incorporating pulse oximetry in conjunction with other clinically-significant variables, tailored to the contexts and settings in which they will be used. This is essential to ensure safe clinical decision-making when the algorithms are used by health workers with limited skills, as well as to strike the necessary balance between early identification of the severely ill and maintaining the viability of often fragile secondary and higher-level care systems by avoiding over-referral.^{53, 198}

Thirdly, there is a pressing need for well-designed health systems and implementation research evaluating pulse oximetry as part of a suite of quality-assured system- or facility-wide interventions. Such efforts should attempt to bridge the gap between the diagnostic and prognostic roles of pulse oximetry in a contextualised manner by basing outcome measures on proposed use-cases and building on previous work on strategies to improve its institutional adoption.^{153, 198} This research should include adults, assess cost-effectiveness with robust

economic evaluation methods, and include Asia, as high-quality evidence for the use of pulse oximetry pertinent to this region is sorely lacking.

Fourthly, less common roles for pulse oximetry, such as its use as a trust-building and communication aid between healthcare workers and patients or caregivers with limited health literacy should be further explored.¹⁸⁸

5.2.3.5 Conclusions from this study

When used for the assessment of AFI in LMICs, pulse oximetry may assist clinicians in diagnosing and treating severe paediatric respiratory illnesses and making referrals to higher-level care. It may also reduce mortality from this condition if used as part of a holistic package of interventions which takes local context into account. The evidence upon which these conclusions are based is not widely generalisable and is of poor quality. Thus, health facilities or systems intending to implement pulse oximetry should also consider evidence from the wider implementation science literature, given the limitations of systematic reviews in synthesizing evidence on systems approaches to specific complex interventions.

5.3 Cost-effectiveness analysis of pulse oximetry in rural northern Thailand

The second part of this chapter builds on the conclusions above, as well as the areas for further research earlier described.

As it is uncertain whether supplementation of clinical assessment with pulse oximetry as a clinical decision support tool for the primary care management of ARI is cost-effective, a modelling study was carried out to answer this question in children <5 years, since this is the age group for which the strongest evidence is available. The cost-effectiveness of extending pulse oximetry to other age groups was then subsequently assessed, given that the pulse oximeters purchased for use in children <5 years can also be used in the management of older patients with ARI.

This study was based, as far as possible, on real-world data from rural northern Thailand which included patients of all ages in an attempt to address the knowledge gap pertaining to the cost-effectiveness of pulse oximetry for this use-case in older children and adults, in addition to gathering evidence from Asian contexts.

5.3.1 Methods

5.3.1.1 Setting

Mueang Chiang Rai is a large district of 1,216 km² in northern Thailand. It is situated in Chiang Rai province, which borders Laos and Myanmar, and contains the provincial capital but is mainly rural. In 2016, the district was estimated to have 241,436 residents, served by 32 government-run primary care units (PCUs), as primary health centres (PHCs) in Thailand are known (Figure 5.3). Each PCU is staffed by two to five nurses and public health officers overseen by family medicine doctors at the sole provincial hospital, and provides care for approximately 5,000 people per year. The furthest PCU from the provincial hospital, which serves as the first referral hospital for PCUs in the district, is two hours' drive away. Thailand is a middle income Southeast Asian country with healthcare delivered free at the point of care, including medications, at public sector facilities below community hospital level.⁷⁸ However, in rural, less affluent districts such as Mueang Chiang Rai, access to healthcare, which is delivered largely by the government, can be limited. Pulse oximetry was not available at Mueang Chiang Rai PCUs prior to the COVID-19 pandemic.¹¹²

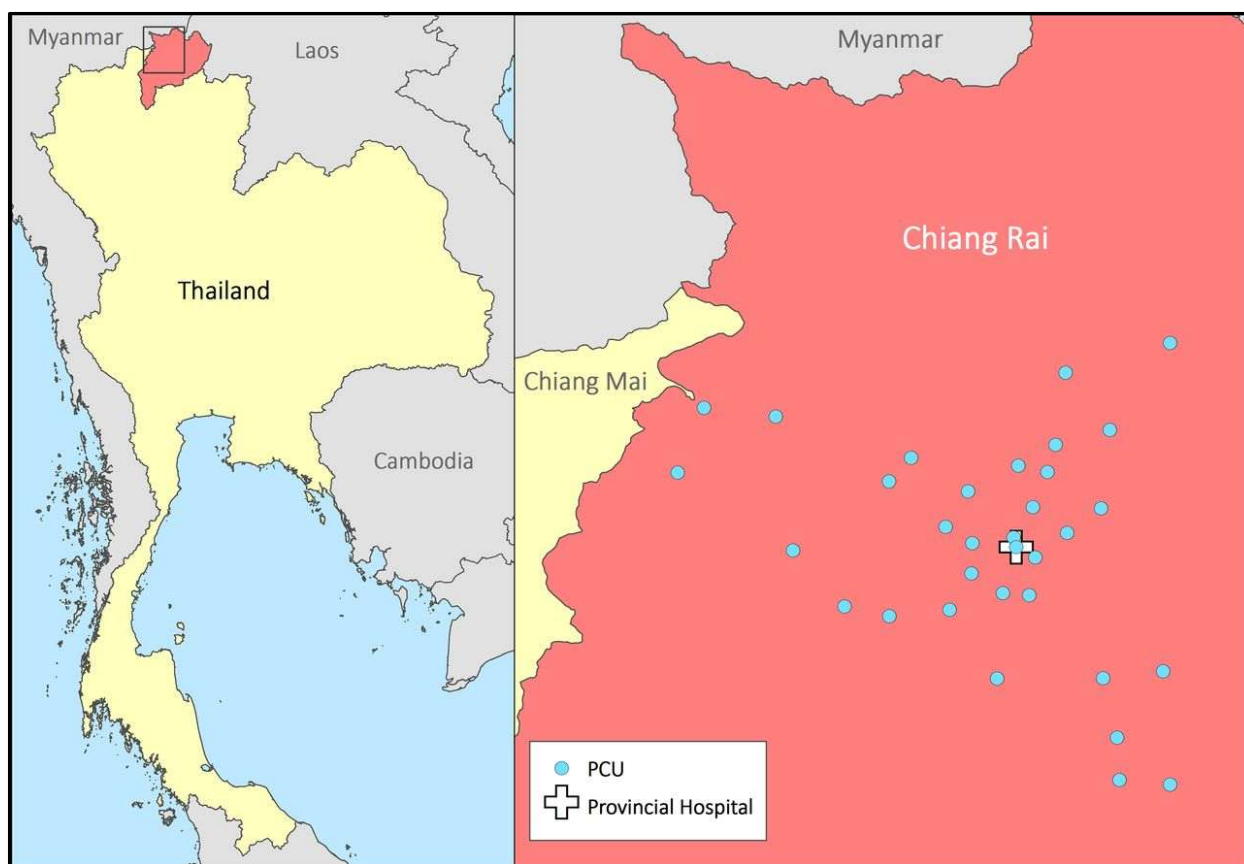


Figure 5.3. Location of Mueang Chiang Rai district within Thailand and the 32 primary care units (PCUs) included in this study. Adapted with permission from Greer et al., 2018.¹¹²

5.3.1.2 Study design and participants

A model-based cost-effectiveness evaluation was conducted comparing the current management of ARI in Mueang Chiang Rai PCUs with a hypothetical scenario where ARI management is improved by providing each PCU with two low-cost handheld pulse oximeters designed specifically for use in LMIC settings,¹⁹⁹ associated equipment such as probes and batteries, and relevant staff training and monitoring. The study was based on data collected for a retrospective review of acute infection management and antibiotic prescribing practices over two years from 1 January 2015 to 31 December 2016 in Mueang Chiang Rai PCUs.¹¹² Briefly, patients of any age were identified who met at least one of the following criteria for acute

infection: systemic antibiotic prescription; International Statistical Classification of Diseases (ICD) 10 code for infection; fever as the chief complaint; or documented temperature $>37.5^{\circ}\text{C}$ at the PCU. Of 762,868 patients who attended, 83,661 met the inclusion criteria for acute infection, of which 49,958 (59.7%) had ARIs. The last group of patients, comprising 49,400 with URTIs and 558 with lower respiratory tract infections (LRTIs), and whose characteristics are shown in Table 5.5, formed the patient cohort for this cost-effectiveness analysis. To maintain the focus on ARI, patients diagnosed with chronic respiratory infections or bronchitis of unknown acuity were excluded from the study cohort. An adult patient was defined as one aged ≥ 15 years old, to align with the definition used in the observational study.

Patient category	Number, n (% of total)	Median age, years (IQR)	Number with URTI (% of category)	Number with URTI prescribed antibiotics (% of number with URTI in category)	Number with LRTI (% of category)
Children <5 years	14,075 (28.2)	2 (1-3)	13,825 (98.2)	3,688 (26.7)	250 (1.8)
Children 5-14 years	11,741 (23.5)	8 (6-11)	11,642 (99.2)	4,653 (40.0)	99 (0.8)
Adults	24,142 (48.3)	45 (29-58)	23,933 (99.1)	9,696 (40.5)	209 (0.9)
All patients	49,958 (100.0)	13 (4-44)	49,400 (98.9)	18,037 (36.5)	558 (1.1)

Table 5.5. Characteristics of included patients (n=49,958). Adults were defined as patients ≥ 15 years old.

Fever was defined as documented temperature $>37.5^{\circ}\text{C}$ at the time of presentation to the primary care unit. IQR, interquartile range; URTI, upper respiratory tract infection; LRTI, lower respiratory tract infection.

5.3.1.3 Base case

For each patient category (children <5 years, children 5-14 years, and adults), a decision tree model was constructed comparing standard of care with pulse oximetry-aided ARI management, the structure of which is shown in Figure 5.4. Model parameters were derived from a combination of data from the retrospective review cohort as well as data from the published literature (Table 5.6). The clinical outcomes of interest were antibiotic prescription for URTI and death from severe LRTI. A health system plus limited societal perspective was adopted, including the cost of antibiotic resistance in the Thai setting. In brief, the latter cost was calculated using the three-component model constructed by Shrestha et al. for the Thai context with broad-spectrum penicillins as the antibiotic of interest; the three components are the correlation coefficients between human antibiotic consumption and subsequent resistance, the economic costs of antibiotic resistance for five sentinel pathogens, and consumption data for antibiotic classes driving resistance in these organisms.²⁰⁰

The time horizon was one year. No discounting or age-weighting was applied, in line with guidance established since the Global Burden of Disease 2010 report,²⁰¹ and given the acute nature of the disease of interest.²⁰² All costs related to equipment purchase and maintenance, as well as staff training and monitoring, were annualised over the expected two-year lifespan of a pulse oximeter using the straight-line method.

Cost-effectiveness in children <5 years was first estimated taking into consideration only the direct costs of pulse oximetry (i.e., the costs of equipment, maintenance, training, and monitoring), after which a second estimate was calculated considering both incremental direct and downstream costs, examples of the latter being the cost of antibiotics, antibiotic resistance, and hospitalisation. Cost-effectiveness was expressed in terms of incremental cost-effectiveness ratios (ICERs) per disability-adjusted life year (DALY) averted, encompassing only changes in years of life lost due to premature mortality and disregarding any impact on

morbidity or disability. The willingness-to-pay or cost-effectiveness threshold i.e., the maximum cost per DALY averted that the Thai health system is willing to pay was \$8,624 per DALY averted, or 1.2 times the mean 2020 GDP, as per the recommendations of the Thai health technology assessment commissioners.^{203, 204} The additional costs and health gains of extending pulse oximetry to older patients were then computed for each of the other two patient categories.

To estimate the expected number of DALYs averted annually with the use of pulse oximetry, the mean age group-specific life expectancy from WHO data on Thailand was calculated.²⁰⁵

All costs were adjusted for inflation based on the relevant country Consumer Price Indices and expressed in 2021 US dollars.²⁰⁶ The analysis was performed using Excel (Microsoft, Redmond, USA), with the decision trees constructed using the Plant-A-Tree plug-in (Saw Swee Hock School of Public Health, Singapore and Health Intervention and Technology Assessment Programme, Thailand).

5.3.1.4 Assumptions

Several key assumptions were made when constructing the decision tree models. Firstly, the true percentage of severe LRTI was assumed to be 8%, a value between the percentages of patients diagnosed as having severe disease with (15.9%) and without (3.9%) the use of pulse oximetry from the only randomised controlled trial of this intervention in a LMIC primary care setting, as per the systematic review reported earlier in this chapter.¹⁷⁹ Based on these values, therefore, the diagnostic sensitivity of pulse oximetry plus clinical assessment for severe LRTI was estimated to be 80% and the specificity to be 90%, compared to the sensitivity and specificity of clinical assessment alone of 60% and 75%, respectively.²⁰⁷ This approach is well-established when performing economic evaluations of interventions, including pulse oximetry in other settings.^{202, 208}

Secondly, given the non-specific nature of LRTI signs and symptoms, the limited skillset of PCU staff, and the lack of diagnostic investigations, all LRTIs were assumed to be treated as community-acquired pneumonia requiring antibiotic prescription, and all severe LRTIs were assumed to require referral to hospital for admission. Given the limited range of antibiotics available and local prescribing guidelines,²⁰⁹ all antibiotic prescriptions were assumed to be for amoxicillin.

Thirdly, all patients with severe LRTI who were incorrectly diagnosed with non-severe disease and who re-presented following treatment failure were assumed to warrant referral to hospital and would attend. Fourthly, it was assumed that all patients prescribed antibiotics were fully compliant; that all URTIs were self-limiting and cured regardless of whether antibiotics were prescribed;^{132, 210} and that any reduction in antibiotic prescription occurred in patients with URTIs only. It was also assumed that the provincial hospital had the capacity and infrastructure to manage increased referral rates of patients with LRTI arising from the use of pulse oximetry; that re-presentations, hospital length of stay (LOS), and in-hospital and in-community mortality would decrease due to earlier detection of severely ill patients as well as overdiagnosis; that the incidence of severe LRTI was similar across all patient categories; and that the annual distribution of patient presentations and outcomes over the two years of data were equal.

Finally, the lifespan of a pulse oximeter was assumed to be two years, with a requirement for one replacement probe per device every six months, based on experience and manufacturer guidance.²¹¹

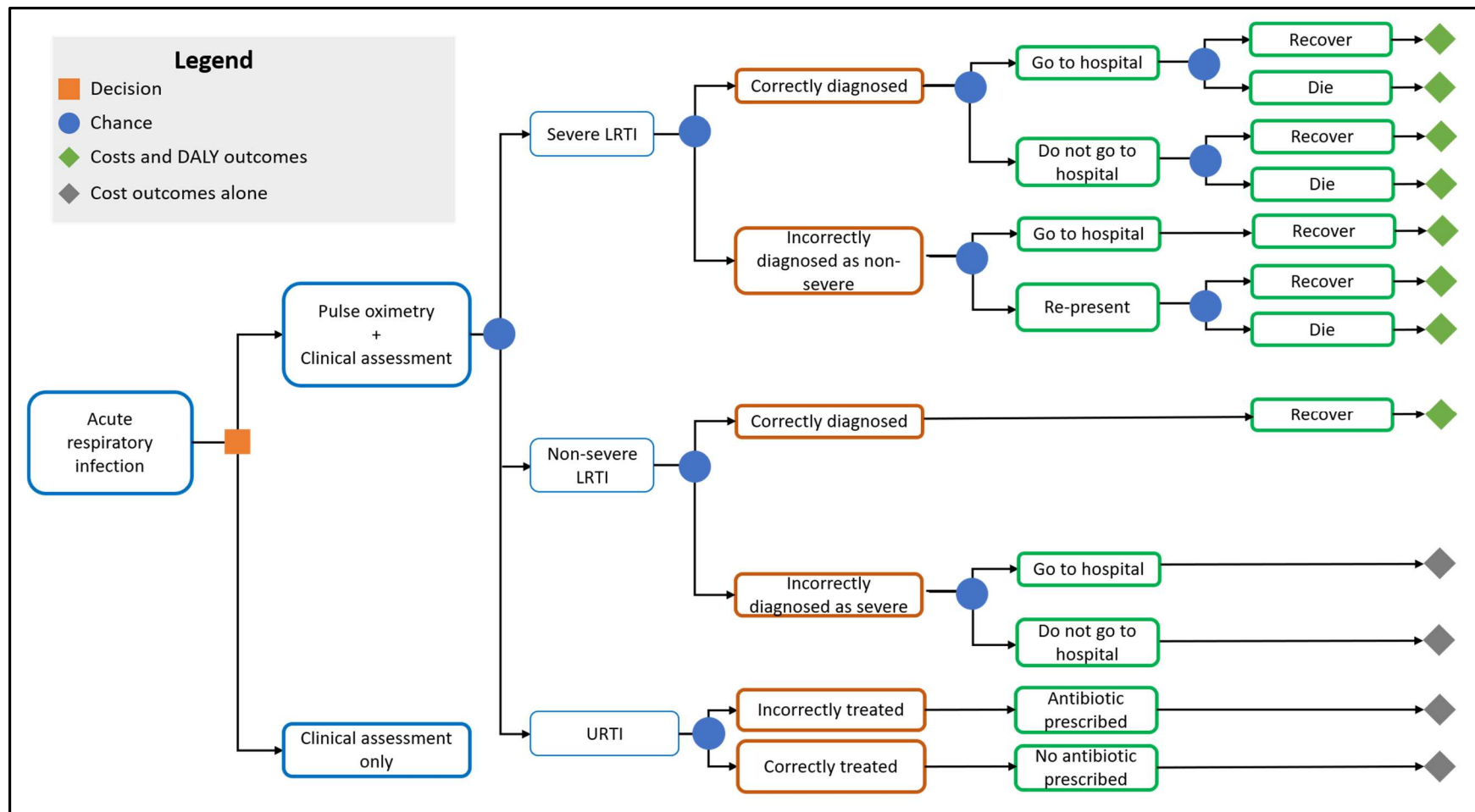


Figure 5.4. Decision tree model structure. The chance nodes arising from the ‘Clinical assessment only’ internal node are similar to those arising from the ‘Pulse oximetry + clinical assessment’ internal node. Parameters are shown in Table 5.6. DALY, disability-adjusted life year; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.

Parameter	Value	Data source
Number of primary care facilities, n	32	Ref ¹¹²
Percentage of patients with ARI who have LRTI, %	1.1; see Table 5.5 for age-stratified values	Ref ¹¹²
Percentage of patients with LRTI who have severe disease, %	8	Ref ¹⁷⁹
Percentage of patients with severe LRTI correctly diagnosed without pulse oximetry, %	60	Ref ²⁰⁷
Percentage of patients with severe LRTI correctly diagnosed with pulse oximetry, %	80	Adapted from ref ¹⁷⁹
Percentage of patients with non-severe LRTI incorrectly diagnosed with severe LRTI without pulse oximetry, %	25	Assumed
Percentage of patients with non-severe LRTI incorrectly diagnosed with severe LRTI with pulse oximetry, %	10	Assumed
Percentage of patients with URTI treated with antibiotics without pulse oximetry, %	36.5; see Table 5.5 for age-stratified values	Ref ¹¹²
Relative reduction in antibiotic prescription with pulse oximetry and clinical guideline retraining, %	50	Ref ¹⁷¹
Percentage of patients with severe LRTI diagnosed without pulse oximetry who recover without hospital admission, %	65	Ref ²¹²
Relative increase in recovery without hospital admission in patients with severe LRTI diagnosed with pulse oximetry, %	10	Assumed
Percentage of patients with severe LRTI who re-present who go to hospital, %	100	Assumed
Percentage of patients initially diagnosed with severe LRTI who go to hospital, %	80	Ref ²¹³
Percentage of patients with non-severe LRTI incorrectly diagnosed as severe who go to hospital, %	75	Assumed
Percentage of in-hospital deaths of patients correctly diagnosed with severe LRTI without pulse oximetry, %	10	Ref ^{213, 214}
Relative reduction in in-hospital deaths of patients correctly diagnosed with severe LRTI with pulse oximetry, %	20	Ref ^{172, 173}
Percentage of in-hospital deaths of patients with severe LRTI incorrectly diagnosed as non-	10	Ref ^{213, 214}

severe without pulse oximetry who re-present, %		
Relative reduction in in-hospital deaths of patients with severe LRTI incorrectly diagnosed as non-severe with pulse oximetry who re-present, %	20	Ref ^{172, 173}
Median hospital LOS of patients with severe LRTI diagnosed without pulse oximetry and of re-presentations with severe LRTI, days	5.34	Medical Records Department, Chiang Rai Prachanukroh Hospital (personal communication, 21 September 2021)
Median LOS of hospitalised patients with severe LRTI correctly diagnosed with pulse oximetry, days	4.01	Assumed at 75% of median LOS
Median LOS of hospitalised patients with non-severe LRTI incorrectly diagnosed as severe with pulse oximetry, days	2.67	Assumed at 50% of median LOS
Purchase cost of one pulse oximeter (includes one each of universal, paediatric, and neonatal probes), US\$	275	Ref ^{199, 215}
Maintenance cost of one pulse oximeter per year (includes replacement probes and batteries), US\$	55	Ref ^{199, 211}
Cost of district-wide staff training per year (initial training plus two refreshers) and monitoring at 0.2 primary health worker FTE, US\$	1,324.75	Chiang Rai Provincial Public Health Office (personal communication, 2 August 2022), ref ¹⁸⁰
Cost of extra staff time per primary care unit per year at 0.05 primary health worker FTE, US\$	331.19	Chiang Rai Provincial Public Health Office (personal communication, 2 August 2022)
Cost of one course of amoxicillin, US\$	0.61 for children <5 years, 0.91 for children 5-14 years, 1.21 for adults	Ref ²¹⁶
Cost of antimicrobial resistance associated with one course of amoxicillin, US\$	11.80	Ref ²⁰⁰
Cost of one occupied bed-day at provincial hospital, US\$	658.46	Finance Department, Chiang Rai Prachanukroh Hospital (personal communication, 21 September 2021)

Table 5.6. Decision tree model parameters for the base case analysis. Parameters apply to all age groups unless explicitly stated. Costs were adjusted for inflation and expressed in 2021 US dollars. FTE, full-time equivalent; LOS, length of stay; LRTI, lower respiratory tract infection; Ref, reference; URTI, upper respiratory tract infection.

5.3.1.5 Sensitivity analyses

To account for uncertainty, four deterministic scenario sensitivity analyses were performed by varying key model parameters in branches of the decision trees where pulse oximetry was used, with increasingly conservative assumptions regarding the performance and benefits of using the pulse oximeters.

In the first, the sensitivity and specificity of pulse oximetry plus clinical assessment for the diagnosis of severe LRTI was reduced to 70% and 85%, respectively and the mortality benefits were halved. In the second, the median hospital LOS of admitted patients was not reduced with pulse oximetry and the reduction in antibiotic prescriptions in each patient category was lower at 25%, with no antibiotic resistance cost; the base case sensitivity, specificity, and mortality estimates were maintained. In the third, the reduced performance characteristics and mortality benefits of pulse oximetry plus clinical assessment from the first sensitivity analysis were combined with the increased costs from the second. Finally, in a worst-case scenario the values from the third sensitivity analysis were combined with no reduction in inappropriate antibiotic prescriptions.

5.3.2 Results

The results of this cost-effectiveness analysis are reported here in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline.²¹⁷ The completed CHEERS checklist can be found in Appendix 5.6.

5.3.2.1 Cost-effectiveness of pulse oximetry in children <5 years old

The annual direct costs of providing all 32 PCUs with two pulse oximeters, associated equipment (universal, paediatric, and neonatal probes, and batteries), maintenance, training, and monitoring was \$24,243. This intervention resulted in several health gains among children <5 years, the principal benefit being a reduction in deaths by 0.19 per 100,000 patients

annually. In this cohort of 14,075 children <5 years, pulse oximetry, thus, resulted in an annual gain of 2.0 DALYs averted. When direct costs only were considered, the incremental cost per DALY averted was \$11,876, exceeding the cost-effectiveness threshold of \$8,624.

However, in the models the adoption of pulse oximetry also reduced inappropriate antibiotic prescribing for URTIs and length of stay for hospitalised patients. In the under-five cohort, for example, \$11,651 was saved annually through improved antibiotic stewardship (\$573 by averting the cost of inappropriate prescriptions and \$11,078 by averting the cost of antibiotic resistance associated with these prescriptions). This is in addition to \$25,349 saved through reduction in lengths of stay i.e., a total of \$37,000. The total cost saving per year, after accounting for the \$24,243 direct cost of pulse oximetry in this cohort, was \$12,757. When both direct and downstream costs were considered, therefore, augmentation of clinical assessment with pulse oximetry in children <5 years with ARI dominated standard care.

5.3.2.2 Cost-effectiveness of extending pulse oximetry to all patients

Extending pulse oximetry to older children 5-14 years and adults reduced deaths by 0.09 per 100,000 patients each year in each category, equivalent to gains of 0.7 and 0.9 DALYs averted, respectively. Cost savings in these patient categories totaled \$24,849 and \$52,944, respectively. The cost savings in older patients were mainly driven by reductions in inappropriate antibiotic prescribing for URTIs, particularly in adult patients (Table 5.7). Therefore, given that dominance of pulse oximetry has already been demonstrated for children <5 years and that relatively minimal costs would be incurred to extend the intervention to older patients resulting in the savings previously stated, it is clear that this strategy would also dominate standard care when applied to older children and adults and, thus, also be dominant if used for all patients. The yearly cost saving if clinical assessment of all patients with ARI were supplemented with pulse oximetry was \$90,550.

5.3.2.3 Sensitivity analyses

In all sensitivity analyses, pulse oximetry plus standard care in children <5 years remained dominant over standard care alone. When pulse oximetry was used in older patients with ARI in these analyses, cost savings were still seen even if the contribution related to reduction in inappropriate antibiotic prescription was considerably diminished or non-existent, demonstrating the robustness of its dominance in every age group and when used for all patients. In the worst-case scenario where pulse oximetry plus clinical assessment had only a mild increase in clinical sensitivity and specificity for the diagnosis of severe LRTI of 10% and 15% over standard care, the magnitudes of associated beneficial effects were smaller, and there was no reduction in inappropriate antibiotic prescriptions, annual cost savings of \$4,902 and \$40,727 were still seen for children <5 years and overall, respectively (Table 5.7).

			Base case analysis		Sensitivity analysis 1		Sensitivity analysis 2		Sensitivity analysis 3		Sensitivity analysis 4	
Patient category	DALYs averted per year (base case analysis and sensitivity analysis 2)	DALYs averted per year (sensitivity analyses 1, 3, and 4)	Total cost savings per year, US\$	Antibiotic cost savings per year, US\$	Total cost savings per year, US\$	Antibiotic cost savings per year, US\$	Total cost savings per year, US\$	Antibiotic cost savings per year, US\$	Total cost savings per year, US\$	Antibiotic cost savings per year, US\$	Total cost savings per year, US\$	Antibiotic cost savings per year, US\$
Children <5 years (n=14,075)	2.0	0.4	12,757	11,651	5,972	11,651	18,906	286	5,184	286	4,902	0
Children 5-14 years (n=11,741)*	0.7	0.2	24,849	14,915	22,179	14,915	17,403	534	11,924	534	11,395	0
Adults (n=24,142)*	0.9	0.2	52,944	31,801	47,258	31,801	37,399	1,480	25,897	1,480	24,429	0
All patients (n=49,958)	3.7	0.8	90,550	58,367	75,408	58,367	73,708	2,300	43,004	2,300	40,727	0

Table 5.7. Expected annual changes in disability-adjusted life years (DALYs) and costs if standard primary care management of acute respiratory infection was supplemented with pulse oximetry in Mueang Chiang Rai district, Thailand for the cohort of patients in this study. Monetary values are expressed in 2021 US dollars rounded to the nearest dollar. Sensitivity analysis 1 used the same parameters as the base case analysis but with a lower clinical sensitivity and specificity for diagnosis of severe lower respiratory tract infections with pulse oximetry plus clinical assessment of 70% and 85%, respectively and with the mortality benefits halved. Sensitivity analysis 2 used the sensitivity and specificity values as the base case analysis, but with no reduction in the median hospital length of stay of admitted patients, a lower reduction in antibiotic prescriptions of 25% in each category, and no cost of antibiotic resistance. Sensitivity analysis 3 combined the increased costs in sensitivity analysis 2 with the reduced number of DALYs averted in sensitivity analysis 1. Sensitivity analysis 4 combined the increased costs and reduced number of DALYs averted in sensitivity analysis 3, and assumed no reduction in antibiotic prescribing for upper respiratory tract infections. *Equipment and training costs of pulse oximetry were not included in the calculation of total cost savings for children 5-14 years and adults as these costs would have been incurred with the implementation of pulse oximetry for children <5 years.

5.3.3 Discussion

5.3.3.1 *Summary of main findings*

Augmenting standard primary care management of ARI in children <5 years by non-medically qualified personnel with pulse oximetry as a clinical decision support tool in rural northern Thailand dominated standard care and resulted in a modest number of DALYs averted annually. The magnitude of the mortality benefit is in keeping with a primary care setting, and is consistent with that shown by Colbourn et al. in Malawi.¹⁷⁵

The dominance of pulse oximetry was maintained in all sensitivity analyses. Cost-effectiveness was driven not only by preventing premature death but also by reducing inappropriate antibiotic prescriptions for URTIs. While the antibiotics themselves are cheaply priced, they are associated with a much greater cost in terms of antibiotic resistance which has been accounted for in the models.

This cost-effectiveness analysis also showed that extending the WHO recommendation that pulse oximetry be used as part of the clinical assessment for ARI in young children to older patients resulted in further cost savings. In these patient groups where the incidence of URTI was higher than in children <5 years, up to 60% of the cost savings were from reductions in inappropriate antibiotic prescribing. This benefit is most pronounced in adults, who form the largest group in whom antibiotics are prescribed (Table 3). Therefore, the results lend support for the expansion of pulse oximetry to all age groups, because cost-effectiveness will be maintained even in the absence of any gain in DALYs averted and relatively little additional cost would be incurred to extend this intervention to older patients. Moreover, it is also likely that, beyond the first few years following the introduction of pulse oximetry, staff training and monitoring costs would be expected to drop.

5.3.3.2 Interpretation of main findings

This study complements those of Floyd et al., Moosan et al., and Tesfaye et al. that, to our knowledge, are the only other published cost-effectiveness studies of pulse oximetry in the management of respiratory infections in LMICs.^{202, 208, 218} All three studies demonstrate the cost-effectiveness of pulse oximetry for this purpose. However, Floyd et al. use a different strategy based on a continuous-time deterministic compartmental model, taking a provider perspective and including data from multiple countries.²⁰² Moosan et al. use a broadly similar decision tree approach to ours applied to the Indian setting.²¹⁸ Tesfaye et al. concluded that pulse oximetry was cost-effective on a per diagnosed-case basis in an Ethiopian setting, but their use of an intermediate health outcome, rather than a conventional metric of health gain such as DALYs averted, is contentious.²⁰⁸ Furthermore, unlike this study, none of these assess the impact of pulse oximetry on ARIs other than pneumonia, nor do they consider patients aged ≥ 5 years in their analyses. Given the greater ease of use of pulse oximetry in older children and adults,²¹⁹ as well as its demonstrated utility in reducing inappropriate antibiotic prescriptions,¹⁷¹ these factors should also be considered when assessing the cost-effectiveness of this intervention. The modest estimated number of deaths averted with pulse oximetry is in keeping with a primary care setting, and is consistent with that shown by Colbourn et al. in Malawi.¹⁷⁵

5.3.3.3 Strengths and weaknesses

This is the first study assessing the cost-effectiveness of pulse oximetry in a LMIC rural primary care setting based on highly granular patient-level data. The cost-effectiveness of pulse oximetry in patients aged ≥ 5 years, who have not been the focus of previous comparative studies evaluating this intervention as demonstrated by the findings of the systematic review reported earlier in this chapter, has also been investigated. Of note also, the cost of antimicrobial resistance has been factored into the analysis. It is important for policymakers that

this cost is accounted for when evaluating the cost-effectiveness of interventions which have the potential to improve antimicrobial stewardship, notwithstanding the methodological challenges of doing so. This is especially true for countries like Thailand and other LMICs in South and Southeast Asia where antimicrobial resistance is an urgent public health issue, and where simple, low-cost interventions such as pulse oximetry may be considered for integration into national or sub-national strategic plans targeting antimicrobial resistance.²²⁰ Nevertheless, even if the cost of antimicrobial resistance was assumed to be zero or no change in antibiotic prescribing practices occurred, pulse oximetry remained a cost-effective intervention.

Nevertheless, in terms of generalisability, the findings of this cost-effectiveness analysis may not be totally applicable to all rural LMIC settings due to differences in disease epidemiology and health systems; additionally, while the models have been adapted to the rural Thai setting as far as possible, the use of data from studies conducted outside Southeast Asia to generate certain model parameters adds another layer of uncertainty. Despite this, they are useful in establishing a baseline understanding of the cost-effectiveness of this simple yet often overlooked clinical decision aid in LMICs more generally, especially as ARIs form a considerable percentage of acute infective primary care presentations in these countries (59.7% in our cohort).^{221, 222} Measuring oxygen saturation can also help identify patients severely ill due to non-respiratory causes such as malaria, given that symptoms may overlap extensively, thus broadening the clinical utility of pulse oximetry.^{223, 224} In this cohort, 55% had a documented fever at presentation or gave a history of acute fever, which supports the usefulness of pulse oximetry in the initial assessment of acutely febrile patients.

A further constraint on generalisability, which relates to how policymakers may interpret these findings, is how individual components of their health systems are funded. While this study demonstrated cost-effectiveness of pulse oximetry from the perspective which considers the health system as a whole, this may still not be sufficiently compelling for its adoption if one component, such as PCUs or their equivalents, is expected to bear the costs but the benefits

are enjoyed by others such as hospitals (through reduced lengths of stay) and society in general (through reduced antibiotic resistance). This is especially true if each component is responsible for setting its own budget, as this silo budgeting is a well-known barrier to the implementation of new healthcare technologies.²²⁵

There are several other limitations to this study besides potential lack of generalisability. First, there were no actual patient data on hospitalizations or re-presentations, as patients are able to present independently to the provincial hospital and there is no robust data linkage system connecting the hospital and PCUs. Second, because there is a paucity of data on the clinical impact of pulse oximetry in older children and adults in LMICs, findings from the literature pertaining to children <5 years old had to be extrapolated to these patient categories. Third, most data from the literature were derived principally from studies conducted in LMICs outside Southeast Asia, as no relevant studies carried out in this region featured in the results of the systematic review reported previously. To mitigate this, the potential impacts of pulse oximetry were adapted, as far as possible, to the socio-economic conditions in Thailand; for example, it is likely that most patients referred to hospital in Thailand will attend,²¹³ unlike in many African countries.¹⁷⁹ Furthermore, several of the assumptions were derived based on local experience or what was felt to be reasonable, rather than from objective data. Fourth, quality adjustment of the years of life gained was not performed due to the scarcity of data on quality-adjusted life-year loss due to community-acquired pneumonia in non-elderly patients.^{226, 227} Nevertheless, given the acute nature of the disease and the young median age of the population, it is likely that recovery is associated with a return to pre-morbid health status. Fifth, while the incidence of LRTI relative to URTI in children <5 years, as well as the incidence of LRTI in children <5 years relative to that in older patients, is in keeping with reported findings in the literature,^{228, 229} the incidence of LRTI relative to URTI in the study cohort is lower than reported in other primary care settings.^{230, 231} This may be due a combination of the ability of patients to present directly to hospitals and private sector primary care facilities as noted in

Chapter 4, exclusion of patients with chronic respiratory infections, diagnostic inaccuracy, and context-specific epidemiological differences. However, it should be noted cost-effectiveness would further increase if the percentage of patients with LRTI were higher. Lastly, it must be borne in mind that while the models were largely based on real-world data, these data did not come from randomised controlled trials and values for certain parameters thus had to be assumed.

5.3.3.4 Conclusions from this study

This model-based cost-effectiveness analysis of pulse oximetry has shown that it is a cost-effective adjunct for the management of ARI in rural northern Thailand which not only saves lives but improves antibiotic stewardship. The findings have implications for health policy, principally in Thailand but also for those of its LMIC neighbours in South and Southeast Asia which have similar disease epidemiology and health systems. They provide support from an economic perspective for the WHO recommendation that pulse oximetry be implemented in such settings for the management of febrile children <5 years,¹⁵¹ in whom randomised controlled trial evidence of clinical benefit is strongest. The models also suggest that pulse oximetry is cost-effective in other patient categories; therefore, further clinical studies of pulse oximetry in older children and adults are merited.

5.4 Conclusions

In South and Southeast Asian peripheral primary care settings where ARI forms the majority of AFI presentations, augmenting clinical assessment with pulse oximetry to detect severely unwell patients and reduce inappropriate antibiotic prescribing is likely to be cost-effective. However, this is premised upon the rollout being part of an approach guided by strong, context-appropriate change management strategies, as with implementation of any new healthcare technology, and having regard to impacts on other components of often fragile health systems.

Robust training programmes and clinical guidelines are essential to any implementation plan, in part to avoid overburdening secondary care which, in turn, should have its capacity strengthened, especially if hospital resources are also limited.¹⁵⁴ In the context of rural primary care settings manned by staff with limited clinical skillsets, therefore, a first step could be the introduction of pulse oximetry as part of an algorithmic clinical decision support tool for AFI management bundled with appropriate upskilling, followed by evaluation of its effectiveness under field conditions.

CHAPTER 6 | EVALUATION OF A PUTATIVE NOVEL MULTIPLEX RAPID DIAGNOSTIC TEST IN THE PRIMARY CARE MANAGEMENT OF ACUTE FEBRILE ILLNESS

This chapter draws upon work published in:

1. **Chew R**, Lohavittayavikant S, Mayer M, Day NPJ, Lubell Y. Perceptions and priorities for the development of multiplex rapid diagnostic tests for acute non-malarial fever in rural South and Southeast Asia: An international modified e-Delphi survey. *PLoS Negl Trop Dis*. 2022;16(11):e0010685.
2. **Chew R**, Painter C, Pan-ngum W, Day NPJ, Lubell Y. Cost-effectiveness analysis of a multiplex lateral flow rapid diagnostic test for acute non-malarial febrile illness in rural Cambodia and Bangladesh. *Lancet Reg Health Southeast Asia*. 2024;23:100389.

6.1 Introduction

The woeful lack of point-of-care diagnostics tailored towards acute febrile illness (AFI) in South and Southeast Asia, and which are suitable for use in rural and remote primary care settings of tropical low-income and middle-income countries (LMICs),²³² have been described previously in Chapter 2 ('Background'). The exception is, of course, the malaria diagnostic test (RDT) but, as has also been described in Chapter 2 and proven by the results of the observational study reported in Chapter 4, the incidence of malaria in rural South and Southeast Asia is now minimal, laying starkly bare the need for a similar diagnostic able to diagnose the most important non-malarial febrile illnesses (NMFIs).

Nevertheless, fingerprick blood-based rapid diagnostic tests for several other infectious diseases based on lateral flow technology e.g., HIV and Ebola virus disease, have been

developed and rolled out in both high- and low-resource settings.^{233, 234} Like malaria RDTs, which also utilise lateral flow technology,²³⁵ these are generally immunoassays based on the detection of microbial antigens and/or antibodies against the causative pathogens, although nucleic acid-based assays have more recently been developed.²³⁶

The test kits comprise of a recognition layer containing the detection sites, combined with a porous membrane which draws the fluid to be tested past the detection sites by capillary action.²³⁷ They are low-cost, simple to operate, require no specialised equipment, and can be used at the point of care, returning results in 30 minutes or less, thus making them ideal for use in low-resource settings.^{238, 239} However, none are specifically targeted towards the needs of patients and primary healthcare workers in rural South and Southeast Asia. In any case, the widespread uptake of these tests in LMIC settings is hindered by well-described technical, biological, social, infrastructural, regulatory, and economic barriers.²⁴⁰ Where tests are available, access is difficult as they are often found in secondary or higher-level facilities located a considerable distance from rural villages.

The chief challenge for those seeking to develop such lateral flow RDTs (LF-RDTs) for NMFI in South and Southeast Asia is the myriad infectious diseases prevalent in the region. The use of multiple single-disease LF-RDTs is unlikely to be cost-effective or logistically feasible, and is sub-optimal for patient comfort. Multiplex LF-RDTs able to detect several analytes from a single biological specimen, such as capillary blood from a fingerprick, would be a logical solution, allowing low- and semi-skilled rural primary healthcare workers to guide patient management with the minimum amount of test substrate and little additional training, given their familiarity with malaria RDTs and the ease of use of LF-RDTs more generally. However, ascertainment of the most important infective aetiologies of NMFI to aid the development of relevant multiplex LF-RDTs is hampered by the lack of reliable epidemiological data from this

region covering not just incidence of pathogenic aetiologies, but also disease burden in terms of morbidity and mortality.³⁸

Although the work described in Chapter 4 ('Defining the epidemiology of acute febrile illness in rural South and Southeast Asian primary care') partially addresses some of these knowledge gaps, there is still a high degree of uncertainty in prioritisation of pathogens for inclusion in such tests. Furthermore, what little published evidence there is comes mainly from cities but, as mentioned in Chapter 2, most of the population in South and Southeast Asia still live rurally.⁴⁰ In addition, there is growing interest in augmenting pathogen-based diagnostics by assaying host biomarkers of inflammation in parallel, with several such tests commercially available.²⁴¹ These biomarkers can be broadly categorised by use-case. The first of these use-cases is diagnostic i.e., differentiation of viral from non-viral infections, thus improving antimicrobial stewardship.²⁴² The second is prognostic i.e., prediction or indication of severe disease, thus improving the identification of patients who require escalation of care.²⁴³ It is, however, yet unclear which use-cases most of these host biomarkers fulfil. In any case, regardless of clinical utility, any such novel multiplex LF-RDTs must also be cost-effective to justify the investment of research, governmental, and industry players towards their development.

Having established the pressing need for novel multiplex LF-RDTs for NMFI in rural South and Southeast Asia, the focus of the research reported in this chapter is the generation of alternative, but methodologically sound, evidence to help overcome the main stumbling blocks to their development despite the current paucity of relevant and robust epidemiological data.

6.2 Priority-setting Delphi survey

Expert opinion, if obtained in systematic and appropriately-curated manner to minimise bias, is an acceptable alternative to aid decision-making in the absence of reliable data. As such, a

modified e-Delphi survey was first conducted to obtain expert consensus on pathogen-specific and host inflammatory biomarker analytes which should be prioritised for inclusion in multiplex LF-RDTs with fingerprick blood as the test substrate, for use in acutely febrile rural residents of South and Southeast Asian LMICs who test negative for malaria and in whom the source of infection is unclear to the generally low or semi-skilled treating healthcare worker. This study also aimed to explore the reasoning and contextual background underlying the selection of these analytes.

6.2.1 Methods

6.2.1.1 Study design

This modified e-Delphi survey was conducted over two rounds from 20 April to 20 June 2022, and delivered via anonymous web-based questionnaires administered through a bespoke platform. For clarification, unlike conventional Delphi surveys which begin with open-ended questionnaires to determine the response options for subsequent rounds, one form of modified Delphi survey begins with pre-selected options and a pre-determined number of rounds.²⁴⁴ These modifications are suitable for this study, given that the causative organisms, and pathogen and host biomarkers of interest have been widely described in the literature,^{39, 40, 245} what is not known is their relative importance in informing the development of multiplex LF-RDTs. Such modifications are widely accepted as appropriate if foundational information is available and usable,²⁴⁶ as in this case. Modified Delphi surveys also have the advantage of maximising the response rate in the initial round.²⁴⁷

Prior to the launch of the survey, two experts who would have otherwise been invited as panellists were asked to review the questionnaire to ensure face validity, readability, and usability. The questionnaire is available in Appendix 6.1.

Given the likely spatio-temporal heterogeneity in disease profiles, three regional panels were assembled: South Asia (India, Bangladesh, Pakistan, and Nepal), Mainland Southeast Asia (Thailand, Laos, Myanmar, Peninsular Malaysia, and Cambodia), and Maritime Southeast Asia (Indonesia, Timor-Leste, and the Philippines). Countries were selected to ensure adequate geographical representation, with at least one small country (in terms of relative population size) included per panel.

6.2.1.2 Participant selection

A total of 84 experts (seven from each country) were invited to participate in each round. Potential panellists were shortlisted through searches of national infectious diseases and/or tropical medicine specialty society office-bearers; leaders of health-related non-governmental organisations and governmental bodies; researchers from university departments or faculties; and recommendations of experts already selected. The final list was constructed based on work experience, expertise and reputation, involvement in health policymaking, and publication record. To balance perspectives, at least 30% of each regional panel were in non-clinical roles and at least 25% were women. Panellists had three weeks to complete each round of the survey, and were able to save and return to their responses if they were unable to complete each round in one sitting. Reminder emails were sent weekly to optimise participation rates.

6.2.1.3 First round

In the first round, panellists were provided with four scenarios in which they were required to rank seven analytes from a list of pathogen-specific and host inflammatory biomarkers for hypothetical LF-RDTs for acute (≤ 14 days duration) non-malarial fever of unclear source to be developed for year-round use in each region. The four scenarios corresponded to four patient categories stratified by age and level of care i.e., children (age > 28 days and < 15 years) and adults (age ≥ 15 years, this definition being used to align with that in the observational study)

seeking healthcare in the community from village health workers (VHWs) or primary health centres (PHCs), and being admitted to rural first-referral hospitals with limited diagnostic capacity, respectively. Neonates were not included because neonatal febrile illness generally requires assessment and thorough investigation in secondary or higher-level care.²⁴⁸

Pathogen biomarker options were based on a recent systematic review of published aetiological studies and case reports on NMFI in South and Southeast Asia,⁴⁰ while host inflammatory biomarker options were selected on the basis of biological plausibility and a non-systematic survey of the literature.^{39, 245} Participants were able to recommend non-listed analytes as well as refine the provided choices, such as specifying a particular type of antigen, and were asked to explain the reasoning behind their decisions for each scenario. If a host inflammatory biomarker was selected, participants were required to state its perceived utility from the following options: 'differentiation of viral and non-viral fever', 'as a marker of severity', 'both of these reasons', or 'other'.

To assess the perceived value of the multiplex LF-RDTs in these patient categories, participants were asked whether they would find such a test with a minimum sensitivity of 75% and minimum specificity of 90% across all targets helpful to guide clinical decision-making, and whether they would recommend its inclusion in electronic algorithm-based clinical decision support tools for use in their countries. Finally, to provide further context, participants were asked to rank what they perceived to be the five commonest causes of AFI in their regions in terms of annual incidence. Consensus was achieved if $\geq 80\%$ of the participants for each region agreed on a particular response. Questions for which consensus was achieved in the first round were not repeated.

At the conclusion of the first round, participants were invited to provide free-text feedback on the survey structure and questions. Free-text suggestions for improvement were analysed thematically and used to inform the subsequent iteration of the questionnaire.

Changes were made based on the number of times an issue was raised, the practicality of the suggested change, and its relevance to the context of the survey.

6.2.1.4 Second round

All panellists were re-invited to participate in the second round run two weeks after the end of the first, unless they explicitly declined to participate in the first round. The latter (n=10) were replaced in the second round, while maintaining the gender and clinician balance described previously.

In this round, only options that had been selected in the first round for each scenario were included. First-round respondents who participated in the second round were shown their previous answers to each question. To assist participants in reaching consensus, the frequencies of every analyte selected in each rank position, along with their sum of weighted scores, were shown graphically. An analyte ranked first was assigned a weighted score seven times more than if it was ranked last. Similarly, for the question on the commonest causes of acute febrile illness, an aetiology ranked first was assigned a weighted score five times more than if it was ranked last. The factors influencing participant reasoning for their rankings from the first round were analysed thematically and presented as discrete options in this round.

In the event that consensus for each rank position was unable to be reached by the end of the second round, agreement was quantified by constructing rank lists of the seven highest-scoring analytes for each scenario and of the five highest-scoring aetiologies of febrile illness were constructed.

Statistical analyses were performed using Microsoft Excel (Microsoft, Washington, USA). The list of panellists who participated in either round of the survey is shown in Appendix 6.2.

6.2.2 Results

Thirty-six expert panellists participated in the first round and 44 in the second round, giving overall response rates of 43% and 52%, respectively. Thirty-four of the 36 (94%) first round-respondents also participated in the second round; in this round, regional panel response rates were between 38% and 66%. A summary of participant demographic and professional background details by region for both rounds are shown in Table 6.1.

6.2.2.1 First round

In all panels, there was consensus that such multiplex LF-RDTs would help clinical decision-making in all target patient populations, and for the incorporation of these tests into electronic algorithm-based clinical decision support tools for use in their respective countries.

The reasons given by participants for the ordering of their rank lists were distilled into the following statements, which were used as response options in the second round: 'disease prevalence and/or incidence in this age group and care setting', 'potential disease severity and need (or otherwise) for antimicrobial therapy or referral', 'host biomarkers are more useful than aetiological diagnosis in this age group and care setting', 'aetiological diagnosis is more useful than host biomarkers in this age group and care setting', 'pathogens for which there are available RDTs should be prioritised', 'pathogens for which there are no available RDTs should be prioritised', and 'other'.

Region	Characteristic		First round, n (%)	Second round, n (%)	
Mainland Southeast Asia [n = 19 (54%) and 23 (66%) in rounds 1 and 2, respectively]	Country	Thailand	2 (11)	5 (22)	
		Laos	5 (26)	5 (22)	
		Cambodia	3 (16)	3 (13)	
		Myanmar	4 (21)	4 (17)	
		Peninsular Malaysia	5 (26)	6 (26)	
	Gender	Male	15 (79)	17 (74)	
		Female	4 (21)	6 (26)	
	Professional role	Clinical	Clinical infectious diseases	8 (42)	10 (43)
			Clinical infectious diseases and medical microbiology	4 (21)	5 (22)
			Other	1 (5)	2 (9)
		Non-clinical	Medical microbiology	3 (16)	3 (13)
			Epidemiology	2 (11)	1 (4)
			Microbiology	1 (5)	2 (9)
	Years of experience	0 to 5	0 (0)	1 (4)	
		>5 to 10	1 (5)	1 (4)	
>10 to 15		4 (21)	5 (22)		
>15 to 20		3 (16)	3 (13)		
>20		11 (58)	13 (57)		
Maritime Southeast Asia [n = 6 (29%) and 8 (38%) in rounds 1 and 2, respectively]	Country	Indonesia	2 (33)	3 (38)	
		Philippines	1 (17)	1 (13)	
		Timor-Leste	3 (50)	4 (50)	
	Gender	Male	1 (17)	3 (38)	
		Female	5 (83)	5 (62)	
	Professional role	Clinical	Clinical infectious diseases	5 (83)	5 (63)
			Clinical infectious diseases and medical microbiology	0 (0)	1 (13)
			Other	1 (17)	2 (25)
	Years of experience	>5 to 10	2 (33)	3 (38)	

		>10 to 15	3 (50)	2 (25)	
		>20	1 (17)	3 (38)	
South Asia [n = 11 (39%) and 13 (46%) in rounds 1 and 2, respectively]	Country		India	2 (18)	2 (15)
			Nepal	3 (27)	4 (31)
			Pakistan	4 (36)	5 (38)
			Bangladesh	2 (18)	2 (15)
	Gender		Male	7 (64)	7 (54)
			Female	4 (36)	6 (46)
	Professional role	Clinical	Clinical infectious diseases	7 (64)	7 (54)
			Clinical infectious diseases and medical microbiology	1 (9)	1 (8)
			Other	1 (9)	1 (8)
		Non-clinical	Medical microbiology	1 (9)	2 (15)
			Public health	0 (0)	1 (8)
			Other	1 (9)	1 (8)
	Years of experience		>10 to 15	0 (0)	3 (23)
>15 to 20			4 (36)	3 (23)	
>20			7 (64)	7 (54)	

Table 6.1. Regional panel participant demographic and professional background details.

6.2.2.2 Second round

The consensus threshold was not reached for any position in any rank list. Therefore, for each region the seven highest-scoring analytes for each scenario and the five highest-scoring aetiologies of AFI, based on the sums of their weighted scores, were used to construct the rank lists.

Across all regions, in both primary and secondary care settings and for both paediatric and adult patients dengue NS1 and typhoidal *Salmonella* antigens occupied the top two rank positions (Figures 6.1, 6.2, and 6.3). This is in keeping with the perception that dengue and enteric fevers are among the top five causes of AFI in all regions (Figure 6.4), and with the unsurprising finding that perceived disease incidence and/or prevalence was a primary factor in analyte selection (Figure 6.5). Also, in line with current evidence on the near-elimination of malaria, the disease was thought to be a leading cause of AFI only in Maritime Southeast Asia (Figure 4).

In mainland Southeast Asia, *Burkholderia pseudomallei*, *Orientia tsutsugamushi*, and *Rickettsia* antigens also featured in the rank lists for each scenario, as did *Leptospira* antigen in maritime Southeast Asia (Figures 6.1, 6.2, and 6.3). While only *Rickettsia* was listed among the top five aetiologies of AFI in mainland Southeast Asia (Figure 6.4), the inclusion of these organisms is reflective of another major factor influencing analyte selection i.e., the prioritisation of pathogens which require specific directed antimicrobial therapy and have the potential to cause severe disease (Figure 6.5).

There was a clear preference for antigen-based pathogen biomarkers over serological analytes, including for pathogens like typhoidal *Salmonella* where such capillary blood-based rapid tests are not yet available (Figures 6.1, 6.2, and 6.3). This finding also reflects the view of

the majority of respondents that pathogens for which there are no readily available RDTs should be prioritised for inclusion when developing multiplex LF-RDTs (Figure 6.5).

The only host inflammatory biomarker which featured prominently in this survey was C-reactive protein (CRP). CRP was included in all rank lists except those for adult secondary care in Mainland and Maritime Southeast Asia (Figures 6.1, 6.2, and 6.3). However, it was most frequently found in the bottom half of rank lists, indicative of the majority opinion that host biomarkers are less useful than microbiological diagnosis (Figure 6.5).

Furthermore, while twenty-eight (64%) respondents across all panels ranked CRP in one or more scenarios, there was little agreement on use-case. Eight (29%) believed it was a good discriminator between viral and non-viral infections in all scenarios in which CRP featured in their rank lists, while two (7%) believed it to be a good marker of disease severity. A further eight (29%) thought CRP was able to fulfil both use-cases, while 10 (36%) were of the opinion that use-case varies depending on patient age and care setting.

For the scenario-based questions, the top-ranked three analytes in each rank list were unchanged between the first and second rounds although their individual positions varied slightly, except for the Maritime Southeast Asia and South Asia adult secondary care rank lists where the top-ranked two analytes were constant between rounds. The top-ranked analyte in all rank lists in the first round was either dengue NS1 antigen or typhoidal *Salmonella* antigen, demonstrating a degree of convergence at the end of the survey as both these analytes occupied the top two positions in all lists in the second round. The top three perceived aetiologies of AFI in all regions were also unchanged between rounds.

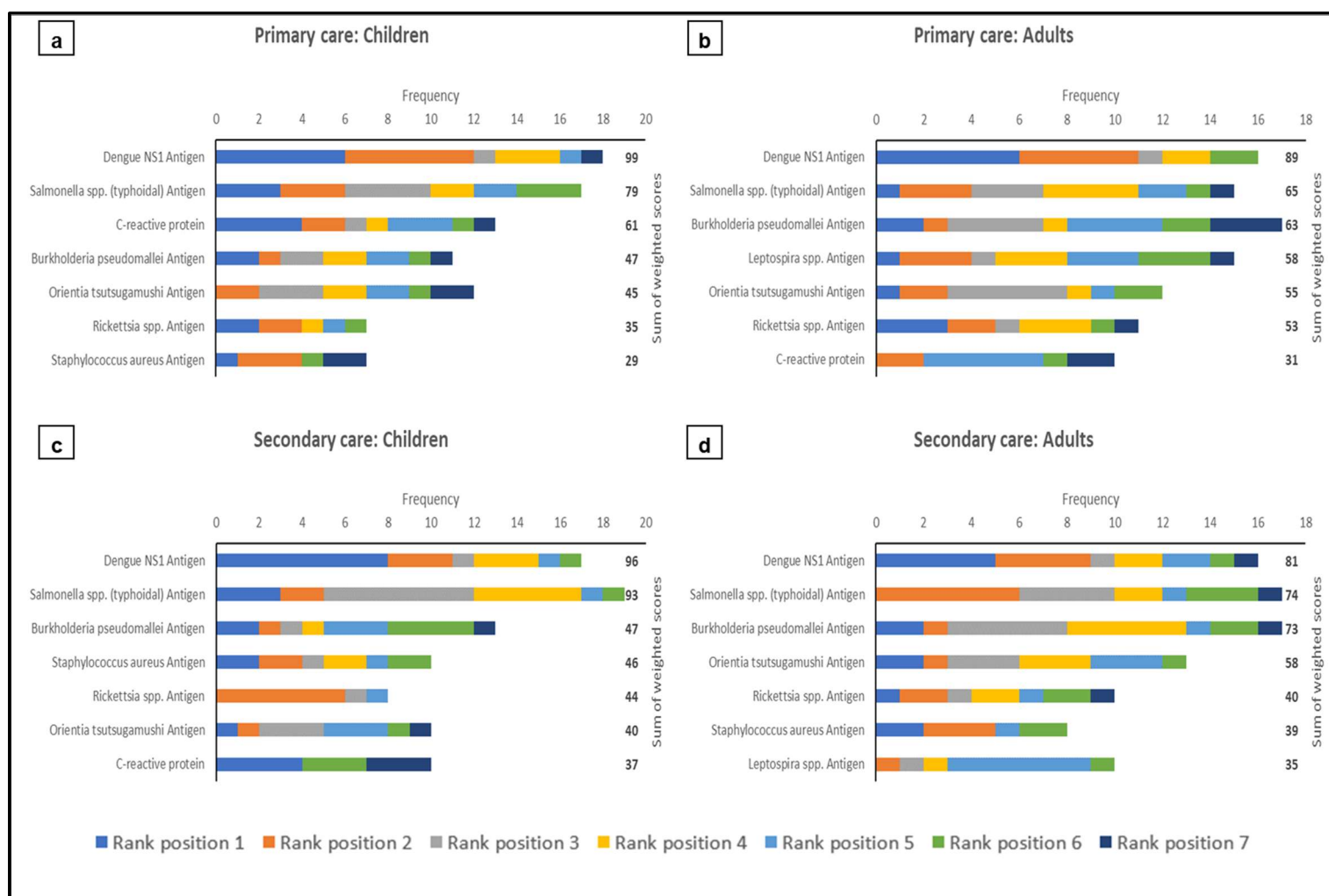


Figure 6.1. The top seven analytes, in descending order of priority based on sum of weighted scores, which should be considered for inclusion in multiplex lateral flow rapid diagnostic tests for acute non-malarial fever using fingerprick blood as the test substrate, in the following patient populations in rural Mainland Southeast Asia: (a) Children presenting to primary care settings (b) Adults presenting to primary care settings (c) Children being admitted to secondary care settings (d) Adults being admitted to secondary care settings. Children were defined as patients aged >28 days and <15 years. An analyte in rank position 1 was weighted seven times more than an analyte in rank position 7; the maximum sum of weighted scores per analyte was 161.

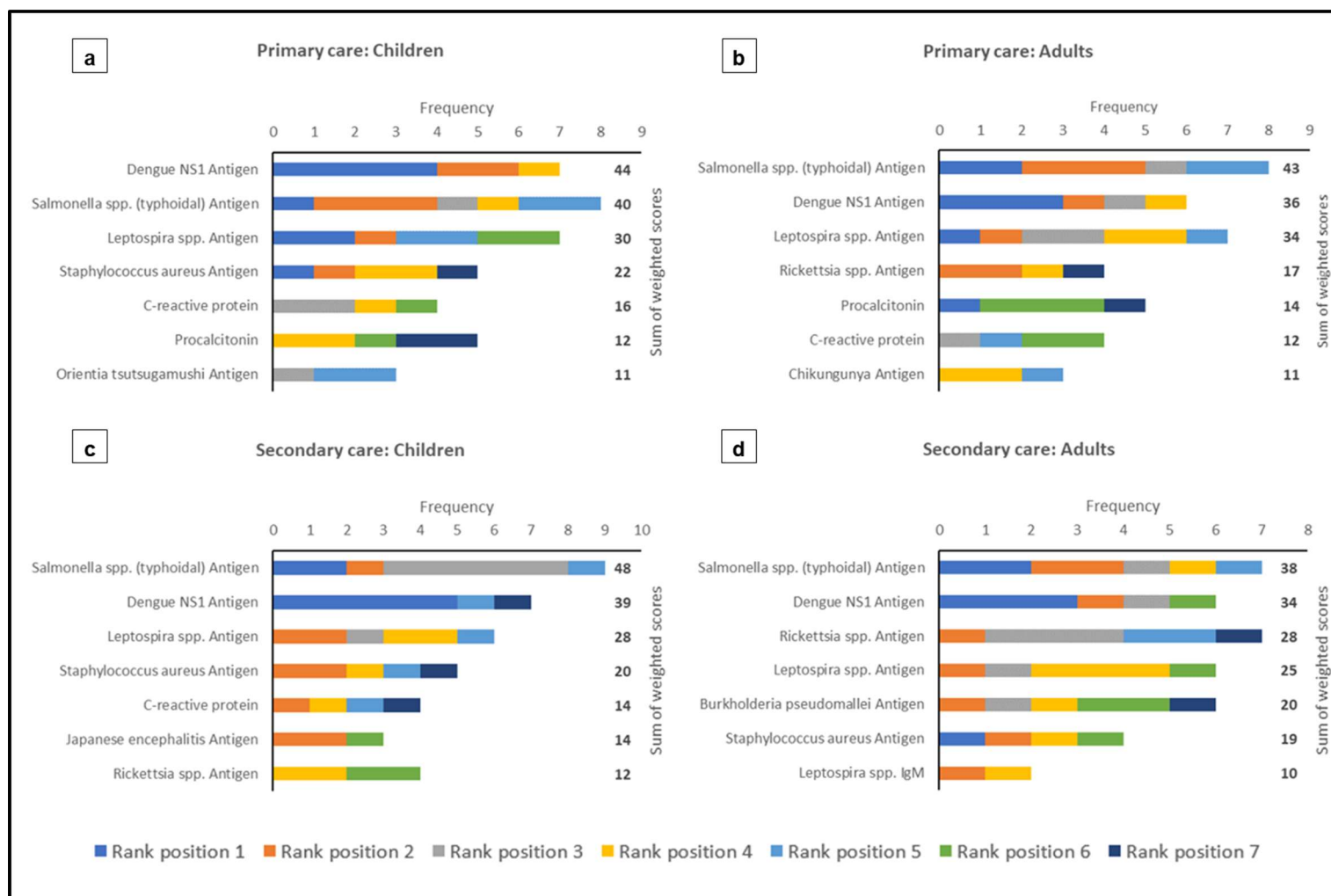


Figure 6.2. The top seven analytes, in descending order of priority based on sum of weighted scores, which should be considered for inclusion in multiplex lateral flow rapid diagnostic tests for acute non-malarial fever using fingerprick blood as the test substrate, in the following patient populations in rural Maritime Southeast Asia: (a) Children presenting to primary care settings (b) Adults presenting to primary care settings (c) Children being admitted to secondary care settings (d) Adults being admitted to secondary care settings. Children were defined as patients aged >28 days and <15 years. An analyte in rank position 1 was weighted seven times more than an analyte in rank position 7; the maximum sum of weighted scores per analyte was 56.

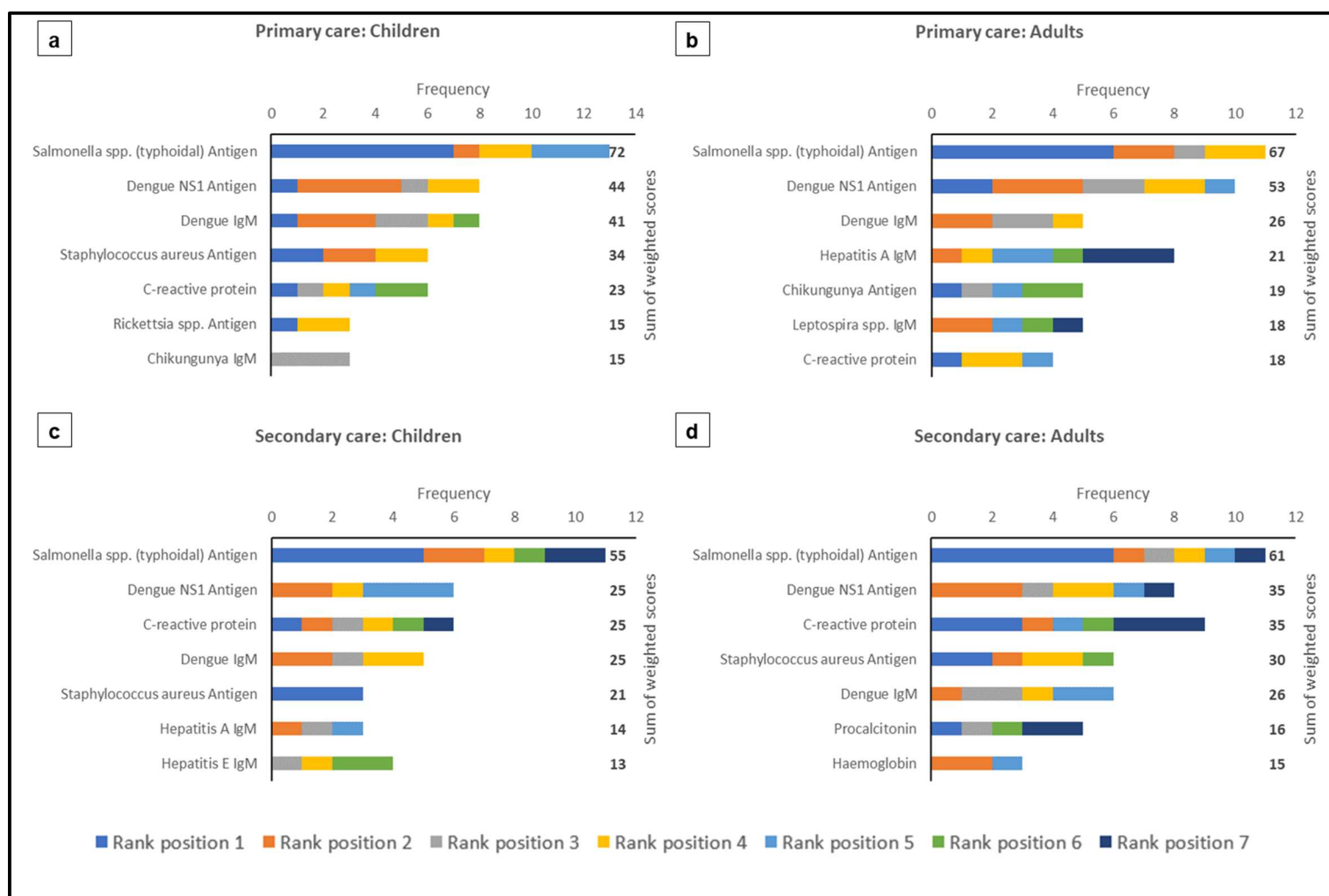


Figure 6.3. The top seven analytes, in descending order of priority based on sum of weighted scores, which should be considered for inclusion in multiplex lateral flow rapid diagnostic tests for acute non-malarial fever using fingerprick blood as the test substrate, in the following patient populations in rural South Asia: (a) Children presenting to primary care settings (b) Adults presenting to primary care settings (c) Children being admitted to secondary care settings (d) Adults being admitted to secondary care settings. Children were defined as patients aged >28 days and <15 years. An analyte in rank position 1 was weighted seven times more than an analyte in rank position 7; the maximum sum of weighted scores per analyte was 91.

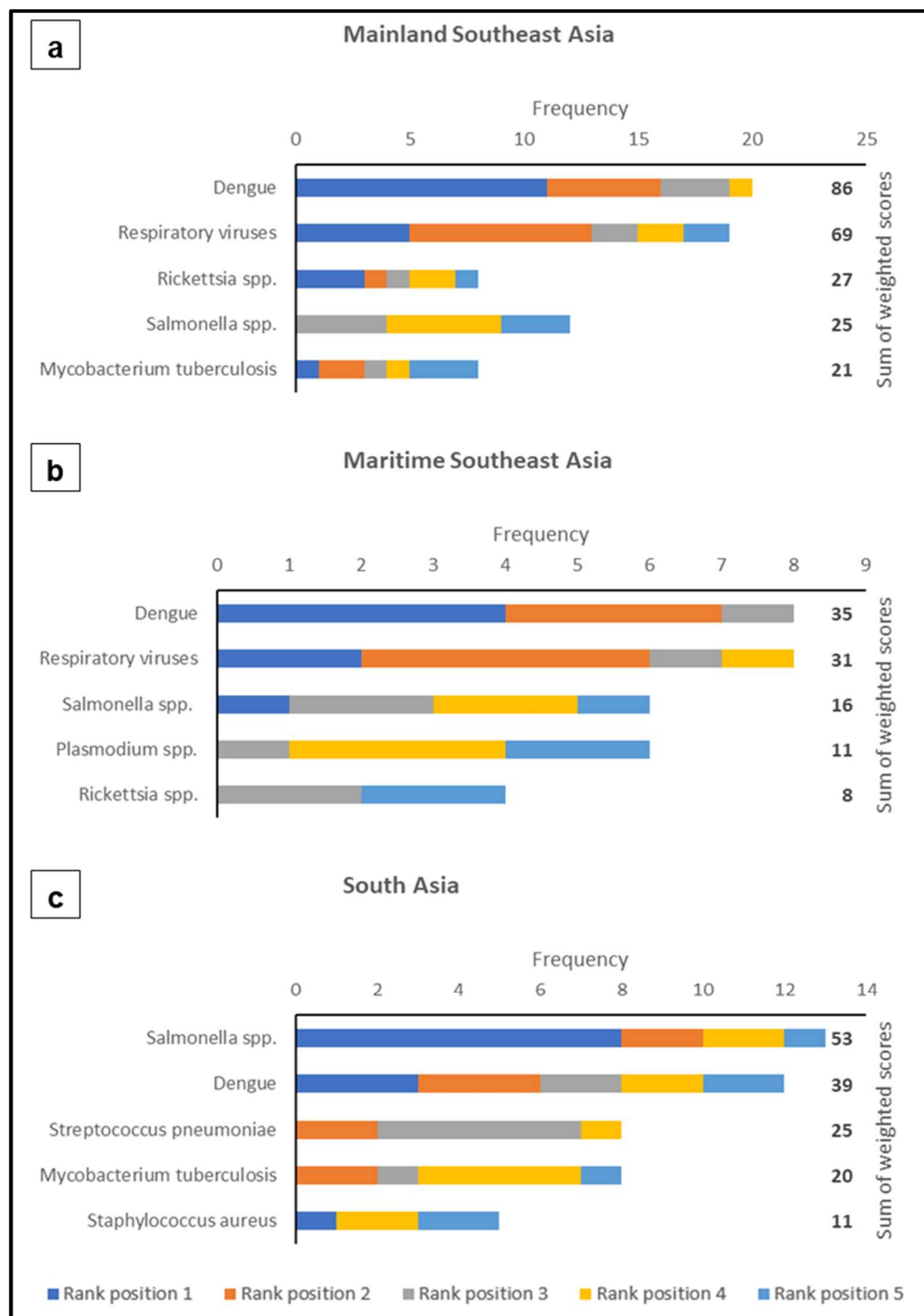


Figure 6.4. The top five commonest aetiologies of acute fever, in descending order of perceived annual incidence based on sum of weighted scores, in the following regions: (a) Mainland Southeast Asia (b) Maritime Southeast Asia (c) South Asia. An analyte in rank position 1 was weighted five times more than an analyte in rank position 5; the maximum sum of weighted scores per aetiology was 115 for Mainland Southeast Asia, 40 for Maritime Southeast Asia, and 65 for South Asia.

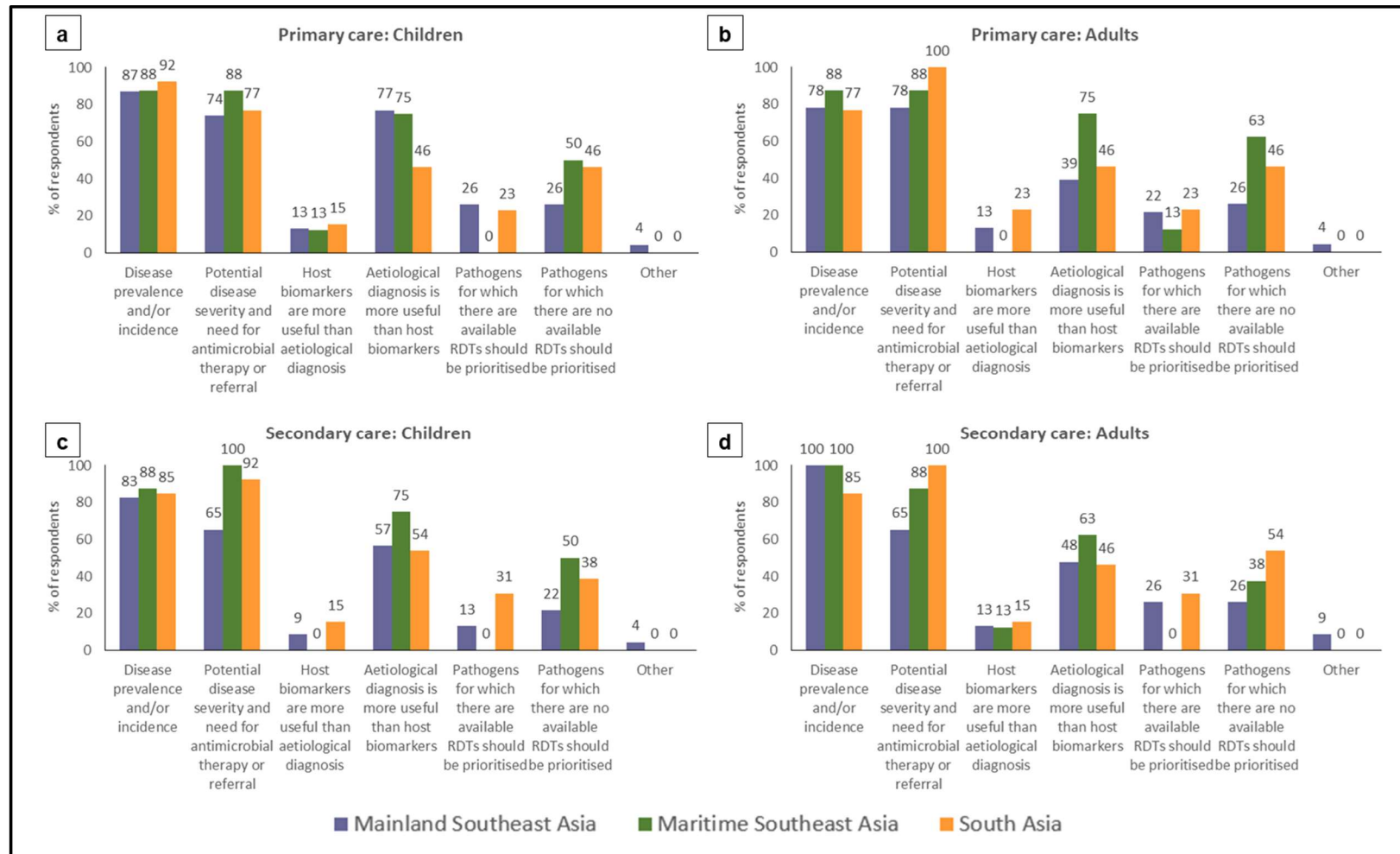


Figure 6.5. Reasons underlying the rankings made by individual expert participants of analytes which should be prioritised for inclusion in multiplex lateral flow rapid diagnostic tests for acute non-malarial fever using fingerprick blood as the test substrate, in the following patient populations: (a) Children presenting to primary care settings (b) Adults presenting to primary care settings (c) Children being admitted to secondary care settings (d) Adults being admitted to secondary care settings. Children were defined as patients aged >28 days and <15 years. RDT, rapid diagnostic test.

6.2.3 Discussion

6.2.3.1 Summary of main findings

The results of this survey indicate that multiplex LF-RDTs for non-malarial AFI to be developed for use in South and Southeast Asia should be able to diagnose dengue and enteric fever in all age groups and care settings. There was also a clear desire for the development of LF-RDTs for pathogens not readily detected by existing technologies, and for these new tests to diagnose diseases directly through antigen detection. Pathogen biomarkers were prioritised over host biomarkers, for which the only contender for inclusion was CRP although there was little agreement on use-case. The majority of the other pathogen biomarkers selected reflect the almost equal consideration given to clinical and epidemiological burdens of disease. Importantly, there was strong and early consensus that such LF-RDTs would aid clinical decision-making and that they should be incorporated into algorithm-based clinical decision support tools.

6.2.3.2 Interpretation of main findings

These results complement and extend previous work by Osborn et al. which, at the time this study was conducted, is the only other study which has attempted to address this important question. They conducted a global prioritisation exercise for a cartridge-based diagnostic test for pathogens causing severe febrile illness without a known source in patients presenting to secondary care.²⁴⁹ Unlike their study, this Delphi survey concentrated on acute NMFI in both primary and secondary care settings with patients stratified by age, included host inflammatory biomarkers as options, and adopted a more granular regional focus. Both studies had typhoidal *Salmonella* as a top priority pathogen in addition to leptospirosis and rickettsioses, but dengue and melioidosis were also recognised as other major priorities in this work, given its emphasis on rural South and Southeast Asia. Additionally, for each pathogen the perceptions of what

participants deemed to be the ideal analyte were explored, as well as the motivations and reasoning behind their choices. The findings of this study, therefore, add further layers of context which are essential to ensuring acceptability and applicability, two key challenges facing the development and implementation of any such multiplex LF-RDTs developed for use in these regions.²⁵⁰ Importantly, the results have the potential to influence the development of multiplex LF-RDTs for the diagnosis of non-malarial AFI in South and Southeast Asian settings, such as the DPP Fever Panel II Asia (Chembio Diagnostics Inc., New York, USA), which is at a late stage of development and not yet commercially available.²⁵¹ It includes a broad range of antibody and antigen analytes but does not include an assay for enteric fever, which is a key omission according to the results of this modified Delphi survey.

6.2.3.2 Strengths and weaknesses

This study has several strengths. Firstly, the modified Delphi method is well-suited to address the research question, given the challenges in collecting comprehensive epidemiological data before commencing work on multiplex LF-RDT development. The Delphi survey is a well-established technique facilitating consensus decision-making and avoiding domination by individual experts, as it is anonymous, systematic, iterative, and inclusive of a range of opinions.^{252, 253} Secondly, best practice in the conduct of Delphi surveys was followed by pre-specifying the consensus definition, panellist selection criteria, and closing criterion, and by providing timely, well-structured controlled feedback.^{244, 254} In addition, generalisability was maximised through assembling appropriately-sized panels of suitably qualified members from diverse backgrounds and countries,²⁵⁴ and by taking steps to ensure that the response rate for each panel exceeded the approximately 30% response rate typical of online surveys.²⁵⁵ Thirdly, the participant retention rate between the two rounds was high. However, by re-inviting panellists who did not participate in the first round, the possibility of false consensus was avoided and optimal representation of perspectives ensured.²⁵⁶ Fourthly, although response

stability was not a closing criterion, the consistency of the top-ranked two to three responses to each question between rounds is indicative of the reliability of the results.^{244, 257}

The principal weakness of this study is that consensus, as per the prespecified definition, was not reached with regard to analyte rankings. However, this possibility was anticipated given that the greater the number of analytes to be ranked, the less likely consensus would be achieved for all rank positions. Thus, an alternative method of analyte prioritisation based on sums of weighted scores was pre-specified. Secondly, for pragmatic reasons only experts from 12 out of the 15 LMICs in South and Southeast Asia were invited to be panellists. However, because panellist selection was weighted towards large countries both in terms of area and population, the survey results are still likely to be of considerable benefit in informing the development of multiplex LF-RDTs to be used in these regions. Thirdly, while panellist selection intended to achieve a diversity of perspectives, the majority of respondents had clinical backgrounds. Given that Delphi surveys depend heavily on expert opinion, it is possible that the preferences expressed are biased towards clinical utility with less weight placed on equally important factors such as usability, acceptability, ease of implementation, and economic viability of the putative LF-RDT, as well as market practicalities. The use of controlled feedback and, as such, the inability of panellists to engage in open discussion further limits their ability to raise such issues for consideration.²⁵⁸

6.2.3.3 Areas for future research

Several important questions for future research were identified in the course of this study. The first is the validation of setting-specific CRP use-cases and the determination of cut-off levels to ensure sufficient sensitivity and specificity for each use-case.

The second is the development and validation of antigen-based LF-RDTs for typhoidal *Salmonella*, since no such tests are currently available despite the interest demonstrated by this

study. All commercially-available tests for enteric fever detect immunoglobulin M (IgM) and/or immunoglobulin G (IgG) with moderate sensitivity and specificity.²⁵⁹ A more promising immunochromatographic dual-path platform test detecting immunoglobulin A (IgA) to *S. Typhi* haemolysin and lipopolysaccharide antigens is at a late stage of development, with pre-clinical evaluations showing sensitivity and specificity >90%. However, this test requires a reader.²⁶⁰

The last concerns implementation research on contextual and other factors influencing the uptake of commercially available non-multiplex RDTs whose analytes were included in the rank lists produced through this study. It is essential to understand the reasons why CRP and dengue RDTs, for example, are not used as widely as would be expected and why variations in uptake between settings exist,²²⁵ because these may also be applicable to any multiplex LF-RDTs developed. These reasons are setting-dependent, but are often economic, for example lack of evidence of cost-effectiveness or related to how the RDTs are funded or priced.²⁴⁰ A further economic problem is silo budgeting, where costs are incurred from the budget devoted to one area of the health system but the economic benefits are seen in another.²²⁵ This is even more problematic when the benefits are more abstract, such as reduction in antibiotic resistance. Other reasons may relate to lack of confidence of healthcare workers or policymakers on the quality and usability of the RDTs, and impacts on healthcare workflows in the target implementation settings or on public health policy more broadly.^{240, 261} For example, busy healthcare workers may have little time to integrate multi-step RDTs requiring more time than they have for a standard patient encounter. Policymakers may also have concerns about over-testing or negative impacts on clinical autonomy that reliance on testing may promote. The ability and willingness of manufacturers to navigate multiple regulatory environments, having regard to all the preceding reasons, is also crucial to ensure availability, which in turn is a prerequisite for widespread uptake. Nevertheless, it may be the case that multiplexing may

address some of the issues which have led to low uptake of single-plex assays, lending further support for multiplex LF-RDT development.

6.2.3.4 Conclusions from this study

The findings of this study are of high value in informing analyte selection for multiplex LF-RDT development. In general, while current commercially-available LF-RDT technologies do not yet permit the detection of more than two to three analytes from capillary blood, new diagnostic methods which allow detection of more analytes without an increase in sample volume are in development. Examples of these are clustered regularly interspaced short palindromic repeats (CRISPR)-, aptamer-, and Slow Off-Rate Modified Aptamer (SOMAmer)-based multiplex assays which will also facilitate adaptation of the analyte panels, making them more context-specific.^{262,}

²⁶³ The seven-item rank lists constructed will, thus, serve as a reference point as to which analytes to prioritise for inclusion in expanded panels in line with the Target Product Profile for multiplex multi-analyte diagnostic platforms for AFI published by the World Health Organization (WHO).²⁶⁴

6.3 Cost-effectiveness analysis of a putative multiplex lateral flow rapid diagnostic test for acute febrile illness in Cambodia and Bangladesh

The main finding from the modified e-Delphi survey was that multiplex LF-RDTs for NMFI in rural South and Southeast Asia should, at the minimum, be able to diagnose acute enteric fever and dengue in patients of all ages, excluding neonates, with at least 75% sensitivity and 90% specificity. CRP may also be a useful analyte in such LF-RDTs, as there is evidence for its ability to differentiate between bacterial and viral causes of AFI and, thus, promote antimicrobial stewardship by reducing inappropriate antibiotic prescriptions. Indeed, a meta-analysis of studies performed in Asia and Africa showed that a CRP level >40 mg/ml had a sensitivity of

74% [95% confidence interval (CI) 70–77%] for detecting bacterial infections in acutely febrile patients.²⁶⁵

While such a multiplex test has not yet been developed, assessment of its potential cost-effectiveness could assist in guiding the research and policymaking processes that will underpin its successful development and implementation in the target settings. This study aimed, therefore, to assess the cost-effectiveness in two tropical lower-middle income countries, one in Southeast Asia (Cambodia) and one in South Asia (Bangladesh), of a novel putative multiplex LF-RDT which measures CRP in addition to being able to diagnose acute enteric fever (e.g., by detecting typhoidal *Salmonella* antigens) and dengue (e.g., by detecting dengue NS1 antigen and dengue IgM) in patients with acute NMFI, in line with the results of the Delphi survey.

6.3.1 Methods

6.3.1.1 Setting

Cambodia is a lower-middle income country in mainland Southeast Asia with a population of 16.6 million, 75% of which live in rural areas, according to World Bank statistics from 2021.²⁶⁶
²⁶⁷ Bangladesh, in South Asia, is also a lower-middle income country but with a much larger population of 169.4 million and a rural population percentage of 61%.^{268, 269} Cambodia and Bangladesh have young populations, with 29% and 26% aged <15 years, respectively.^{270, 271} They also suffer from heavy burdens of enteric fever and dengue, prevalence estimates of which are shown in Table 6.2.

As has been described previously, in both these countries the majority of rural primary healthcare is delivered by the government through a network of PHCs and VHWs. PHCs are manned by non-medically qualified health workers who have undergone a few months' training, while VHWs are lay people with even less training.^{64, 65} Like in many other lower-middle income countries, quality of care at PHCs and by VHWs is sub-optimal owing to low clinical skill levels

and unavailability of diagnostics suited to these settings. As shown in Chapter 4, many, if not most, of these primary healthcare providers are not likely to have the skills to formulate syndromic diagnoses.

6.3.1.2 Study design and participants

This was a model-based cost-effectiveness analysis comparing current management of acute NMFI, in which a diagnosis is made solely on clinical grounds without diagnostic aids, with a hypothetical counterfactual where management is augmented by a novel putative multiplex LF-RDT able to diagnose acute enteric fever and dengue using capillary blood as the test substrate, in addition to measuring CRP levels to aid in the differentiation of bacterial and viral causes of acute NMFI not attributable to enteric fever or dengue.

The participant cohort for this modelling study was drawn from patients recruited in Battambang and Pailin provinces in Cambodia, and in Chattogram Division in Bangladesh, during the 12-month period between 21 March 2022 and 21 March 2023 for the observational study of the epidemiology of AFI in rural primary care detailed in Chapter 4. In brief, patients who presented acutely to PHCs involved in the study, and who had an axillary temperature at presentation ≥ 37.5 or $< 35.5^{\circ}\text{C}$, or who had a history of fever in the 24 hours prior to presentation, and whose presentation was not due to accident or trauma and was not within three days of routine immunisations were eligible to participate. Only patients presenting to PHCs were included, since VHWs are unable to prescribe antibiotics and diagnosing enteric fever and dengue is not within their remit.

For the purposes of this cost-effectiveness analysis, only those participants older than 28 days residing in designated villages which were part of the South and Southeast Asian Community-based Trials Network (SEACTN) Rural Febrile Illness (RFI) project (82 villages in Cambodia and 143 villages in Bangladesh) were included,⁵³ to allow calculation of incidence

estimates. In line with the use-case for the multiplex LF-RDT mentioned earlier in this chapter, neonates were specifically excluded as fever in this age group generally requires assessment in hospital.²⁴⁸ The total populations of the Cambodian and Bangladeshi study villages were 65,567 and 115,962 persons, respectively. During this 12-month period, 5,430 and 9,585 patients residing in study villages and who were not neonates were recruited in Cambodia and Bangladesh, respectively. Dividing these by the total populations of the study villages yielded annual incidence estimates of patients with acute febrile illness who sought care at PHCs per 100,000 population of 8,262 in Cambodia and 8,266 in Bangladesh. All were tested with malaria RDTs but in Cambodia none returned a positive result and only 137 (1.4%) tested positive in Bangladesh. Aetiological data from the observational study are not yet available, hence country-specific published estimates for the incidence of enteric fever and dengue were used in the models.²⁷²⁻²⁷⁴ Age group-specific incidence estimates for the following age groups by country are shown in Table 6.2: children <5 years old, children 5–14 years old, and adults (defined as those aged ≥ 15 years, for consistency with the definition used in the observational study).

6.3.1.3 Base case

A decision tree model was constructed to compare the standard of care with multiplex LF-RDT-aided management for the abovementioned age groups. Like previous economic evaluations of other LF-RDTs in the South and Southeast Asian context,²⁷⁵⁻²⁷⁸ this model type was selected on the basis of the multiplex LF-RDT being similar to other well-established RDTs, such as those for malaria, in terms of ease of use and interpretation, short time to diagnosis, established acceptability to patients and health workers, and that the principal factor being influenced is clinical decision-making. The structure of the decision tree is shown in Figure 6.6, and a summary of the recommended interpretation and management for positive test components is shown in Table 6.3. Separate analyses were performed for Bangladesh and Cambodia. Model

parameters were derived from a combination of data from the observational study as well as data from the published literature, and are shown in Table 6.2.

The outcomes of interest were disability-adjusted life-years (DALYs) averted for enteric fever, hospitalisations averted for dengue, total antibiotic prescriptions, inappropriate empirical antibiotic prescriptions averted, and total costs. A health system plus limited societal perspective where costs of antibiotic resistance were incorporated was adopted. As was done in the cost-effectiveness analysis reported in Chapter 5 ('Evaluation of pulse oximetry in the primary care management of acute febrile illness'), the latter cost was calculated using the three-component model constructed by Shrestha et al. with broad-spectrum penicillins and quinolones as the antibiotic classes of interest and adapted for the Cambodian and Bangladeshi contexts based on their gross domestic products (GDP) relative to that of Thailand (the context in which the estimates were derived); the three components are the correlation coefficients between human antibiotic consumption and subsequent resistance, the economic costs of antibiotic resistance for five sentinel pathogens, and consumption data for antibiotic classes driving resistance in these organisms.²⁰⁰ Acquisition costs of antibiotics were calculated for each age group to reflect the variation in antibiotic course prescriptions in each group.

Costs were adjusted for inflation to the 2022 cost year based on the relevant country Consumer Price Indices, and expressed in US dollars. The time horizon was one year, and no discounting or age-weighting was applied, in line with guidance established since the Global Burden of Disease 2010 report,²⁰¹ and given the acute nature of the diseases of interest. Thus, although the modelled time period was one year, the DALYs accrued within this time period included the full years of life lost from the patient's life expectancy. Cost-effectiveness was expressed as an incremental cost-effectiveness ratio (ICER), in terms of an incremental cost per DALY. Currently neither Bangladesh or Cambodia have explicit or accepted willingness-to-pay, or cost-effectiveness, thresholds. As such, the means of the opportunity cost-based thresholds

for Bangladesh and Cambodia reported by Woods et al. were used and inflated to 2022 values (\$357 for Cambodia and \$388 for Bangladesh).²⁷⁹ For comparison, and given this uncertainty, the less conservative figure of the national per capita GDP was also used as a secondary willingness-to-pay threshold. This is in line with the lower bound for the willingness-to-pay threshold of one to three times per capita GDP recommended by the WHO CHOosing Interventions that are Cost-Effective (WHO-CHOICE) programme, which does not take into account opportunity costs.²⁸⁰ The 2022 per capita GDP values for Cambodia and Bangladesh are \$1,765 and \$2,687, respectively.^{281, 282}

All analyses were performed using Excel (Microsoft, Washington, USA).

Parameter	Cambodia	Bangladesh	Data source(s)
Cost of multiplex LF-RDT, US\$	5 (1–15)		Ref ²⁶⁴
Annual incidence of acute NMFI per 100,000 population presenting to primary healthcare providers	8,262	8,266	Data from observational study described in Chapter 4
Percentage of patients with acute NMFI presenting to primary healthcare providers in the following age groups			
(a) Children <5 years	2.04	3.81	
(b) Children 5 – 14 years	14.8	17.1	
(c) Adults	83.2	79.1	
Mean age of patients with acute NMFI presenting to primary healthcare providers, years	34	28	Data from observational study described in Chapter 4
Annual incidence of enteric fever per 100,000 population	211.5 (181.1–794.1)	641.2 (527.2–779.8)	Ref ²⁷²
Annual incidence of dengue per 100,000 population	1030 (927–1133)	1644 (1507–1712)	Ref ^{273, 274}
Probability of non- enteric fever bacterial cause for acute febrile illness, %	15.9 (10–20)		Ref ⁴⁴
Sensitivity of clinical assessment for diagnosing enteric fever, %	50 (40–56.8)		Adapted from ref ²⁸³ , using the point estimates from this study as the upper bounds for the model
Specificity of clinical assessment for diagnosing enteric fever, %	75 (60–87.9)		
Sensitivity of clinical assessment for diagnosing dengue, %	93 (86–96)		Ref ²⁸⁴
Specificity of clinical assessment for diagnosing dengue, %	31 (18–48)		
Sensitivity of clinical assessment for diagnosing bacterial cause for acute febrile illness, %	70.2 (65–75)		Ref ²⁶⁵
Specificity of clinical assessment for diagnosing bacterial cause for acute febrile illness, %	56.8 (52–62)		
Sensitivity of enteric fever antigen test in multiplex LF-RDT, %	85 (75–90)		Assumed

Specificity of enteric fever antigen test in multiplex LF-RDT, %	95 (90–98)	
Sensitivity of combined dengue NS1 antigen and IgM test in multiplex LF-RDT, %	85 (75–90)	
Specificity of combined dengue NS1 antigen and IgM test in multiplex LF-RDT, %	95 (90–98)	
Sensitivity of CRP test (cut-off 40 mg/L) in multiplex LF-RDT for diagnosing bacterial cause for acute febrile illness, %	74 (70–77)	Ref ²⁶⁵
Specificity of CRP test (cut-off 40 mg/L) in multiplex LF-RDT for diagnosing bacterial cause for acute febrile illness, %	84 (81–87)	
Duration of illness for enteric fever, days	14 (7–21)	Ref ²⁸⁵
Mortality from enteric fever (diagnosed and appropriately treated), %	0.75 (0.6–0.9)	Ref ²⁸⁶
Mortality from enteric fever (undiagnosed), %	1 (0.8–1.2)	Ref ²⁸⁶
Percentage with undiagnosed enteric fever who are hospitalized for severe disease, %	12 (0.8–50)	Assumed
Percentage with diagnosed enteric fever who are hospitalized for severe disease, %	6 (0.4–25)	Ref ²⁸⁷
Length of stay of patients hospitalized for severe enteric fever, days	6 (3–9)	
Disability weight for enteric fever not requiring hospitalisation	0.051 (0.032–0.074)	Ref ²⁸⁸
Disability weight for enteric fever requiring hospitalisation	0.133 (0.088–0.190)	
Duration of illness for dengue, days	4.5 (2–7)	Ref ^{289, 290}
Percentage diagnosed with dengue who are hospitalised, %	13.6 (12–15)	Ref ²⁹¹
Length of stay of patients hospitalized for dengue, days	4.5 (2–7)	Ref ^{289, 290}

Cost of one seven-day course of ciprofloxacin (first-line enteric fever treatment), US\$	0.46 for children <5 years, 0.91 for children 5–14 years, 1.82 for adults	0.46 for children <5 years, 0.91 for children 5–14 years, 1.82 for adults	Based on price per 500 mg tablet from Battambang PHD (personal communication 20 March 2023) for Cambodia, and mean of highest and lowest prices per 500 mg tablet from ref ²⁹² for Bangladesh
Cost of antimicrobial resistance due to one course of ciprofloxacin, US\$	4.65 (3.72–5.58)	7.07 (5.66–8.48)	GDP per capita-adjusted cost of antimicrobial resistance due to one course of ciprofloxacin in Thailand described in ref ²⁰⁰
Cost of one five-day course of amoxicillin (empirical antibiotic if bacterial cause suspected for acute febrile illness), US\$	0.90 for children <5 years, 1.80 for children 5–14 years, 3.60 for adults	0.45 for children <5 years, 0.91 for children 5–14 years, 1.82 for adults	Based on price per 250 mg tablet from Battambang PHD (personal communication 20 March 2023) for Cambodia, and mean of highest and lowest prices per 250 mg tablet from ref ²⁹³ for Bangladesh
Cost of antimicrobial resistance due to one course of amoxicillin, US\$	2.49 (1.99–2.99)	3.79 (3.03–4.55)	GDP per capita-adjusted cost of antimicrobial resistance due to one course of amoxicillin in Thailand described in ref ²⁰⁰
Cost of one primary healthcare encounter, US\$	6.89 (5.51–8.27)	2.83 (2.26–3.39)	Ref ^{294, 295}
Cost of one occupied hospital bed-day, US\$	32.39 (28.66–34.29)	22.33 (17.86–26.79)	
Weighted cost of hospitalisation for dengue, US\$	10.36 (8.29–12.43)	5.48 (4.38–6.58)	
Weighted cost of hospitalisation for enteric fever diagnosed in primary care, US\$	18.14 (14.51–21.77)	10.70 (8.56–12.84)	
Weighted cost of hospitalisation for enteric fever not diagnosed in primary care, US\$	29.38 (23.50–35.26)	18.56 (14.85–22.27)	

Table 6.2. Decision tree model parameters for the base case analysis. CRP, C-reactive protein; GDP, gross domestic product; PHD, Provincial Health Department; LF-RDT, lateral flow rapid diagnostic test; ref, reference. Costs were adjusted for inflation and expressed in 2022 US dollars.

Positive multiplex LF-RDT component	Recommended interpretation	Recommended management
Dengue	Patient has dengue	Referral to hospital for admission
Enteric fever	Patient has enteric fever	Ciprofloxacin
CRP (>40 mg/L)	Patient has a bacterial infection (not enteric fever if enteric fever test is negative, otherwise enteric fever if enteric fever test also positive)	Amoxicillin unless enteric fever test also positive, in which case ciprofloxacin
None	Patient has a viral infection	No antibiotics

Table 6.3. Summary of recommended interpretation and management for positive multiplex LF-RDT test components. LF-RDT, lateral flow rapid diagnostic test.

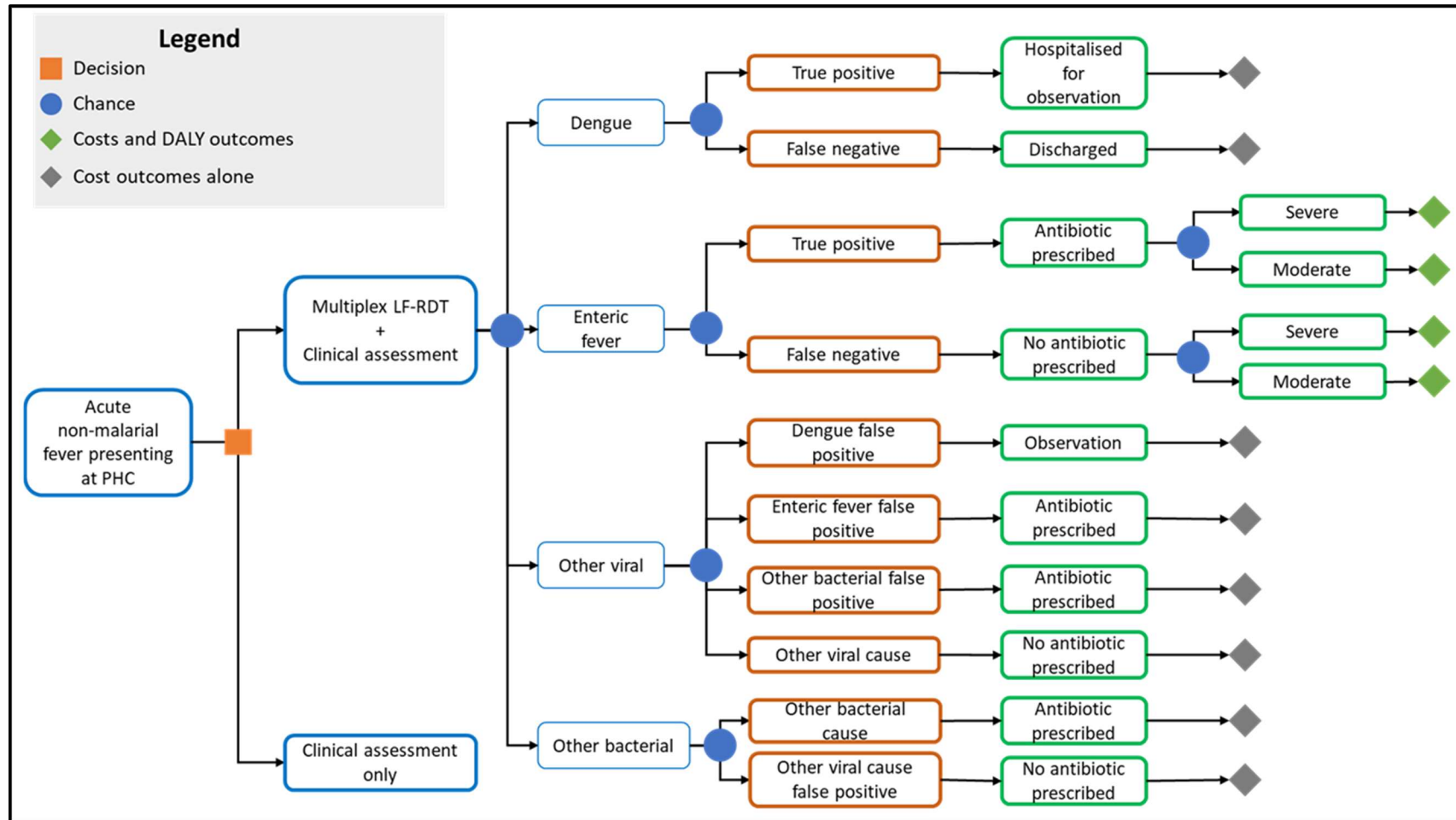


Figure 6.6. Decision tree model structure. The chance nodes arising from the ‘Clinical assessment only’ internal node are similar to those arising from the ‘Multiplex LF-RDT + Clinical assessment’ internal node. Parameters are shown in Table 6.2. DALY, disability-adjusted life year; LF-RDT, lateral flow rapid diagnostic test; PHC, primary health centre.

6.3.1.4 Assumptions

Several assumptions were used in the model. Firstly, the sensitivity and specificity of the multiplex LF-RDT for both enteric fever and dengue was assumed to be 85% (range 75–90%) and 95% (range 90–98%), respectively. These values were chosen bearing in mind the WHO-recommended performance characteristics for multiplex rapid diagnostic tests for acute febrile illness,²⁹⁶ the minimum performance metric requirements for a diagnostic assay to be clinically useful,²⁹⁷ and the constraints placed on sensitivity with a very small volume of substrate.²³⁷ This approach is well-established when performing economic evaluations of interventions.²⁹⁸

Secondly, ciprofloxacin was assumed to be the appropriate treatment for all cases of enteric fever, notwithstanding the increasing rates of drug resistance in the region.²⁹⁹ Thirdly, full compliance by healthcare workers with multiplex LF-RDT-guided clinical management and by patients with their management plans was assumed. Fourth, amoxicillin was assumed to be the default antibiotic prescription for acute NMFI not caused by enteric fever and for which a bacterial cause is suspected. This assumption was made given that amoxicillin was the antibiotic most prescribed for undifferentiated fever in these settings based on preliminary analysis of the data from the observational study performed at the time this cost-effectiveness analysis was conducted,⁵³ and is also in line with the limited formularies available in rural Cambodian and Bangladeshi PHCs. Fifth, the cost of the multiplex LF-RDT was assumed to be \$5, the optimal full cost to the payer recommended by the WHO for multiplex multi-analyte diagnostic tests for acute febrile illness.²⁹⁶ Cost containment is also aided by the operational similarity of the multiplex LF-RDT to malaria rapid diagnostic tests, and its rollout leveraging existing malaria control programme training and monitoring activities. Sixth, in the absence of detailed information on age-group specific disease incidence, the same country-wide incidence estimates were assumed to apply across all age groups. Seventh, it was assumed that undiagnosed (and, therefore, inappropriately treated) enteric fever cases were twice as likely to

require hospitalisation than correctly diagnosed and treated cases, but in the absence of data it was conservatively assumed that correct diagnosis and treatment of enteric fever reduced mortality from 1% to 0.75%. Eighth, to avoid overcomplicating the model structure with all of the possible test result combinations from the multiplex LF-RDT, it was assumed that false positives could only arise from the 'other viral infection' group (e.g., no true dengue cases could produce false positive test results for enteric fever and vice versa). Lastly, it is important to note that the main use-case of the dengue component of the multiplex LF-RDT is minimisation of inappropriate referrals to hospital. However, since it cannot predict development of severe dengue (which occurs around the seventh day of illness) and for which treatment is supportive only, we assumed that the intervention would have no mortality impact on dengue true positives and false negatives. Of note, while all patients diagnosed with dengue at the primary care level will be referred to hospital, only 13.6% will ultimately be admitted as some false-positives will be given alternative diagnoses and some true-positives will not be admitted.²⁹¹

6.3.1.5 Sensitivity and scenario analyses

The complexity of this model is higher than that constructed for the cost-effectiveness analysis described in Chapter 5, owing to the number of components of the multiplex LF-RDT and the correspondingly higher number of possible diagnoses. Therefore, a more sophisticated approach to sensitivity analysis was taken compared to the simplified deterministic method used previously.

Both deterministic (one-way) and probabilistic sensitivity analyses were performed. In the former, outcomes were assessed using the lower and upper estimates of each of the model parameters sequentially to assess the effect of uncertainty in individual parameters, displaying these as a tornado plot. For parameters without available confidence intervals and standard deviations to inform the upper and lower bounds, a default variation of 20% of the mean parameter value was assumed.

In the probabilistic sensitivity analysis, standard assumptions were made regarding the distribution of each parameter (β for individual probabilities and percentages, Dirichlet for multivariate probabilities and percentages, and γ for costs). Parameter values were randomly drawn from their respective distributions in a Monte Carlo simulation, with results from 1,000 model iterations displayed in the form of a scatter plot. Mortality from enteric fever was varied such that undiagnosed enteric fever would always have a value equal to or higher than that of diagnosed and appropriately treated enteric fever. A cost-effectiveness acceptability curve was also constructed to illustrate the how the estimated probability of the cost-effectiveness of the intervention changes at different willingness-to-pay thresholds.

Four scenario analyses were also performed. In the first, the percentage sensitivities and specificities of each multiplex LF-RDT component were varied in increments of 10% (range 60–90%) with the condition that they totalled 150%, which is the minimum requirement for a test to be clinically useful.²⁹⁷ This was first done singly while retaining the base case performance characteristics of the remaining two components, and then simultaneously for all three components. The average net monetary benefits per patient tested and threshold cost-effective prices for each of these test performance characteristic combinations were ascertained to determine the most cost-effective potential combination, in the event the technical difficulties associated with producing such a multiplex assay precluded achievement of the performance characteristics described in the base case. The second assessed the impact future upskilling of primary health workers in clinical diagnosis would have on the cost-effectiveness of the multiplex LF-RDT. For this scenario, it was assumed that health workers would be able to formulate syndromic diagnoses based on the criteria used in the observational study and that multiplex LF-RDTs would only be applied to acutely febrile patients with truly no localising symptoms, details of which are shown in Table 6.4, in keeping with the syndromic presentation of the vast majority of enteric fever and dengue cases. In the third, the uncertainty in mortality

benefit was evaluated through scenarios in which there was no benefit and a 50% reduction in mortality from enteric fever arising from use of the multiplex LF-RDT, respectively. Finally, the impact of the societal cost of antimicrobial resistance on cost-effectiveness was assessed by excluding this cost from the model.

Parameter	Cambodia	Bangladesh	Data source
Annual incidence of acute NMFI with no localising symptoms per 100,000 population presenting to primary healthcare providers	5,259	955	Data from observational study described in Chapter 4
Percentage of annual incidence of acute NMFI with no localising symptoms per 100,000 population presenting to primary healthcare providers in			
(a) Children <5 years	2.64	3.52	
(b) Children 5 – 14 years	13.1	13.6	
(c) Adults	84.3	82.8	
Mean age of patients with acute NMFI with no localising symptoms presenting to primary healthcare providers, years	34	28	

Table 6.4. Data on incidence of non-malarial febrile illness with no localising symptoms used to parameterise the model in a scenario where the intervention was only used in such patients. The remaining model parameters were those used in the base case analysis (Table 6.2). NMFI, non-malarial febrile illness.

6.3.2 Results

The results of this cost-effectiveness analysis are reported here in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline.²¹⁷ The completed CHEERS checklist can be found in Appendix 6.3.

6.3.2.1 Base case

In Cambodia, compared to the current standard of care, augmentation of clinical assessment with the novel multiplex LF-RDT nearly tripled the percentage of correct diagnoses from 2,717/8,262 (33%) to 7,505/8,262 (91%) annually, leading to 497 (93%) fewer unnecessary hospitalisations for dengue-negatives. It also resulted in 523 (32%) fewer inappropriate antibiotic prescriptions, and 344 (13%) fewer antibiotic prescriptions overall. On a per-patient basis, hospitalisation costs were reduced from \$7.93 to \$2.20, costs attributable to antimicrobial resistance from \$1.21 to \$0.81, and total costs from \$9.90 to \$8.82. The number of DALYs averted per patient was 0.0012, resulting in the multiplex LF-RDT being dominant when compared with both lower and higher willingness-to-pay thresholds.

In contrast, the intervention more than doubled the number of correct diagnoses from 3,468/8,266 (42%) to 7,455/8,266 (90%) in Bangladesh, resulting in 548 (36%) fewer inappropriate antibiotic prescriptions, although the overall antibiotic prescription rate was little changed (29.3% with use of the multiplex LF-RDT vs. 30.6% without). There were 404 (93%) fewer unnecessary hospitalisations for dengue-negatives, helping to drive the average hospitalisation cost down from \$4.70 to \$2.11. The magnitude of antimicrobial resistance-related costs averted per patient was similar to that seen Cambodia at \$0.40. In this setting, multiplex LF-RDT usage was associated with a slightly higher number of DALYs averted per patient at 0.0041 at an average total cost of \$1.96, resulting in an ICER of \$482 per DALY averted i.e., slightly higher than the lower willingness-to-pay threshold of \$388 per DALY averted but well

below the higher threshold of \$2,687 per DALY averted. At the lower threshold, the threshold price for the multiplex LF-RDT to be cost-effective in Bangladesh was \$4.62 per unit. Table 6.5 compares the key findings of the base-case analysis for Cambodia and Bangladesh.

An important finding is that the increased ability to diagnose enteric fever correctly with the multiplex LF-RDT also reduced inappropriate empirical prescribing of ciprofloxacin considerably (by 70% in Cambodia and 47% in Bangladesh), moving the bulk of inappropriate antibiotic prescribing towards amoxicillin. This is beneficial because ciprofloxacin, with its much broader spectrum of activity compared to amoxicillin, is a bigger driver of antimicrobial resistance and, as such, is associated with a higher societal cost. Additionally, the intervention helps target ciprofloxacin prescriptions towards those in which they are most required i.e., patients with enteric fever.

	Cambodia	Bangladesh
Incremental cost per patient, \$	-1.08	1.96
DALYs averted per patient	0.0012	0.0041
Incremental cost per DALY averted, \$	Cost-saving	482
Lower willingness-to-pay threshold (per DALY averted), \$	357	388
Higher willingness-to-pay threshold (per DALY averted), \$	1,765	2,687
Cost-effectiveness of multiplex LF-RDT	Dominant	Above the lower willingness-to-pay threshold but below the higher threshold

Table 6.5. Key findings of the base-case analysis for Cambodia and Bangladesh. The lower willingness-to-pay thresholds were derived from the means of the opportunity cost-based thresholds for Bangladesh and Cambodia reported by Woods et al.²⁷⁹ inflated to 2022 values. The higher willingness-to-pay thresholds are the 2022 national per capita GDP for each country. DALY, disability-adjusted life-year; LF-RDT, lateral flow rapid diagnostic test.

6.3.2.2 Sensitivity analyses

As can be seen in the results of the deterministic sensitivity analysis shown in Figure 6.7, Cambodia and Bangladesh share seven parameters impacting cost-effectiveness, but their relative importance differs greatly between the two countries. The vast majority of these factors do not relate to the multiplex LF-RDT. The effect of varying the unit price had the same impact on net monetary benefit in both countries, and was of primary importance in both countries respect to the cost-effectiveness thresholds. Differences in mortality between diagnosed and appropriately treated enteric fever and undiagnosed enteric fever had a greater impact than cost of healthcare provision in Bangladesh while the converse is true for Cambodia, reflecting the higher incidence of enteric fever in the former.

The results of the probabilistic sensitivity analysis are shown in Figure 6.8. In Cambodia, the majority of the incremental cost-effect simulation results, as well as the mean result, lie below the x-axis of the scatter plot as well as the cost-effectiveness threshold line, indicating that the ICER of augmenting clinical assessment with the multiplex LF-RDT is likely to be cost-saving as well as fall below the willingness-to-pay threshold, with relatively little uncertainty regarding the number of DALYs averted [Figure 3a(i)]. This is reflected in the associated cost-effectiveness acceptability curve which shows that the ICER of the intervention had a much higher probability of being below the willingness-to-pay threshold, at all willingness-to-pay thresholds including at \$10,000 per DALY averted i.e., in almost 70% of simulations the intervention was cost-saving [Figure 3a(ii)]. In other words, the probability that the data are consistent with the true ICER falling below this threshold is much higher for the intervention than standard of care. In Bangladesh, where the spread of incremental cost-effect pairs is more dispersed i.e., there is higher uncertainty as to the cost-effectiveness of the intervention [Figure 3b(i)]. The point at which 50% of the probabilistic ICERs fell below the willingness-to-pay threshold in Bangladesh occurred when the threshold value exceeded \$500 per DALY averted;

by a threshold value of \$1,000, approximately 67% of probabilistic ICERs fell below the threshold [Figure 3b(ii)].

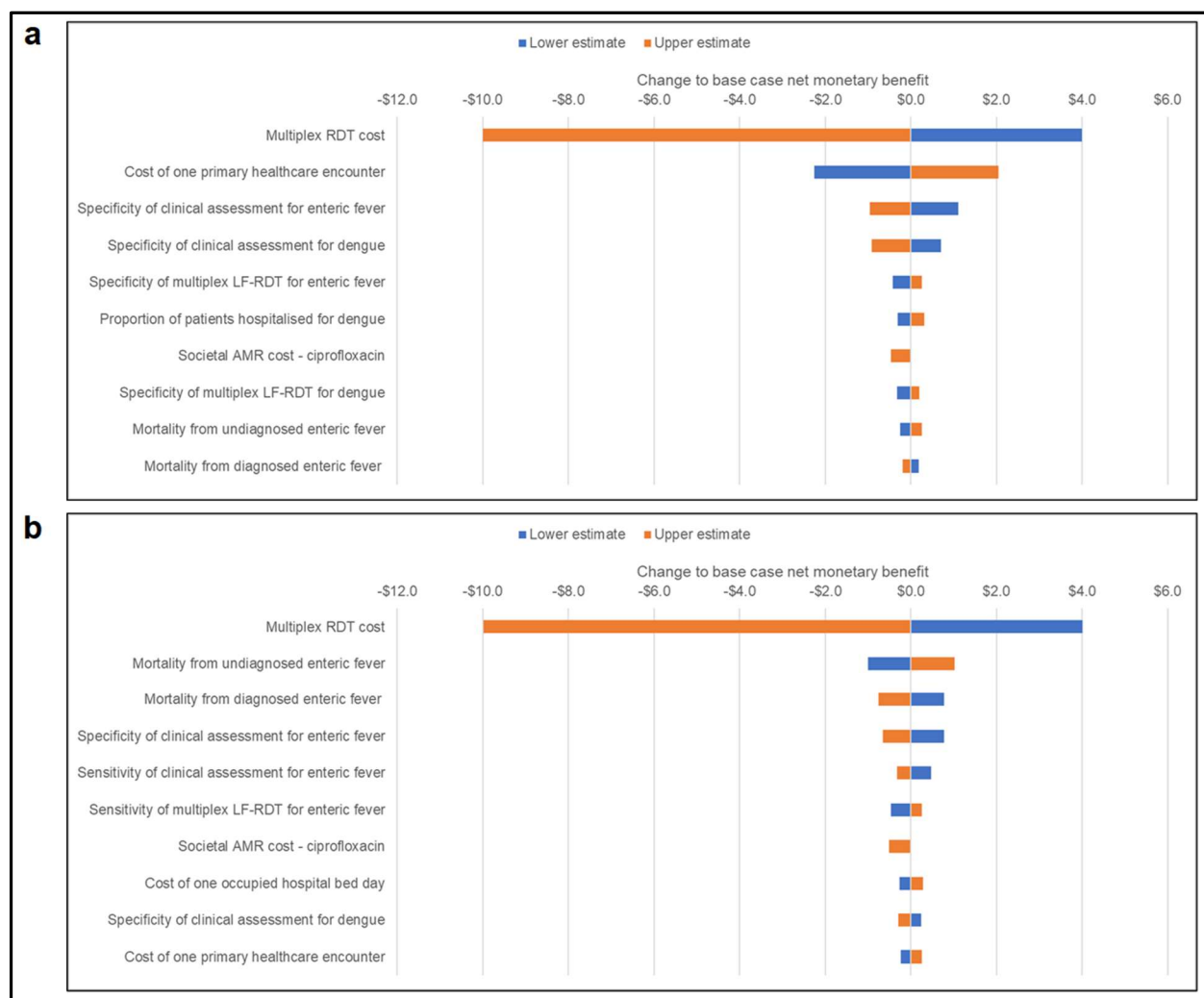


Figure 6.7. Tornado plots for (a) Cambodia and (b) Bangladesh showing the ten most important parameters affecting cost-effectiveness in each country. AMR, antimicrobial resistance; LF-RDT, lateral flow rapid diagnostic test.

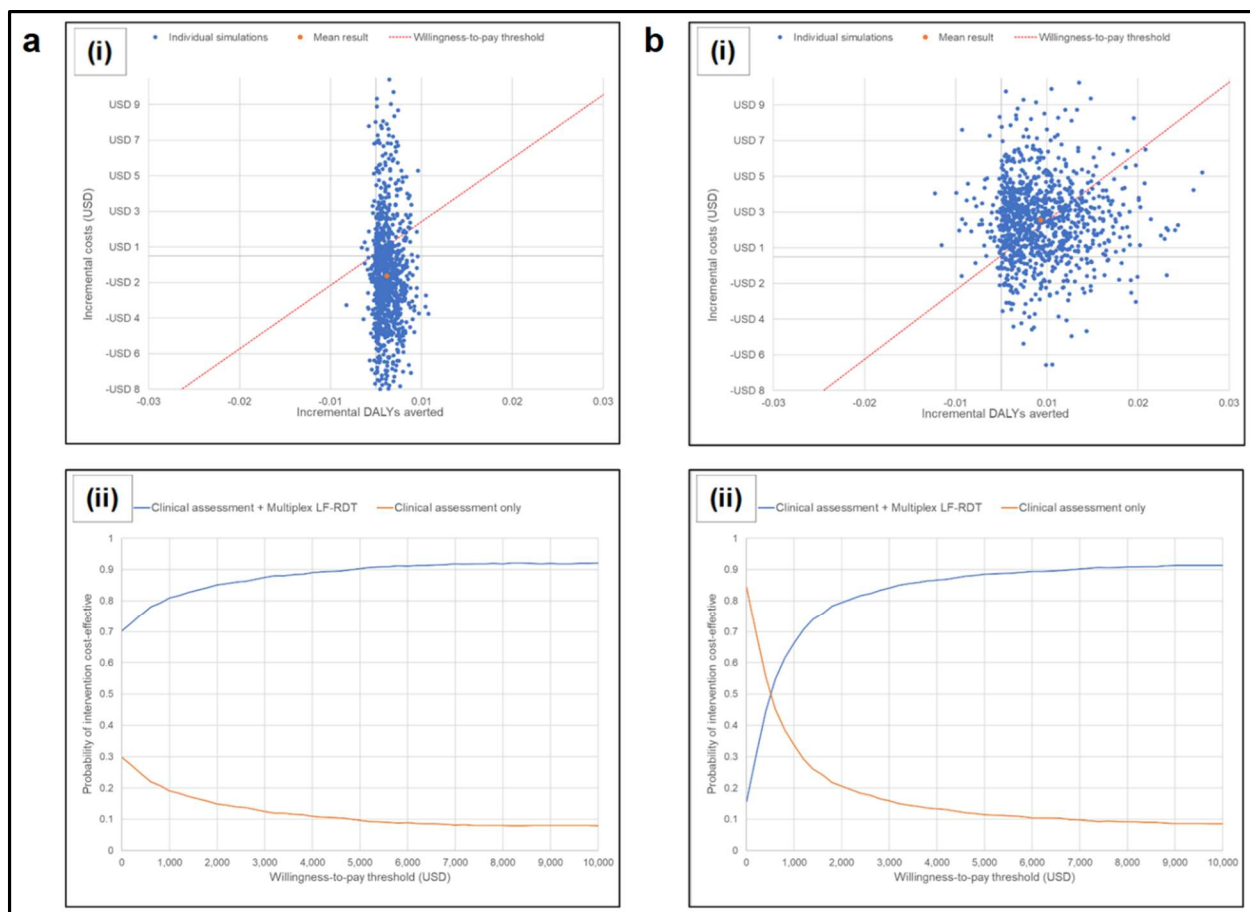


Figure 6.8. (i) Scatter plots of incremental cost-effect pairs for augmentation of clinical assessment with the multiplex LF-RDT obtained from 1,000 Monte Carlo model simulations randomly drawing parameter values from their respective distributions for (a) Cambodia and (b) Bangladesh. Standard assumptions were made regarding the distribution of each parameter (β for individual probabilities and percentages, Dirichlet for multivariate probabilities and percentages, and γ for costs). The conservative opportunity cost-based willingness-to-pay thresholds of \$357 and \$388 per DALY averted in Cambodia and Bangladesh, respectively were used. (ii) Cost-effectiveness acceptability curves for (a) Cambodia and (b) Bangladesh showing how the estimated probability of the cost-effectiveness of clinical assessment augmented by the multiplex LF-RDT vs. clinical assessment alone changes at different willingness-to-pay thresholds. DALY, disability-adjusted life-year; LF-RDT, lateral flow rapid diagnostic test; USD, US\$ at 2022 values.

6.3.2.3 Scenario analyses

When the sensitivity and specificity of the multiplex LF-RDT components were varied individually and together on the condition that they totalled 150%, increasing specificity of any component at the expense of sensitivity resulted in increasing net monetary benefit per patient tested, thus allowing a higher threshold cost-effective price for the multiplex LF-RDT (Table 6.6). This was particularly true for CRP, where a slight increase in specificity from 84% to 90% yielded average net monetary benefits greater than those seen in the base case analysis of \$1.49 and -\$0.38 in Cambodia and Bangladesh, respectively. Nevertheless, this was still insufficient to make the ICER of the multiplex LF-RDT fall beneath the most conservative willingness-to-pay threshold in Bangladesh. Reducing the sensitivity of the dengue component from 85% to 60% and specificity from 95% to 90% also marginally increased the net monetary benefit per patient tested in Bangladesh, although again this was insufficient to bring the ICER below the lower willingness-to-pay threshold. Even if all three components had the same sensitivity and specificity values of 60% and 90%, respectively, the multiplex LF-RDT would still be dominant in Cambodia and the ICER a little higher than the lower willingness-to-pay threshold in Bangladesh.

Using the multiplex LF-RDT only on patients with fever with no true localising symptoms reduced the ICERs greatly (i.e., the tests were used more efficiently), with the intervention remaining dominant in Cambodia and below the lower willingness-to-pay threshold in Bangladesh with an ICER of \$145 per DALY averted. Unsurprisingly, increasing the mortality benefit of appropriately diagnosing and treating enteric fever from 0.25% to 0.5% also drove down the cost per DALY averted in Bangladesh to \$267, lower than the conservative willingness-to-pay threshold of \$388. This cost was multiplied nearly ten-fold to \$2,417 per DALY averted were there no mortality benefit, which considerably exceeds the lower threshold but remains below the upper per capita GDP-based threshold of \$2,687. In Cambodia, however,

multiplex LF-RDT-guided clinical management remained dominant regardless of whether it had an effect on enteric fever mortality, reflecting the findings of the deterministic sensitivity analysis. The dominance of the intervention in Cambodia was also seen when the cost of antimicrobial resistance was excluded from the model, whereas this raised the ICER in Bangladesh from \$482 to \$579 per DALY averted, which is still clearly under the upper willingness-to-pay threshold.

Multiplex LF-RDT component	Sensitivity, %	Specificity, %	Cambodia		Bangladesh	
			Average net monetary benefit*, US\$	Threshold cost-effective price, US\$	Average net monetary benefit*, US\$	Threshold cost-effective price, US\$
Enteric fever diagnostic test	90	60	-1.40	3.60	-2.23	2.77
	80	70	-0.70	4.30	-2.11	2.89
	70	80	0.01	5.01	-1.99	3.01
	60	90	0.72	5.72	-1.87	3.13
Dengue diagnostic test	90	60	-0.85	4.15	-1.34	3.66
	80	70	-0.07	4.93	-0.97	4.03
	70	80	0.71	5.71	-0.60	4.40
	60	90	1.49	6.49	-0.24	4.76
CRP test	90	60	0.48	5.48	-1.18	3.82
	80	70	0.93	5.93	-0.82	4.18
	70	80	1.39	6.39	-0.45	4.55
	60	90	1.84	6.84	-0.09	4.91
All components	90	60	-4.09	0.91	-3.49	1.51
	80	70	-2.54	2.46	-2.93	2.07
	70	80	-0.83	4.17	-2.25	2.75
	60	90	1.04	6.04	-1.44	3.56

Table 6.6. Effect of varying sensitivity and specificity for each multiplex LF-RDT component singly while maintaining the test performance of the remaining two as per the base case, and simultaneously for all components. The base case average net monetary benefits were \$1.49 and -\$0.38 in Cambodia and Bangladesh, respectively. Threshold cost-effective prices were calculated by subtracting average net monetary benefits from the \$5 base case cost of the multiplex LF-RDT. CRP, C-reactive protein; LF-RDT, lateral flow rapid diagnostic test. Costs were adjusted for inflation and expressed in 2022 US dollars. *The average net monetary benefit was calculated based on a multiplex LF-RDT price of \$5 per unit.

6.3.3 Discussion

6.3.3.1 Summary of main findings

The principal finding from this cost-effectiveness analysis is that a putative multiplex LF-RDT using capillary blood as the test substrate with the ability to diagnose enteric fever and dengue, and measure CRP to distinguish between other viral and non-viral causes of acute fever would be dominant, i.e., both clinically superior and cost-saving, in Cambodia.

In Bangladesh, the ICER of implementing the multiplex LF-RDT would be below the widely used per capita GDP willingness-to-pay threshold, but not with respect to the more conservative opportunity cost-based threshold. This is borne out by the results of the probabilistic sensitivity analyses. Despite the number of DALYs averted through the use of the multiplex LF-RDT in Bangladesh being more than triple that in Cambodia, as reflected by higher disease incidences in the former, cost savings were fewer due to the lower societal cost of antimicrobial resistance and lower cost of healthcare provision in both hospital and primary care settings. As a result, the average net monetary benefit per patient tested of more judicious antibiotic prescribing, avoiding hospital admission in those testing negative for dengue, and more accurate diagnosis and management of enteric fever were unable to exceed the average total cost, 55% of which comprised the \$5 price of a multiplex LF-RDT.

However, it should be noted that the estimates of the cost-effectiveness of the multiplex LF-RDT produced in this analysis were conservative. For one, only a modest health benefit from improved diagnosis was incorporated in the model i.e., reduced hospitalisations and mortality from enteric fever, with no other mortality or morbidity benefit included for improved diagnosis and treatment of dengue and other bacterial or viral infections. Given the low levels of incremental costs, even small further increases in the estimated incremental DALYs averted would increase the cost-effectiveness of the multiplex LF-RDT substantially, as can be seen in

Bangladesh where a reduction of enteric fever mortality in the intervention arm of the model from the base case figure of 0.75% to 0.5% drove the cost per DALY averted considerably under the conservative opportunity-cost based willingness-to-pay threshold.

6.3.3.2 Interpretation of main findings

As can be seen from the results of the Delphi survey reported earlier in this chapter, the need for such a multiplex LF-RDT in rural South and Southeast Asia is urgent. However, no evaluation of its potential cost-effectiveness has been conducted, much less at a country level. The principal contribution of the results of this study, therefore, is that they provide guidance for researchers and industry partners working on diagnostics for use in LMICs in terms of performance characteristic and pricing targets, as well as providing policymakers with a baseline economic viewpoint on which to make decisions concerning such tests in future. For example, the price of the multiplex LF-RDT could be set higher in high-income countries (HICs), should it be marketed there, in order to lower the price in LMICs, thus ensuring cost-effectiveness in as many countries as possible.

The results also bolster the limited evidence provided by other cost-effectiveness analyses in South and Southeast Asian primary care settings of LF-RDTs which singularly test for enteric fever, dengue, and CRP (or other host biomarker associated with bacterial infection). In two modelling studies set in rural Laos, the pathogen-agnostic nature of CRP was likely to be highly cost-effective despite heterogeneity in the causes of NMFI. This was true when an antibiotic prescribing threshold of 40 mg/L, similar to that used in this study, was applied, and also when a more liberal threshold of 20 mg/L was used.^{275, 277} In one of these studies, a dengue LF-RDT with both sensitivity and specificity of 95% was dominant.²⁷⁵ Another modelling study of a commercially-available typhoid IgM LF-RDT in Cambodian children with suspected enteric fever did not find it to be cost-effective, but used an intermediate outcome measure (additional treatment success), rather than DALY averted. Moreover, the sensitivity of this test

was only 59%, as opposed to 85% in this study.²⁷⁶ There are even fewer studies pertaining to South Asia, but a modelling study of CRP-guided antibiotic prescription in Afghan primary care facilities concluded that it was highly cost-effective with an incremental cost of \$14 per additional correctly treated case, even with a very low cut-off of 10 mg/L.²⁷⁸ Notably, the costs of the tests used in these studies were all <\$5. Considering the results of this analysis in the light of these others, the multiplex LF-RDT would likely be cost-effective in at least several other South and Southeast Asian countries, especially given the high prevalences of enteric fever and dengue in the region. For instance, a shift from diagnosing dengue clinically, which prioritises sensitivity, to diagnosis via the multiplex LF-RDT, which prioritises specificity, would prevent over-referral to hospital which would reduce secondary care costs and ensure capacity during periods of high demand, such as dengue outbreaks.

Furthermore, in view of the likely constraint on sensitivity imposed by small substrate volumes, the components of the multiplex LF-RDT which could preferentially have their sensitivities reduced while optimising cost-effectiveness have been determined through the first scenario analysis i.e., dengue and CRP tests.

6.3.3.3 Strengths and weaknesses

A key strength of this cost-effectiveness analysis is the use of data from the observational study detailed in Chapter 4, which is the largest study on the epidemiology of AFI in rural South and Southeast Asian primary care settings, combined with other country- or region-specific data, to parameterise the model. Furthermore, the model factors in the societal cost of antimicrobial resistance, as it is crucial for policymakers that this cost is accounted for when evaluating the cost-effectiveness of interventions which have the potential to improve antimicrobial stewardship, notwithstanding the methodological challenges. This is especially true for South and Southeast Asian countries where antimicrobial resistance is an urgent public health issue,³⁰⁰ and where simple, low-cost interventions such as this multiplex LF-RDT may be

considered for integration into national or sub-national strategic plans targeting antimicrobial resistance. Furthermore, the results clearly demonstrate the economic benefits of the potential of the multiplex LF-RDT to shift the burden of inappropriate prescribing from the high societal-cost antibiotic ciprofloxacin to the relatively lower societal-cost amoxicillin, despite only modest reductions in overall antibiotic prescription rates.

Nonetheless, this study has several limitations. First, the data on which costs of healthcare provision in Bangladesh are based are not contemporary and, thus, may be much higher than estimated, especially given advances at the secondary care level. Were this to be the case, then the ICER of the multiplex LF-RDT would tend towards being beneath the willingness-to-pay threshold in Bangladesh as well, since hospitalisation costs comprise the bulk of the total costs there. Second, due to an absence of robust data it was assumed that augmenting clinical assessment with the multiplex LF-RDT resulted in only a very small absolute reduction in mortality from enteric fever and no other mortality or morbidity difference between the two arms of the model, but it is conceivable that earlier diagnosis and better directed therapy for other bacterial infections would reduce complications including mortality. In both settings, this would increase the number of DALYs averted, again predisposing the ICER of the intervention towards being beneath the willingness-to-pay threshold, an effect which would be of more importance in Bangladesh. A more complex model which extends the one-year time horizon and captures transitions between health states may give more detailed results than our conservative estimates. Third, no official willingness-to-pay thresholds set by policymakers against which the cost-effectiveness of the multiplex LF-RDT could be benchmarked were available; additionally, it should be recognized that there is an element of subjectivity and different approaches to threshold-setting. Policymakers may, thus, use thresholds as only one factor in their decision-making and may also elect to have different thresholds for different interventions because of differing societal values. These values and

associated thresholds may, therefore, change over time and not just due to inflation. Lastly, the model was developed based on 12 months' worth of epidemiological data. Thus, while intra-year seasonal variation in acute NMFI incidence was accounted for, it was not possible for inter-year variation to be similarly considered. Furthermore, as with the cost-effectiveness analysis described in Chapter 5, while the models were based as far as possible on real-world data, these were not from randomised controlled trials and values for some parameters had to be assumed.

6.3.3.4 Areas for future research

Several key areas for future study in order to improve the informativeness of the analysis for policymaking have been identified in the course of this study, one of which is contemporaneous quantification of healthcare provision costs in Bangladesh.

In addition, since it is unlikely that this multiplex LF-RDT will be developed and rolled out at scale in the very near future, the results of the second scenario analysis indicate that upskilling PHC staff in Cambodia and Bangladesh in formulating syndromic diagnoses in the interim will be beneficial. This is because not only will the total spend on test kits be reduced, but cost-effectiveness will also be increased if they were only used for patients with fever but no true localising symptoms; however, PHC workers first need to be trained to identify this subset of patients. There is plenty of scope to do this because, as shown in the observational epidemiological study reported in Chapter 4, the level of agreement between the syndromic diagnoses generated algorithmically and diagnoses made by PHC workers in Bangladesh and Cambodia is only low to moderate despite them only needing to identify the affected organ system rather than the actual syndrome. For example, one method of aiding PHC workers to make syndromic diagnoses from symptoms and clinical and vital signs might be to use algorithmic clinical decision support tools. This finding may also be applicable to other countries

in South and Southeast Asia with similar AFI epidemiology and health system developmental status.

Lastly, context-specific evaluations of the key drivers of cost-effectiveness identified in this study will further aid assessment of the generalisability of the cost-effectiveness of this multiplex LF-RDT to other countries, as will consideration of other contextual factors such as healthcare worker adherence to test-guided clinical management when the multiplex LF-RDT has been developed.

6.3.3.5 Conclusions from this study

These estimates of the cost- effectiveness of a multiplex LF-RDT to aid diagnosis and management of patients with NMFI illustrates the potential value of this intervention under the right context-specific conditions. This should provide much-needed impetus from an economic perspective for the development of this multiplex LF-RDT, encourage further studies to determine the optimal configuration of conditions in South and Southeast Asian countries where it may potentially be used, and, where possible, guide adjustment of these e.g., country-specific unit prices to ensure cost-effectiveness.

6.4 Conclusions

This work has determined the priority analytes that should be tested for in putative, as yet undeveloped, multiplex LF-RDTs for rural NMFI in South and Southeast Asian LMIC target markets, chief of which are pathogen biomarkers for enteric fever and dengue.

There also appears to be interest in including the host inflammatory biomarker CRP as part of these multiplex LF-RDTs, supporting the investigation of its use in these low-resource settings. There is already general acceptance of its utility in distinguishing between viral and bacterial febrile illness and reducing inappropriate antibiotic prescriptions in patients with acute respiratory infection (ARI), although the evidence thus far comes mainly from high-income

country (HIC) settings.³⁰¹ Therefore, based on the findings presented in this chapter and the preceding one, one approach could be to combine point-of-care CRP testing with pulse oximetry to optimise management of ARI in the rural South and Southeast Asian primary care context. Symptom elicitation and measurement of peripheral oxygen saturation would first be used to establish whether a patient has ARI and, if so, the type of infection. CRP could then be measured in patients with upper respiratory tract infections (URTIs) to guide prescribing if the treating healthcare worker requires further certainty before deciding on management. With time, robust evidence may emerge that supports measuring CRP to guide management of not just URTIs but for AFI more broadly. There is already evidence to support its use in differentiating bacterial from viral infections, although the optimal cut-off value for this is not well-established.³⁰² The use of CRP for prognostication in AFI has also been proposed, but there is even less high-quality evidence for this, which is also hampered by the lack of a consensus definition for severe illness.^{303, 304}

If such a multiplex LF-RDT were to be successfully developed with the ideal performance characteristics and priced as per the WHO Target Product Profile for multiplex multi-analyte diagnostic platforms for AFI,²⁶⁴ cost-effectiveness is likely in at least some, if not most or all, target markets. In the primary care context, cost-effectiveness would be increased by aiding and upskilling health workers to reduce the proportion of patients diagnosed as having fever of unclear source due to clinical skill limitations and only using the LF-RDT on the subset of patients who truly have this diagnosis, such as by the use of algorithms that systematically assess symptoms and vital signs. In the next chapter, one such novel algorithm developed based on the findings of the work reported up to this point and which integrates symptoms, vital signs, danger signs, and RDTs, will be explored.

CHAPTER 7 | EVALUATION OF AN ELECTRONIC CLINICAL DECISION SUPPORT ALGORITHM TO IMPROVE PRIMARY CARE MANAGEMENT OF ACUTE FEBRILE ILLNESS

This chapter draws upon work published in: **Chew R**, Liverani M, Wynberg E, Rekol H, Nguon C, Dysoley L, et al. Evaluation of an electronic clinical decision support algorithm to improve primary care management of acute febrile illness in rural Cambodia: protocol for a cluster-randomized trial. BMJ Open. 2024;14(10):e089616.

7.1 Introduction

The research reported in the preceding chapters has yielded several important findings regarding the epidemiology and management of acute febrile illness (AFI) by primary care providers in rural South and Southeast Asia which lend themselves well to further investigation with the aim of improving clinical practice.

In Chapter 4 ('Defining the epidemiology of acute febrile illness in rural South and Southeast Asian primary care'), the scale of the mismatch between the diagnoses in patients with non-malarial febrile illness (NMFI) made by healthcare workers in primary health centres (PHCs) and those made algorithmically by expert consensus rules based on vital sign and symptom data was shown to be not unsubstantial. In addition, a large number of patients whose care should have been escalated based on severely deranged vital signs and presence of danger signs were not. The threshold for antibiotic prescription was low, resulting in 24% of patients being prescribed them in spite of upper respiratory tract infections (URTIs), which are almost always viral, making up the bulk of presentations. Chapter 5 ('Evaluation of pulse oximetry in the primary care management of acute febrile illness') showed that there is evidence to support the use of pulse oximetry in detecting patients with AFI who are critically ill and that

its implementation in PHCs, even if confined to those with acute respiratory infection (ARI), would likely be cost-effective. Chapter 6 demonstrated a very high degree of support among regional experts for the adoption of a simple lateral flow rapid diagnostic test (LF-RDT) which may include measurement of C-reactive protein (CRP) levels as part of a decision support algorithm for rural healthcare workers. Such support was also evident from the findings of a recent mixed-methods study conducted among PHC staff in Cambodia,³⁰⁵ and from the findings of a wide-ranging stakeholder analysis in Laos.¹⁹

Given these findings, an intervention in the form of an algorithmic clinical decision support tool that integrates the malaria RDTs currently in use with pulse oximetry, CRP point-of-care tests, training in measurement and interpretation of vital signs as well as recognition of danger signs, and assistance with formulation of syndromic diagnoses may help improve clinical management, particular in the domains of antibiotic prescribing and targeting of hospital referrals. The use of algorithms based on clinical symptoms and signs, such as the World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI), is also well-established. However, these algorithms are only relevant to children <5 years old, are principally paper-based and, where electronic versions have been evaluated, have not been shown to improve clinical management.³⁰⁶ Electronic clinical decision support algorithms (eCDSAs) accessed on mobile devices may be a more efficient and user-friendly way of deploying such clinical decision support assistance to rural PHCs, with encouraging results from one study in sub-Saharan Africa.³⁰⁷ However, to date no such eCDSA tailored to rural South and Southeast Asian primary care settings has been developed or assessed under real-world conditions. Nevertheless, putative app-based eCDSAs tailored to these settings show promise given the successful execution of the observational study described in Chapter 4, for which data collection was conducted by healthcare workers using tablet device-based algorithmic apps.

Therefore, the expert-derived decision rules for the formulation of syndromic diagnoses used in the observational study (Tables 4.2–4.4) have been adapted and integrated with malaria and CRP rapid tests, pulse oximetry, and management plans derived from local specialist clinical expertise and/or national or sub-national guidelines (where these exist) to create an eCDSA called EDAM (Electronic clinical Decision support for Acute fever Management) for the diagnosis and management of acute fever in South and Southeast Asia. EDAM will take the form of an app deployable on mobile devices, such as smartphones and tablets, with the capability to function without an Internet connection. Of note, CRP rapid tests and pulse oximetry are currently not routinely used as part of the primary care management of AFI in the settings where this trial is to be run.

This chapter sets out a protocol for a cluster-randomised trial of EDAM and associated relevant training, aiming to determine whether this intervention can improve routine clinical management of patients with AFI, primarily in terms of more appropriate antibiotic prescribing. As part of the broader evaluation of EDAM, its usability and acceptability, as well as its cost-effectiveness compared to the current standard of care, will also be assessed, but these components are not detailed in this chapter which focuses solely on the conduct of the trial.

7.2 Methods

7.2.1 Study design

This is a pragmatic, cluster-randomised controlled trial with two study arms consisting of 15 PHCs in the intervention (EDAM-guided clinical management, further details of which are provided below) arm and 15 PHCs in the control (standard care) arm. A PHC will be considered as a cluster, and the assignment of PHCs to arms will be randomly performed by computer as described in Section 7.2.3. The pragmatism of the study was confirmed using the PRagmatic Explanatory

Continuum Indicator Summary (PRECIS)-2 tool,³⁰⁸ with the majority of the study design domains rated ‘very pragmatic’ (Appendix 7.1).

The rationale for this study design is that any study assessing the potential performance of eCDSAs like EDAM must necessarily be pragmatic and conducted in environments as similar to real-world conditions as possible. Otherwise, in a research-oriented context, healthcare worker prescribing and other management practices may be consciously or unconsciously affected. Furthermore, for policy-makers to consider wide-scale eCDSA implementation, what is most needed is a pragmatic implementation study of its impact in routine care. As such, this study will evaluate the introduction of EDAM into routine care with no research staff routinely present. To minimise disruption and alteration of routine care, a waiver of written patient informed consent was requested from the relevant ethics committees, in accordance with the 2016 WHO/Council for International Organizations of Medical Sciences (CIOMS) International Guidance for Health-related Research Involving Humans. In brief, the 2016 CIOMS Guideline 10 states that if all the following conditions are met then a waiver of informed consent could be applied:³⁰⁹

- if the research would not be feasible or practicable to carry out without the waiver or modification
- if the research has important social value
- if the research poses no more than minimal risks to participants

The proposed study design and intervention meet all of these criteria. The infeasibility of obtaining extensive informed consent from each potential participant by research staff has already been explained. In support of this argument, Sim and Dawson, and Dal-Ré et al., state that waiving informed consent is justifiable when the methodological integrity of the study is brought into question.^{310, 311} In order for healthcare systems to be responsive and improve patient care implementation, studies are required to generate evidence for policy change and to ensure that the benefits seen in research settings are translated into routine care. There is precedent for this

waiver, as illustrated by a similar cluster-randomised trial performed recently in Vietnam.³¹² Thus, instead of obtaining written informed consent, which would also disrupt patient care, verbal assent will be obtained prior to the performance of rapid malaria diagnostic and CRP tests, as is usual in clinical practice, and to allow follow-up by research staff. The drawing of fingerprick blood for malaria and CRP rapid tests is also of minimal risk and the blood taken is only being used for direct patient care. Similar to other tests that may be indicated, patients or their legal guardians will be able to refuse these tests, without any other impact on their care.

The research question is of high clinical importance and social value, helping to guide more appropriate antibiotic prescribing by both reducing unnecessary antibiotic prescribing in the community, a key driver of antimicrobial resistance (AMR),^{313, 314} and identifying patients who need referral to hospital and/or antibiotics but may be missed by routine clinical assessment. The EDAM app offers these potential improvements with a low-risk intervention, that could be rapidly scaled-up. Indeed, the components of EDAM (which are described fully below and include pulse oximetry, malaria and CRP rapid tests combined with clinical symptom-based guidelines) have each individually been determined to be of minimal risk and are already widely used for these purposes in other settings. Furthermore, large clinical trials of similar, but not identical, eCDSAs with extensive patient follow-up have previously shown to be effective in primary care settings elsewhere.^{307, 315}

7.2.2 Setting

The study will be conducted in Cambodia where, as described in Chapter 2 ('Background') and Chapter 3 ('Demographic, health, and socio-economic status profiles of villages in rural South and Southeast Asia'), PHCs deliver most of the primary care services and national targeted health programmes to the population, especially in rural areas. Apart from acute care, services provided by PHCs include hygiene, vaccinations, antenatal care, safe delivery and health education.

The PHCs will be selected from among those in rural areas of Battambang province, again through the longstanding collaboration with the non-governmental organisation Action for Health Development (AHEAD) as was done with the observational study of AFI conducted as part of the South and Southeast Asian Community-based Trials Network (SEACTN) Rural Febrile Illness (RFI) project. The PHCs will be drawn from across three Operational Districts (Thmar Koul, MOUNG RUSSEI, and Battambang) as defined by the Battambang Provincial Health Department, with ten selected from each Operational District.

PHCs selected to participate in this study must meet all the following conditions:

- Have healthcare workers authorised to prescribe antibiotics
- Stock antibiotics
- Have a mean antibiotic prescription rate equal to, or greater than, the baseline used for sample size calculations (as described in Section 7.2.9), verified by checking patient logbooks
- Are likely to have at least 150 patients present with AFI within a four- to six-month period, verified by checking patient logbooks and/or numbers recruited into the SEACTN observational study for PHCs previously involved

7.2.3 Randomisation of clusters

Stratified cluster randomisation of PHCs by Operational District will be performed; as mentioned previously, 10 clusters were included per district. A pseudo-randomisation list of allocations to one of two possible arms ('A' or 'B') will be generated using the *ralloc* package in Stata 18.0 (StataCorp, Texas, USA). This list will be merged 1:1 with a list of PHCs. Assignment of arms 'A' and 'B' as either intervention or control will be performed using a physical flip of a coin. Should the coin flip come up heads, arm 'A' will be designated as the intervention arm, but should the coin flip come up tails then arm 'B' will be the intervention arm.

7.2.4 Participant characteristics

Healthcare workers will be advised that use of EDAM should be restricted to patients within a recommended target population. This target population comprises patients meeting all the following inclusion and exclusion criteria, which are the same as those in the observational study minus the requirement to provide consent.

The inclusion criteria are as follows:

- Age ≥ 1 year
- Unscheduled presentation for acute care
- Documented fever ($\geq 37.5^{\circ}\text{C}$ axillary) or hypothermia ($< 35.5^{\circ}\text{C}$) or history of fever in the last 24 hours

The exclusion criteria are as follows:

- Onset of illness > 14 days
- Presenting due to accident or trauma
- Presenting ≤ 3 days after routine immunizations
- Presenting within the follow-up period

Should a patient not meet all criteria, enrolment will not be permitted by the internal logic of the EDAM app. The app will advise healthcare workers in intervention arm PHCs to continue standard practice for non-eligible patients.

Investigators may discontinue a participant from the study at any time if the investigator considers it necessary for any reason, including but not limited to:

- Ineligibility (either arising during the study or having been overlooked during screening)
- Significant protocol deviation
- Significant non-compliance with study requirements

The reason for withdrawal will be recorded. Data from withdrawn participants will be included in the intention-to-treat (primary) analysis but not in any per protocol analyses. Participants also have the right to withdraw from follow-up at any time.

7.2.5 Description of intervention

The intervention is the EDAM app deployed on tablet devices, which utilises data on clinical features including vital signs and pulse oximetry with malaria and CRP rapid tests to guide primary healthcare workers in their clinical decision-making when confronted with patients with AFI, plus all training required for its effective use. This training will include familiarisation with the app interface, as well as measurement and interpretation of vital signs, recognition of observed danger signs, and the use of CRP rapid tests and pulse oximeters.

For the purposes of this study, the EDAM app was constructed using the CommCare platform (Dimagi, Cambridge, USA). This platform was chosen for familiarity reasons among PHC staff with an established link to the SEACTN RFI project, as it was also used to construct the electronic data collection tool used in the observational study.

As part of screening, patients presenting to a PHC in the intervention arm will have their demographic details logged on the EDAM app. Assessment of study eligibility will be performed by a healthcare worker. If the patient is eligible for enrolment, vital signs, including measurement of peripheral oxygen saturation using pulse oximetry, will be performed. One of three possibilities may then ensue:

- The patient meets eligibility criteria and has no danger signs, either measured by the health worker or observed by any of the health worker, patient, or caregiver (Table 7.1). In this case, the patient will be enrolled, EDAM will guide the healthcare worker through the in-built algorithm leading to a suggested initial management plan, which will include a malaria rapid test as per local policy. The measured danger signs are similar to those

used in the observational study. The selection of relevant observed danger signs (e.g., convulsions) was based on established national and international clinical guidelines such as WHO IMCI and the WHO Integrated Management of Adolescent and Adult Illness (IMAI),¹¹⁶⁻¹¹⁸ ratified by a panel of local expert clinicians. All management plans were also devised by local expert clinicians with regard to local guidelines, and approved by the Battambang Provincial Health Department.

- The patient meets eligibility criteria and has one or more measured or observed danger signs. In this case, EDAM will recommend a malaria rapid test and empirical antibiotic prescription (the choice of which will depend on local guidelines) and immediate referral to hospital. The patient will be enrolled and the algorithm will end here.
- The patient does not meet eligibility criteria. In this case, EDAM will inform the healthcare worker that it is not appropriate to be used for this patient and that they should revert to their usual practice in dealing with non-acutely febrile patients. The patient will not be enrolled and the algorithm will end here.

Age group	Measured danger signs	Observed danger signs
Children aged ≥1 to <5 years	• Voice/pain/unresponsive on AVPU scale • SpO₂ <90% • Severely abnormal heart rate i.e., pulse of <80 or >160 beats per minute	• Unable to drink anything or breastfeed • Vomiting everything • Generalized convulsions • Unable to sit upright/stand/walk (when previously able)
Children aged 5 to <15 years	• Voice/pain/unresponsive on AVPU scale • Severely abnormal heart rate i.e., pulse of <70 or >150 beats per minute (5 to <12 years) or <50 or >130 beats per minute (12 to <15 years) • Fast breathing i.e., respiratory rate of ≥40 breaths per minute (5 to <12 years) or ≥30 breaths per minute (12 to <15 years) • SpO₂ <90%	• Unable to drink anything • Vomiting everything • Generalized convulsions • Unable to sit upright/stand/walk independently • New-onset confusion
Adults aged ≥15 years	• Voice/pain/unresponsive on AVPU scale • Severely abnormal heart rate i.e., pulse of <40 or >140 beats per minute) • Fast breathing i.e., respiratory rate of ≥35 breaths per minute • SpO₂ <90% • Systolic blood pressure <90 mmHg	• Unable to drink anything • Vomiting everything • Generalized convulsions • Unable to sit upright/stand/walk independently • New-onset confusion

Table 7.1. Measured and observed danger signs by age group for patients enrolled into the study. AVPU, Alert/Responds to Voice/Responds to Pain/Unresponsive; mmHg, millimetres of mercury; SpO₂, peripheral oxygen saturation.

As mentioned previously, the rules that EDAM uses for generating diagnoses are based on symptoms and vital sign measurements entered by the healthcare worker, and are identical to those used in the observational study which were developed through consensus by an expert panel (Tables 4.2–4.4).

Intervention arm PHCs will each be provided with two sphygmomanometers and two pulse oximeters to mitigate the possibility of equipment failure. Nevertheless, where the algorithm requires a measurement by a machine it will include an option not to enter a result.

Eligible patients will have a malaria rapid test administered early following measurement of vital signs, as is routine for all febrile patients at the study sites. If the test is positive, they will be treated with an anti-malarial, the choice of which is dependent on local guidelines. The structured approach of EDAM, however, as well as its capability to formulate diagnoses and recommend management for non-malarial AFI, extends the current paradigm of malaria-focused AFI management.

CRP rapid tests will be recommended to guide antibiotic prescription at appropriate points in the eCDSA in patients with no danger signs. The tests used in the trial are semi-quantitative with threshold values of 10, 40, and 80 mg/l. If a CRP test is recommended and performed, the following guidance will be given to the healthcare worker:

- CRP <10 mg/l: reassure the patient that antibiotic prescription is not indicated
- CRP >80 mg/l: prescribe antibiotics, the choice of which will depend on local contexts
- CRP 10 –80 mg/l: reassure the patient that antibiotic prescription is not indicated, unless there is concern based on the clinical judgement of the healthcare worker that the patient would suffer an adverse outcome if antibiotics were not prescribed

Schematic overviews of the algorithms for children aged ≥ 1 to <5 years, children aged 5 to <15 years, and adults aged ≥ 15 years are shown in Figures 7.1, 7.2, and 7.3, respectively.

Safety-netting will be recommended for all patients in the intervention arm not being referred, and healthcare workers in both arms will be trained on how to do this.

Healthcare workers will be asked to specify their working diagnosis and degree of confidence in their diagnosis on an ordinal scale. Healthcare worker autonomy in the intervention arm will be maintained, in that they will be allowed to use their discretion and clinical judgement regarding the suggested diagnoses and initial management. EDAM is not intended to be prescriptive, but merely a guide to help the majority of healthcare workers in their decision-

making. This will be reflected in the wording of recommendations within the app. It is recognised that there may be healthcare workers who are more experienced or have higher skill levels than others, and that decision-making may be influenced by factors other than the objective ones considered in EDAM. Where a healthcare worker does not agree with the suggested diagnosis and management, the app will collect data on their reasons so that these can be analysed with the goal of improving future versions of EDAM. It will be emphasised to healthcare workers that overriding the EDAM recommendation is entirely acceptable and that collecting information on the reasons for this will provide important insights for future improvement of the app and algorithm.

Healthcare workers in intervention arm PHCs will be provided with face-to-face training on the use of EDAM. They will also be taught how to use pulse oximeters and CRP rapid tests, which are not available in control arm PHCs, as well as trained on measuring blood pressure, respiratory rate, and pulse rate, and assessing level of consciousness. Training will be conducted by the study team in the local language, Khmer, using a train-the-trainer model prior to patient recruitment, with refresher training conducted on the advice of site coordinators or study monitors. Contact details of the study coordinator and/or field supervisor will be provided to PHCs; these personnel will be available for advice should any queries regarding the study arise.

Healthcare workers in control arm PHCs will receive a simplified version of the EDAM app which will allow them to log patient demographic details as well as conduct patient screening and enrolment, but does not contain the clinical decision support algorithms present in the version used in the intervention arm. Control arm healthcare workers will receive training in the use of the simplified EDAM app, but not in the clinical procedures and use of point-of-care aids that healthcare workers in the intervention arm are taught.

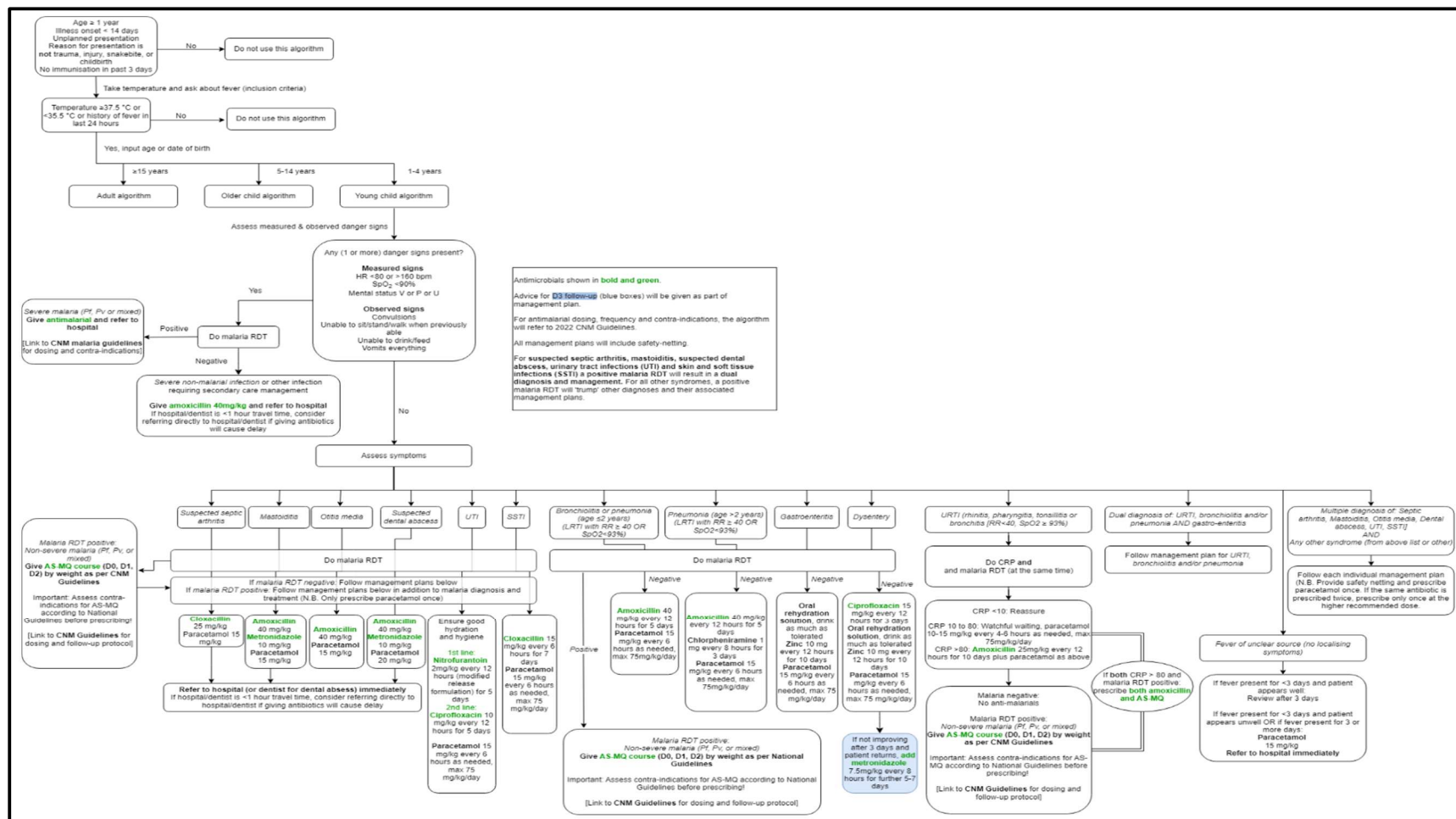


Figure 7.1. Schematic overview of the algorithm for children aged ≥1 year to <5 years. AS-MQ, artesunate-mefloquine; CNM, National Centre for Parasitology, Entomology and Malaria Control; CRP, C-reactive protein; HR, heart rate; LRTI, lower respiratory tract infection; Pf, *Plasmodium falciparum*; PHC, primary health centre; Pv, *Plasmodium vivax*; RDT, rapid diagnostic test; RR, respiratory rate; SSTI, skin and soft tissue infection; SpO₂, peripheral oxygen saturation; URTI, upper respiratory tract infection; UTI, urinary tract infection; V or P or U, responds to voice or pain or is unresponsive.

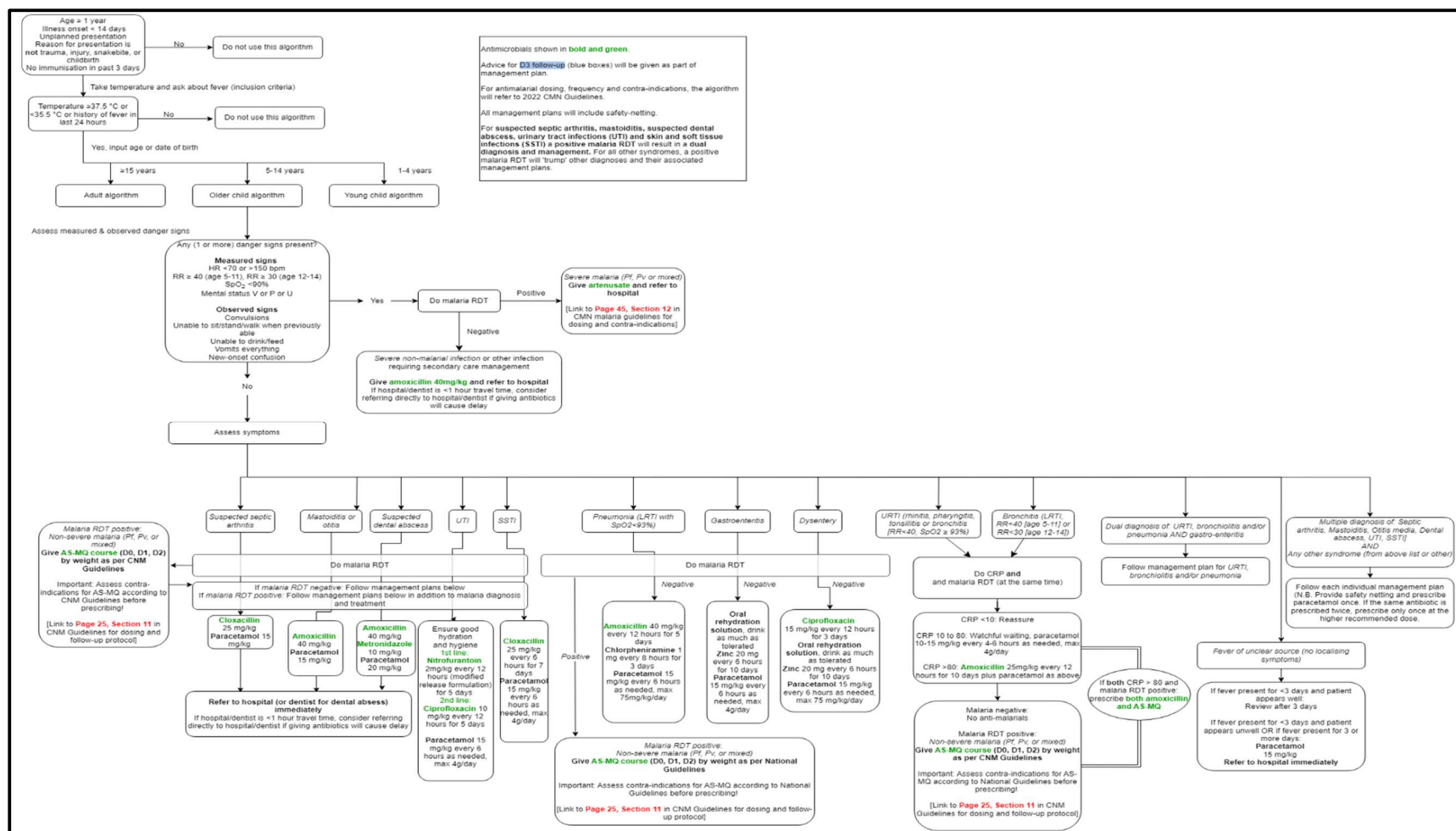


Figure 7.2. Schematic overview of the algorithm for children aged 5 years to <15 years. AS-MQ, artesunate-mefloquine; CNM, National Centre for Parasitology, Entomology and Malaria Control; CRP, C-reactive protein; HR, heart rate; LRTI, lower respiratory tract infection; Pf, *Plasmodium falciparum*; PHC, primary health centre; Pv, *Plasmodium vivax*; RDT, rapid diagnostic test; RR, respiratory rate; SSTI, skin and soft tissue infection; SpO₂, peripheral oxygen saturation; URTI, upper respiratory tract infection; UTI, urinary tract infection; V or P or U, responds to voice or pain or is unresponsive.

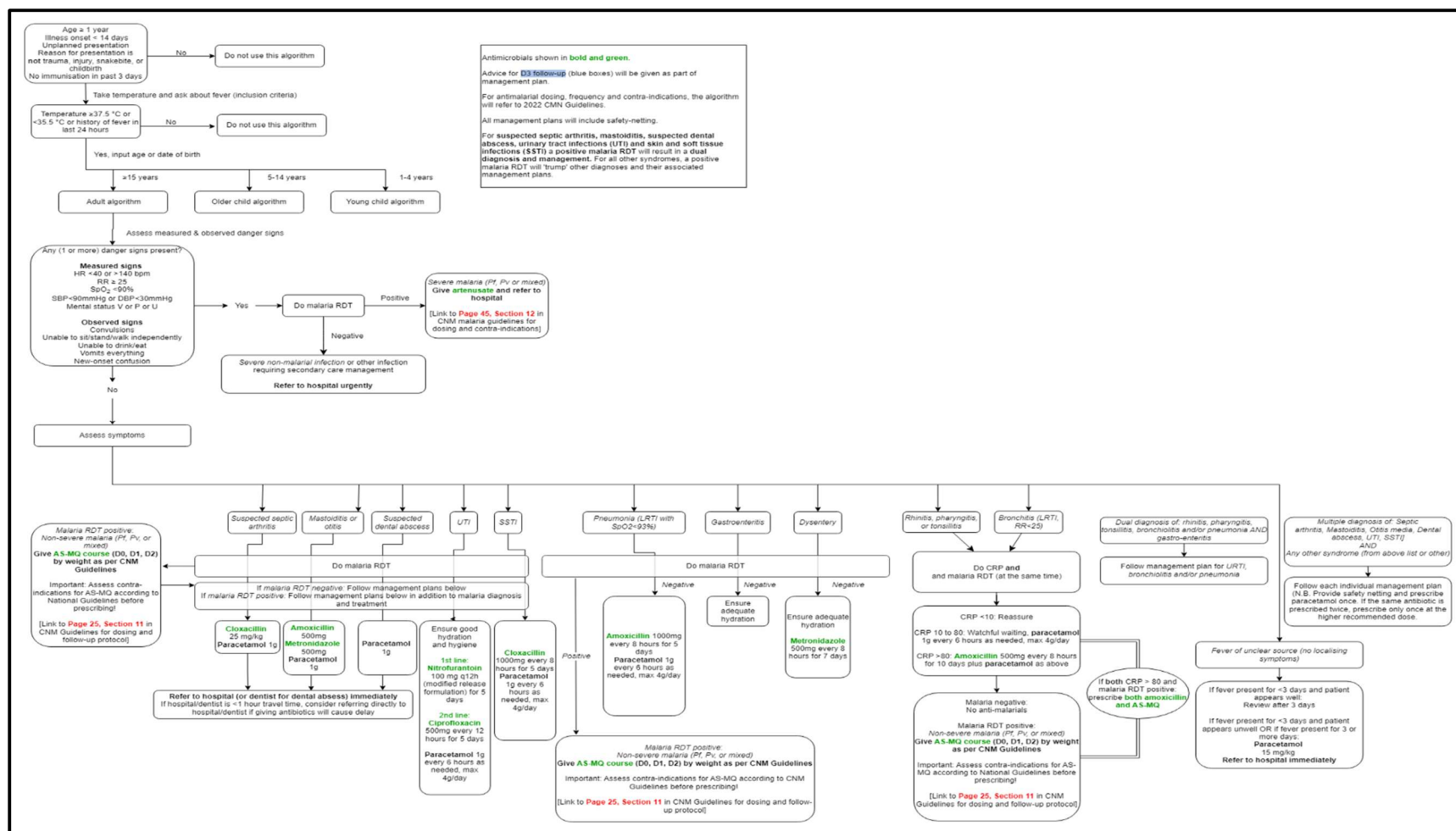


Figure 7.3. Schematic overview of the algorithm for adults aged ≥15 years. AS-MQ, artesunate-mefloquine; CNM, National Centre for Parasitology, Entomology and Malaria Control; CRP, C-reactive protein; DBP, diastolic blood pressure; HR, heart rate; LRTI, lower respiratory tract infection; Pf, *Plasmodium falciparum*; PHC, primary health centre; Pv, *Plasmodium vivax*; RDT, rapid diagnostic test; RR, respiratory rate; SSTI, skin and soft tissue infection; SBP, systolic blood pressure; SpO₂, peripheral oxygen saturation; URTI, upper respiratory tract infection; UTI, urinary tract infection; V or P or U, responds to voice or pain or is unresponsive.

7.2.6 Description of other study procedures and follow-up

Only patients presenting acutely to study PHCs i.e., those without scheduled appointments, will be screened for eligibility. The app will use skip logic and contain prompts for the healthcare worker to check patient eligibility, allowing recruitment and data collection only when the requisite conditions are met.

Patients can be enrolled multiple times during the study period, as the primary objective is to determine the proportion of presentations which result in antibiotic prescription. However, they cannot be re-enrolled if they are within the follow-up period (defined below), as any attendances within this period will be logged as unscheduled re-presentations; this is a secondary outcome measure. If all the following identifiers of a patient are exact matches with those of another patient currently under follow-up, the healthcare worker will confirm that they are not the same person: date of birth (or age if date of birth is not known), gender, and village of residence. Only once this confirmation is provided can the patient be enrolled.

All patients will have a medical history taken and assessed as per usual practice. In intervention arm PHCs this process will be more structured as it will be guided by EDAM. Practice will remain unchanged in control arm PHCs.

Patients will be followed up by telephone at 7 days post-presentation (allow + 2 days); patients who have not recovered by day 7 will be followed up at day 14 (+ 2 days). The following data will be collected at follow up:

- Recovery (self-reported)
- If not recovered, whether symptoms were better, worse, or the same
- Whether they re-presented to another healthcare provider (re-presentations to the same PHC should be captured by the EDAM app)

- If they re-presented, whether they were hospitalised and (if known) whether antibiotics were prescribed

Should a patient be uncontactable by telephone after three attempts, village health workers (VHWs) and village malaria workers (VMWs) will be utilised to locate the patient and conduct the follow-up interviews at day 7 and day 14, as necessary, if the participant survived, or document death, if the participant did not survive. If this is unsuccessful, the patient will be deemed lost to follow up.

One important caveat is that patients who re-present during the follow-up period will be considered as unscheduled attendances secondary to the initial diagnosis, given that unscheduled attendance is a secondary outcome measure. This will also allow determination of whether antibiotics are initially withheld and then given at a subsequent visit. The major limitation of this approach, however, is that some patients may be categorised as unscheduled presentations when their subsequent visit is actually for a new problem or illness.

The trial schedule of enrolment, interventions, and assessments, completed using the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline template,³¹⁶ is shown in Table 7.2. The completed SPIRIT checklist can be found in Appendix 7.2.

	STUDY PERIOD			
	Enrolment	Clinical encounter	Follow up	
TIMEPOINT (DAY)	0	0	7	14
ENROLMENT:				
Eligibility screen	X			
INTERVENTIONS:				
EDAM app		X		
Standard of care		X		
ASSESSMENTS:				
Antibiotic prescription		X		
Hospital referral		X		
Recovery by day 7			X	
Recovery by day 14 (if not recovered by day 7)				X
Death or hospitalization* by day 7			X	
Death or hospitalization* by day 14 (if not recovered by day 7)				X
Re-presentation by day 7			X	
Re-presentation by day 14 (if not recovered by day 7)				X
Antibiotic consumption [†] by day 7			X	
Antibiotic consumption [†] by day 14 (if not recovered by day 7)				X

Table 7.2. Schedule of enrolment, interventions, and assessments. EDAM, Electronic clinical Decision support for Acute fever Management. *If not referred to hospital at the time of clinical encounter. [†]If not prescribed antibiotic at the time of clinical encounter.

Malaria rapid tests are already available at all PHCs as part of standard care. In addition, semi-quantitative lateral flow CRP tests will be available for healthcare workers to use on eligible patients at intervention arm PHCs when prompted by EDAM. If a patient agrees to these tests, a finger-prick blood sample will be taken by the healthcare worker and placed onto the test kit in accordance with manufacturer instructions. Refusals will be recorded in the EDAM app. Other than these finger prick samples as part of the clinical management algorithm, no other samples will be taken. CRP test kits and associated consumables will be re-stocked on a monthly basis and checked to confirm they are properly used for study purposes only. The training for healthcare workers will emphasise respect for patient autonomy and that refusal on their part to be tested should be accepted without reservation. Reasons for patient refusal to be tested will be noted in the app to inform future algorithm development and community engagement activities.

The CRP rapid test which will be used is the Actim® CRP test from Medix Biochemica (Finland; ISO certification ISO13485:2016).³¹⁷ Much like a malaria rapid test, it is a simple lateral flow device that uses capillary blood, obtained through a finger- or heel-prick, and provides a semi-quantitative indication of whether CRP concentrations are <10mg/L, between 10–40mg/L, between 40–80mg/L, or >80mg/L, in under 5 minutes with minimal training requirements. It meets European Union standards (CE-marking) as well as the regulatory requirements of 13 other countries, and has been validated for accuracy in previous studies.^{315, 318} The pulse oximeter which will be used is a Lifebox-Smile Train hand-held device, which is specifically manufactured to be durable for use in resource-limited settings,³¹⁹ and which has been successfully used in SEACTN. Lifebox is a non-governmental organization whose goal is to improve anaesthesia safety through the distribution of pulse oximeters developed for use in low-resource settings. Medix Biochemica and Lifebox played no role in the design of this study, and the investigators declare no conflicts of interest with respect to the choice of these point-of-care aids.

7.2.7 Outcome measures

The primary outcome measure is the proportion of patients with AFI who are prescribed antibiotics in routine primary health care at initial presentation in the intervention and control arms.

Several secondary outcome measures will also be assessed:

- The proportion of patients with AFI with full recovery at 7 and 14 days in intervention and control PHCs.
- The proportion of patients with AFI referred to hospital at presentation in intervention and control PHCs.
- The compliance of healthcare workers in intervention PHCs with the management recommended by EDAM.
- The proportion of patients with AFI with unplanned re-presentations to any healthcare facility at 7 and 14 days (if not fully recovered by 7 days) in intervention and control PHCs.
- The proportion of patients with AFI prescribed antibiotics by a healthcare provider or who independently purchased antibiotics during the follow-up period, as determined by self-report, in intervention and control PHCs.
- The proportion of patients with AFI with severe clinical outcomes (death or hospitalization) at 7 and 14 days (if not fully recovered by 7 days) in intervention and control PHCs, not including those referred to hospital at presentation.
- The proportion of patients with AFI prescribed an antibiotic in intervention PHCs by CRP level (<10 mg/L, between 10 and 80mg/L, >80 mg/L).

7.2.8 Pre- and post-commencement engagement

To gauge early policymaker views on the potential usability and acceptability of the intervention, engagement meetings were held with key stakeholders in the Ministry of Health responsible for medical services, primary care, public health, and digital health and health informatics. Similar

meetings were held with local medical specialists in the fields of adult internal medicine/infectious diseases, paediatrics, and primary care to develop consensus clinical management plans tailored to local conditions as part of the algorithms.

Taking into consideration evidence from similar eCDSAs used in other LMIC settings, such as ePOCT and inSCALE in sub-Saharan Africa,^{307, 320} both these local expert groups were also asked for their views on the interface to inform the development of the EDAM app, which was then further refined by asking a small number of PHC healthcare workers to test the app and offer their opinions on its usability. These stakeholder consultations have informed the version of the EDAM app used in this study. A second round of such meetings will be conducted towards the end of the study to assess stakeholder experiences.

Before randomization of participating PHCs, an overview of the study will be presented to all PHC healthcare workers. Education will also be provided about the role of antibiotics, AMR, and good clinical practice (GCP) for research. Training specific to the study intervention has been described previously. Information on EDAM for patients will be displayed in intervention arm PHCs.

7.2.9 Sample size calculations

The baseline rate of antibiotic prescription was based on the findings from the observational study described in Chapter 4, where the mean percentage of acutely febrile patients prescribed antibiotics was approximately 25%. The ICAT cluster-randomised trial, in which the proportion of patients recruited by age group was broadly similar to that seen in the observational study, showed that the use of CRP rapid tests reduced the antibiotic prescription rate by 36%.³¹² Extrapolating the results of these earlier studies, therefore, it is estimated that EDAM will result in a reduction of antibiotic prescription by approximately one-third i.e., from 25% to 17.5%.

As far as possible, and depending on approval from the local health authority i.e., the Battambang Provincial Health Department, PHCs which were included in the observational study will also participate in this study. Other PHCs which meet the inclusion criteria will be selected for inclusion in this study, if required, to make up a total of 15 PHCs in each of the control and intervention arms. As mentioned previously, each PHC will be treated as a cluster. Given the above, the sample size calculations are based on probabilities of 0.05 and 0.2 for Type I and Type II errors, respectively, and an intra-class correlation coefficient of 0.025, as is common for cluster randomised trials of this nature.^{179, 321} Based on the parameters mentioned previously, including the anticipated reduction of antibiotic prescriptions from 25% to 17.5%, and assuming a patient drop-out rate of 10%, with 15 clusters per arm the target number of patients to be recruited per cluster is 152. In total, therefore, the target number of patients to be recruited is 4560. Sample size calculations were performed in Stata 18.0.

The study is not powered to detect differences within each age group, but subgroup analyses will be conducted among patients aged ≥ 1 to < 5 years (younger children), 5 to < 15 years (older children), and ≥ 15 years (adults). While inclusion of safety endpoints as co-primary objectives was also considered, this was ultimately judged to be infeasible as, based on the results of the observational study, the absolute risk of a composite adverse outcome of death or hospitalisation for longer than three days or persistent symptoms at 28 days post-presentation, was expected to be minimal (this risk was approximately 1.5% in the observational study).

7.2.10 Description of statistical analyses

The primary endpoint is the proportion of patient consultations for AFI which result in antibiotic prescription. The primary comparison between the treatment arms will be a mixed effects logistic regression with the treatment assignment as a fixed effect, and the PHC as a random effect. *P*-values (two-sided) below 0.05 are considered significant. A two-sided 95% confidence interval (CI) for the odds ratio of being prescribed antibiotics will be calculated.

The primary endpoint (proportion of patients given an antibiotic prescription) will also be investigated by subgroup to assess whether any change in antibiotic prescribing is homogeneous across subgroups. Specifically, intervention effects and appropriate tests for heterogeneity will be calculated in the following pre-defined subgroups:

- Age: younger children aged ≥ 1 to < 5 years, older children aged 5 to < 15 years, and adults aged ≥ 15 years
- Sex at birth: male or female
- Patients with a documented fever or hypothermia at presentation vs. patients without

The secondary endpoints will be analysed in a similar manner to the primary endpoint. A detailed Statistical Analysis Plan (SAP) will be developed prior to the completion of recruitment for the study.

7.2.11 Data management

Data will be captured electronically through the EDAM app and submitted to a central server. A data dictionary will be constructed in which all variables are clearly explained. A study logbook of patients screened and recruited will also be maintained for each PHC.

Patients will be assigned a unique composite ID number each time they are enrolled. They will be identified only by their unique ID number in study documents, in data entry and in any electronic databases in order to protect their privacy. The only patient-identifying data entered in the study logbooks will be the names of patients, their villages of residence, and their telephone numbers, for the purposes of carrying out follow-up. No other identifiers will be collected, and these details will not be entered into any databases held or accessed by the study team. All documents will be stored securely and only accessible by study staff and authorised personnel. Any scientific publications or reports will not identify any individual participant/s by name or initials.

Electronic data will not be modifiable by the healthcare worker after submission, although authorised users e.g., site research staff will be able to for data cleaning purposes. Access to the data will be password-protected. Direct access will be granted to authorised representatives from the University of Oxford, the study site partners, and the national ethics committee for monitoring and/or audit of the study to ensure compliance with regulations.

The database and all electronic data will be routinely backed up. In accordance with the Mahidol Oxford Tropical Medicine Research Unit (MORU) Standard Operating Procedures (SOPs), de-identified electronic data will be stored indefinitely on the central server, while paper records will be preserved for five years. Anonymised stored data may be shared with other researchers for future use according to the terms defined in the MORU data sharing policy.³²²

Healthcare workers will be trained prior to study commencement on collection of data using the version of the EDAM app relevant to their PHC. Training materials e.g., videos and slides will be uploaded to the tablet devices in case they need to refer to these.

7.2.12 Data quality assurance

Data validation will be performed to identify errors and thus ensure completeness, validity and data accuracy.

Electronic data checks and field restrictions will prevent errors with extreme values being entered, for instance by having pre-specified ranges for vital sign measurements. Further internal checks of the entered data will be done to look for outliers and errors. Additionally, because data will be transmitted in real time or near-real time to the central server, data cleaning will occur prior to the conclusion of the study allowing for earlier detection and correction of errors if necessary.

The study will be conducted in compliance with this protocol, International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP) and any applicable regulatory requirement(s). Staff involved in data collection, interviews, transcription and data coding will be

appropriately qualified to perform assigned tasks and will be trained on study procedures prior to start of the study. Monitoring will be overseen by the MORU Clinical Trials Support Group (CTSG) to ensure compliance to the study protocol and applicable guidelines and regulations.

7.2.13 Safety considerations

The risks of participation are low. Firstly, as has been established in Chapter 5, measurement of oxygen saturation using pulse oximetry is now considered the ‘fifth vital sign’ and is recommended by the WHO, when possible, in rural LMIC primary care settings,^{116, 148, 149} therefore its use is not controversial. Secondly, symptom- and vital sign-based diagnostic algorithms, such as the WHO IMCI guideline, are also widely used in clinical practice. Lastly, MORU has previously conducted a large clinical trial on CRP-guided treatment in patients with AFI with extensive patient follow up, demonstrating that it is effective in reducing antibiotic prescribing and did not adversely affect patient outcomes.³²³ A decision support tool integrating all three would, therefore, not be expected to pose any elevated risk to patient safety. Healthcare workers in the intervention arm are also able to use their discretion if they do not agree with the management recommended by EDAM. Additionally, as an extra safeguard, they will be trained to provide safety-netting to all patients they recruit.

Furthermore, in line with the principles guiding data and safety monitoring in pragmatic clinical trials,³²⁴ an independent Data and Safety Monitoring Board (DSMB) will be assembled prior to the commencement of the trial. The DSMB will review the protocol and have access to summary data in real time through the electronic trial dashboard; given the anticipated short duration of this study, no interim analyses will be provided, although it may request additional information if necessary. The independent and voting members of this committee will be comprised of between three and five members. The chair will be medically qualified and at least one of the other members of this committee will be a statistician. Should there be an even number

of members then the chair will have the casting vote. The DSMB will determine meeting frequency at its first meeting.

Given the pragmatic nature of this simple intervention, remote monitoring will be undertaken in order to confirm the quality of the research performed to assess and ensure the robustness of the trial results. A monitoring plan will be developed prior to study commencement.

7.2.14 Ethical approval

The study sponsor is the University of Oxford, and the protocol has been approved by the Oxford University Tropical Research Ethics Committee (OxTREC, reference 550-23). The protocol has also been approved by the Cambodian National Ethics Committee for Health Research (NECHR, reference 395-NECHR), and permission to carry out the study has been obtained from the Battambang Provincial Health Department.

Any amendments and modifications will be submitted to the abovementioned boards for review and approval. No changes in protocol conduct will be implemented until approvals of amendments by all relevant boards are obtained.

7.2.15 Trial registration

This study has been registered in the International Standard Randomized Controlled Trial Number (ISRCTN) Registry (reference number ISRCTN15157105).³²⁵

7.2.16 Dissemination plan

The results of the study will be published in an appropriate peer-reviewed journal. Authorship eligibility will be based on the criteria set by the International Committee of Medical Journal Editors,³²⁶ with author contributions described using the Contributor Roles Taxonomy (CRediT).³²⁷

There are no plans to use professional medical writers in the drafting of the manuscript containing the results of the study.

7.2.17 Funding

The funders are the Wellcome Trust (grant number 215604/Z/19/Z) and the Australasian Society for Infectious Diseases (no grant number). The manufacturers of the rapid tests used in the study and their agents or distributors had no role in study design or funding. The investigators have no financial or other conflicts of interest.

7.3 Discussion

This cluster-randomised trial aims to evaluate the impact on antibiotic prescribing of a novel bespoke eCDSA (EDAM) tailored to local primary care contexts, deployable on mobile devices, and integrating simple point-of-care aids. Notably, while EDAM is not a guideline per se, the management plans within the algorithm are heavily guideline-based. Therefore, as recommended by the WHO in its digital health SMART Guidelines Initiative, EDAM was designed with the SMART principles in mind i.e., it is Standards-based, Machine-readable, Adaptive, Requirements-based, and Testable.³²⁸

To recap the main issues confronting rural primary healthcare workers, such as those in the study PHCs, their high workloads and/or low clinical diagnostic and management skill levels mean that hospital referral and antibiotic prescribing are poorly targeted. This leads to detrimental consequences on both a population health and an individual patient level. On the one hand, potentially inappropriate referral of patients to hospital may overburden secondary care and inappropriate antibiotic prescribing (such as to patients in whom antibiotics are not indicated or the prescription of an antibiotic not appropriate to the clinical syndrome) can contribute to the development of AMR. At the same time, patients whose care should be escalated and/or to whom antibiotics should be prescribed may currently be missed, leading to adverse clinical outcomes. Furthermore, unnecessary use of antibiotics exposes patients to the risk of adverse effects, and is known to increase the risk of subsequent acquisition of resistant infections as well as disruption

of the microbiome with a host of associated adverse outcomes.³²⁹ EDAM has the potential to address all these issues in an easy-to-use, tablet-based app, and this study will provide information on its effectiveness in streamlining patient management, including better antibiotic stewardship which will reduce the prevalence of antibiotic resistant bacteria in the population, hence preserving antibiotics for treating serious bacterial infections. A further benefit is the strengthening of the skillsets of PHC health workers, thus increasing the confidence of the rural population in their abilities leading to better care-seeking behaviours which, in turn, aids regional malaria eradication efforts.^{18, 330}

This study has several limitations. Firstly, PHCs included were selected based on the volume of patients seen per month and antibiotic prescribing rates per records in patient logbooks, as described in Section 7.2.2. The results, therefore, may not be fully generalizable to all PHCs, especially those where antibiotic prescription rates are lower. Secondly, there is often more than a single health worker per PHC which may result in intra-cluster heterogeneity.³³¹ However, data will be collected on the clinical decisions made by each app user, allowing future secondary analyses by individual healthcare worker. Thirdly, while the estimated effect size was based on the best available evidence, its accuracy is uncertain which, in turn, may affect the accuracy of the sample size calculations. This is because the sample size was determined partly based on this assumed effect size; therefore, the study is likely to have less power to detect effect sizes smaller than this. Fourthly, the primary outcome was chosen as it is objective and easily measurable. However, assessment of the other benefits of EDAM, both tangible and intangible, is not as easily performed, hence the inclusion of secondary outcomes and a qualitative component to this study.

Notwithstanding the limitations described above, the findings of this study will inform the design of future versions of the EDAM app, since it is by nature easily adaptable, and also the

design of future trials of similar eCDSAs and other digital health interventions targeted towards improving antibiotic stewardship and clinical management in rural populations.

CHAPTER 8 | DISCUSSION

8.1 Synthesis of main findings

Several key themes are evident from the results reported in this thesis, which provides novel and unprecedented multi-disciplinary insights into the primary care epidemiology and management of acute febrile illness (AFI) in under-studied and under-served rural populations of five South and Southeast Asian developing countries.

Crucially, the work in Chapter 4 ('Defining the epidemiology of acute febrile illness in rural South and Southeast Asian primary care') showcases the ongoing principal contribution of AFI, primarily due to upper respiratory tract infections (URTIs), to the burden of acute illness and that, with the exception of Myanmar and areas bordering it, malaria is relatively inconsequential. Fortunately, clinical outcomes are generally good, suggesting that even in the 31% of AFI where the source is unclear, the aetiology is likely to be viral and, thus, self-limiting, with the caveat that patients judged to be too unwell to participate were not enrolled. The number of these patients was small, however, and the overall findings provide new knowledge of the outcomes of rural patients with AFI seen in primary care. While the high rate of full recovery mitigates the non-systematic manner in which referrals to hospital from primary care are made, the manner in which these patients are managed clinically also shines a spotlight on the considerable magnitude of avoidable antibiotic use, which is likely to be an under-estimate given the demonstrated propensity of patients to obtain medications without prescription from pharmacies and drug stores.

No less important is the work in Chapter 3 ('Demographic, health, and socio-economic status profiles of villages in rural South and Southeast Asia') placing the above findings within the contextual parameters of the village settings in which the target population resides and works. While it is unsurprising that the social milieu will necessarily differ between countries

given the variation in progress towards the Sustainable Development Goals,³³² the challenges posed by intra-village and/or inter-province ethnic, linguistic, religious and cultural diversity in each country to improving health services will require careful consideration. There are also clear intra-country disparities in the structural determinants of health, such as literacy and public utilities, as shown by the differences between the three sites in Thailand, which must be addressed to achieve health equity.

Therefore, while the evaluations presented in Chapters 5 ('Evaluation of pulse oximetry in the primary care management of acute febrile illness in rural South and Southeast Asia'), 6 ('Evaluation of a putative novel multiplex rapid diagnostic test in the primary care management of acute febrile illness in rural South and Southeast Asia'), and 7 ('Protocol for a cluster-randomized trial of an electronic clinical decision support algorithm to improve primary care management of acute febrile illness in rural South and Southeast Asia') of interventions to improve primary care management of AFI show promise from clinical and/or economic perspectives, there is still much work that needs to be done to contextualise these results so that any decisions made can be said to be solidly evidence-based. These directions for future research are, again, necessarily multi-faceted and will be outlined later in this chapter, along with the challenges and gaps they must address. What is certain, however, is that future efforts centred on the primary care settings studied in this thesis must have optimising antimicrobial stewardship and the use of scarce secondary care resources as key priorities. It was, therefore, fortuitous that the COronaVirus Disease of 2019 (COVID-19) pandemic steered the research forming the latter half of this thesis in this direction and away from prediction modelling to identify patients at risk of poor clinical outcomes, as was originally intended.

8.2 Strengths and weaknesses

This section, rather than rehashing the strengths and weaknesses of the individual thesis components, will synthesise these longitudinally.

Much of the impact of the research in this thesis – to date and anticipated – is derived from its novelty. While some of the work described in the preceding chapters may appear simple and merely descriptive, their scope and scale, as well as the community engagement that underpinned their design, planning, and execution in low-resource field settings to generate locally meaningful and applicable results must be considered a key strength. In this regard, the ability to draw on the vast collective experience of the Mahidol Oxford Tropical Medicine Research Unit has been invaluable; for instance, the lessons learnt from the South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) were good examples of what, and what not, to do when the studies comprising this thesis were being planned.³³³ An example of the former was the emphasis on only capturing essential data in the case report forms, in order to make data collection as easy a process as possible for time-poor primary health workers, to speed up patient recruitment and mitigate selection bias. Hastening patient recruitment was crucial, given the delays imposed by the COVID-19 pandemic. Additionally, placing sensitivity to context and recognition of the need for capacity-building front and centre was essential in ensuring not just the success of primary data collection but also the sustained and ongoing engagement of country partners and stakeholders, including health policy decision-makers at sub-national and national levels. This approach is in line with best practice in global health research,^{334, 335} and bodes well not just for further projects but also implementing and scaling-up potential interventions to improve AFI management.

Nonetheless, there are several shortcomings which should be borne in mind. The first of these pertains to the generalisability of the findings. While this research was centred on the main types of primary care provider in rural South and Southeast Asia, namely village health workers (VHWs), village malaria workers (VMWs), and primary health centres (PHCs), the paucity of severely unwell patients enrolled into the observational epidemiological study is likely indicative of spectrum bias. The results reported in this thesis are, therefore, not likely to be

applicable to primary care settings attended by severely unwell patients, such as acute outpatient clinics in first-referral hospitals or private healthcare facilities. Secondly, the evaluations of potential interventions performed, in particular the cost-effectiveness analyses, have largely been from the perspectives of the healthcare payer and healthcare providers. This is because, in such resource-poor settings, the public sector delivers the bulk of care provision. Despite this, however, other perspectives such as those of the patient, health system, and society are no less important,³³⁶ especially for patients as care-seeking in rural South and Southeast Asia often imposes considerable out-of-pocket costs and loss of income.³³⁷ Thirdly, despite this research being conducted during the early years of the COVID-19 pandemic, there was no exploration of its impact, especially on AFI epidemiology. Lastly, a huge quantity of highly granular data has been collected at the individual patient and village level. This thesis provides a high-level overview of the findings which, while necessary to set the scene for future work, contains limited site- or patient group-specific analyses. Deeper dives into the data will be vital for tailoring the development and implementation of interventions and policy at the local level.

8.3 Directions for future research

Similar to the approach taken in the previous section, guiding principles to steer the direction of research that will complement and advance the individual recommendations for future work presented in the chapters of this thesis are described in this section.

In the first instance, an effort should be made to synthesise the findings reported in this thesis with those of the other major projects conducted in this phase of the South and Southeast Asian Community-based Trials Network (SEACTN).⁵³ For example, triangulating the results of the village profiling exercise (Chapter 3) with the results of the household health survey will paint a richer contextual picture,¹⁰⁶ in the same way as synthesising the results of the primary care observational study (Chapter 4) with the results of its secondary care counterpart as well

as causes of death reported via the verbal autopsy project will reveal a fuller, more informative view of the regional epidemiology of AFI. It is, of course, obvious that further integrating these synthesised results with those of the stakeholder analyses will provide a solid evidence-based impetus to drive future research in the directions which will most benefit the health of the rural South and Southeast Asian population.

Notwithstanding the above, an equally important next step that should be taken is to establish a platform for active surveillance of AFI. This is because the village profiling and observational studies, while crucial in deepening understanding of the epidemiology of AFI in rural South and Southeast Asia, are but snapshots at a particular period of time, on which the findings of the subsequent components of this thesis are also highly dependent. The conclusions drawn at the present time may quickly become obsolete due to the rapid demographic and socio-economic changes occurring in the region, for example due to the effects of urbanisation and the increasing double burden of communicable and non-communicable diseases that accompany this epidemiological transition.³³⁸ The epidemiology of climate-sensitive infectious diseases, such as dengue and other arboviral diseases,³³⁹ is also likely to change, especially in countries particularly susceptible to climate change such as Bangladesh.³⁴⁰ Climate change and human encroachment into forested areas, such as for agriculture or housing, also encourage the emergence of new infectious diseases.^{341, 342} A possible active surveillance approach leveraging the now well-established SEACTN infrastructure, as shown in Figure 8.1, will enable the provision of contemporary, actionable information on AFI epidemiology to ensure optimal patient care as well as inform public health programming and outbreak responses. To avoid the ascertainment bias which was a weakness of the observational study, other primary care settings not studied in this thesis should be included as part of the surveillance strategy.

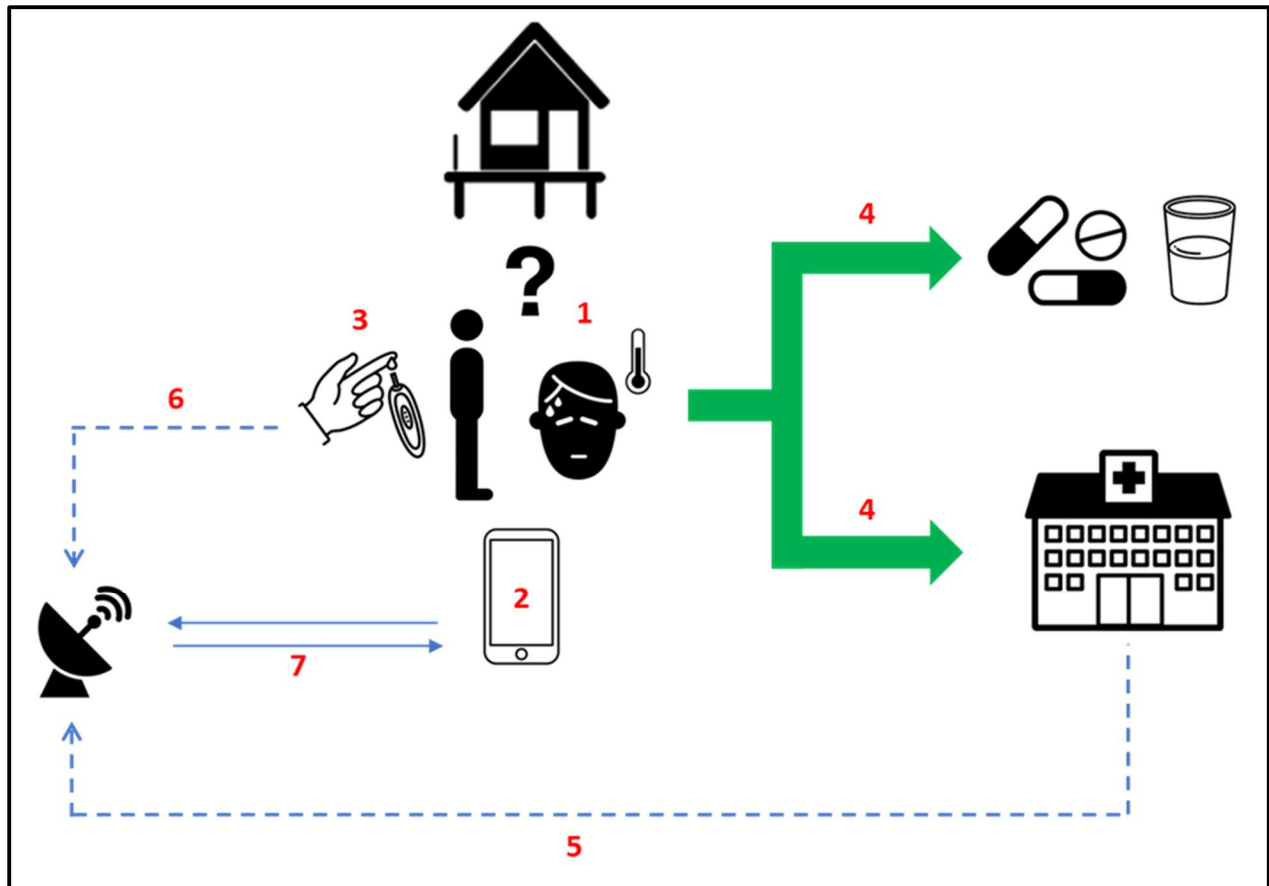


Figure 8.1. Integrating clinical care with active surveillance of acute febrile illness (AFI) leveraging the South and Southeast Asian Community-based Trials Network infrastructure.⁵³ [1] Patient with AFI presents to primary healthcare worker. [2, 3] Electronic clinical decision support algorithms (eCDSAs) on mobile devices assist the health worker in patient management, which may include point-of-care testing. [4] Healthcare worker makes a decision on patient disposition i.e., community-based treatment or referral for higher-level care guided by the eCDSA. [5] Referral facilities function as sentinel nodes, periodically providing data from patients attending with AFI. [6] A proportion of clinical samples collected from patients with AFI are transported to reference laboratories for analysis. [7] Data from sentinel nodes and reference laboratories are integrated with data collected in primary care settings, allowing periodic updating of eCDSAs to reflect seasonal and longitudinal changes in AFI epidemiology.

Updating the evaluations of the interventions to improve AFI management described in Chapters 5–7 of this thesis in the light of changing AFI epidemiology will also be key in ensuring their continued fitness-for-purpose. As described in the previous section, these evaluations, especially economic, must expand the range of perspectives considered to include patients, healthcare workers, and the wider society. The use-cases of the interventions themselves should also be subject to further investigation. This should be done not just to enhance their performances for currently proposed use-cases e.g., determining optimum cut-off C-reactive protein (CRP) values to distinguish between bacterial and viral infections, but also to consider whether the scope of their use-cases can be extended. For example, fever may not necessarily be a feature in some patients with URTI, such as the elderly, hence exploring the performance of CRP testing in this group of patients may help increase its impact on antimicrobial stewardship. The approaches taken in such future work should be tailored to the target patient populations and may require adjunctive interventions or methodologies not forming part of this thesis. Ideally, future research on interventions should be strategically planned and involve the health system as a whole, or at least as many components of it as possible. There are several arguments that support this approach. First, the work described in Chapters 3 and 4 show that many patients self-medicate and that patients who perceive themselves as severely ill do not generally visit PHCs or VHWs/VMWs. Second, the systematic review of the impact of pulse oximetry in low- and middle-income country (LMIC) settings showed the necessity of a system-wide approach for maximum beneficial effect. This was also amply demonstrated by the Antibiotics Smart Use programme in Thailand.

Furthermore, the context in which the shifts in the epidemiology of AFI will take place will also be altered, for example through impacts of industrialisation and climate change on migration, food security, political stability, and economic activity.^{343, 344} It will, therefore, be important to periodically repeat and expand the village profiling exercise, as well as explore

alternative methods which may be superior to the key informant interviews utilised in this thesis. Qualitative and public engagement research exploring important themes such as determinants of health-seeking behaviour and clinical decision-making should also be conducted to complement the previously mentioned primarily quantitative clinical and epidemiological studies. These will add a further layer of understanding of the complexities facing efforts – both research and practice – to improve AFI management, which is particularly important in this region where the target populations and healthcare systems have as many differences as they have similarities.³⁴⁵ The importance and potential impact of such studies is huge, as demonstrated by the scant evidence pertaining to South and Southeast Asia which is currently available.^{346, 347}

Finally, with the large quantities of highly granular data amassed through the primary care observational study of AFI epidemiology, its secondary care counterpart, and the EDAM trial described in Chapter 7, it would be remiss not to attempt harnessing machine learning techniques to develop predictive models. These models have the potential to span a wide range of use-cases, from prediction of causative organisms and adverse clinical outcomes to outbreak forecasting, given that clinical, epidemiological, and spatio-temporal data have been collected. Exploration of how such models can be used to improve rural health, for example through augmentation of more basic electronic clinical decision support algorithms (eCDSAs) based on expert rules such as that described in Chapter 7, will be ground-breaking. This is because, to date, such efforts have primarily been focused on high-income settings, with only two eCDSAs for the diagnosis and management of AFI in the community having been developed and piloted in LMIC settings, both in Africa.^{307, 348} The predictive models, and their associated eCDSAs, can be further refined as new point-of-care diagnostic and prognostic tests are developed and deployed. They can also be regularly updated should data from active surveillance be available, underscoring the importance of establishing a surveillance platform as earlier described.

8.4 Reflection

This thesis concludes with a brief reflection on my doctoral study journey, which I have undertaken in tandem with being a Clinical Researcher responsible for the coordination of the SEACTN.

It gives me great pleasure to state that I have enjoyed every moment of the past three years and have grown exponentially as a global health researcher. Part of this is, of course, attributable to having a role besides that of a doctoral candidate as well as the numerous formal training courses in which I have been fortunate to participate, with subjects as diverse as artificial intelligence and machine learning, health economics, mathematical modelling of infectious diseases, and qualitative research methods. Additionally, while at times challenging, it has been pivotal for my development as an academic to be able to design, steer, and oversee large projects which involved primary data collection through to completion, secure in the knowledge that I had the backing of a dedicated team of peers and more experienced researchers with multi-disciplinary expertise, all of whom were fully invested not just in the success of the projects but also the achievement of my goals. Perhaps the most instructive component of conducting primary research has been being heavily involved in the legwork needed to get the studies off the ground across multiple countries. Not only have I gained an appreciation for the hard work of field and supporting staff, such as study monitors, but I have also developed higher levels of patience and resilience given the challenges posed by the COVID-19 pandemic and the inherent difficulties of doing research in low-resource rural and remote environments.

I have no doubt that the honing of my research, project management, supervisory, and science communication skills over the first two years of my candidature, as well as the flexibility accorded to me in carrying out my day-to-day work, were critical in driving my progression towards being an independent researcher. I have already taken the first steps by being awarded

two grants as Principal Investigator during my doctoral study, one to run the cluster-randomised trial described in Chapter 7 and the other to develop and evaluate a novel molecular diagnostic test for tuberculosis, through a translational research project currently being conducted in collaboration with colleagues from Thailand, Myanmar, and the Philippines. Winning the 2023 Oxford Tropical Network Asia Programme Three-minute Thesis Competition was the icing on the cake.

Working under the tutelage of good role models has also taught me that producing high-quality outputs, while the main yardstick, is not sufficient to be considered an excellent scientist, but that good academic citizenship is just as important. I am, therefore, grateful for the opportunity to demonstrate this by being an Associate Editor for the journal *Transactions of the Royal Society of Tropical Medicine & Hygiene*, a member of a Wellcome Trust grant advisory committee, a grant peer reviewer for the Australasian College for Infection Prevention and Control, and a Master's degree dissertation supervisor for a University of Oxford student.

Lastly, I cannot emphasise enough how much it has benefited my personal and professional growth to have had the privilege of living and working in Thailand coupled with the opportunity for frequent travel to the various SEACTN sites. While Southeast Asia is not alien to me, given that I was born and grew up in this region, I have still had the opportunity to attain upper intermediate fluency in a new language and become highly familiar with a new culture. Most importantly, however, I have gained a much better understanding of the nuances and complexities of global health, and it is these lessons that will be most helpful in shaping the success of the research I intend to carry out in this field in future.

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APPENDICES

Appendix 3.1 Village profiling – Data Collection Form template

SECTION 1: LOCATION		
1.1	Village name (if more than one name exists, enter the official name first followed by any other names, separated by “/”)	
1.2	Village code (government) (where available)	
1.3	Village code (SEACTN)	
1.4	Sub-district/upazila/township name	
1.5	Sub-district/upazila/township code	
1.6	District name	
1.7	District code	
1.8	Province/division/state name	
1.9	Province/division/state name	
SECTION 2: SOCIO-ECONOMIC CONDITIONS <i>[To be collected by telephone or by visiting villages; best to talk to other programmes professionals, census officials, local authorities or villagers]</i>		
2.1.1	What is the total population in the village?	_____ people
2.1.2	What is the source of this information?	☐ Official census ☐ Headcount ☐ Personal knowledge estimate ☐ Other – please specify _____
2.1.3	If not a personal knowledge estimate, when was this data collected (year)?	☐ Year _____ ☐ Not known
2.1.4	To your knowledge, how many households are there in the village?	_____ households

2.2.1	What is the majority ethnic group in the village (select one option)?	☐ [Site-specific options] ☐ Other – please specify _____ ☐ No dominant ethnicity
2.2.2	Which languages are used by the people of the village (select all that apply)?	☐ [Site-specific options] ☐ Other – please specify _____
2.2.3	What are the main religions practiced in the village (select all that apply)?	☐ Buddhism ☐ Christianity ☐ Hinduism ☐ Islam ☐ Animism or traditional folk religion ☐ Other – please specify _____
2.3.1	If you randomly picked 20 adults* (of any gender) in this village, how many would have finished 5 years of schooling? <i>*An adult is a person aged 18 years and above</i>	_____ people
2.3.2	What if you only picked 20 male adults in this village, how many would have finished 5 years of schooling?	_____ males
2.3.3	What if you only picked 20 female adults in this village, how many would have finished 5 years of schooling?	_____ females
SECTION 3: HEALTH SERVICES AND INFRASTRUCTURE [To be collected by telephone; SEACTN or other health workers are more likely to have adequate knowledge for this question]		
3.1	What are the existing health services available in the village or within 30 minutes' walk (select all that apply)?	☐ Government primary health centre ☐ Other government primary health facility – please specify _____ ☐ Non-government health centre ☐ Other non-government primary health facility – please specify _____ ☐ Private clinic ☐ Pharmacy

		☐ Other shop selling medicines ☐ Other – please specify _____ ☐ None
3.1.1	<i>[Only show this question if the answer to 3.1 is 'None']</i> What is the type of health facility closest to the village (select one only) and how long is the travel time to this facility?	☐ Government primary health centre ☐ Other government primary health facility – please specify _____ ☐ Non-government health centre ☐ Other non-government primary health facility – please specify _____ ☐ Private clinic ☐ Pharmacy ☐ Other shop selling medicines ☐ Other – please specify _____ Travel time _____ minutes by ☐ foot ☐ motor vehicle
3.2	Which types of healthcare workers provide health services in the village (select all that apply)?	☐ Medical doctor ☐ Nurse ☐ Pharmacist ☐ Government village/community health worker/healthcare assistant ☐ Non-government village/community health worker ☐ Traditional healer ☐ Traditional birth attendant ☐ Auxiliary midwife ☐ Malaria post worker ☐ Informal healthcare provider ☐ Other – please specify _____
3.3	Where do seriously ill people first go for treatment (select all that apply)?	☐ Government primary health centre

		☐ Other government primary health facility – please specify _____ ☐ Non-government primary health centre ☐ Other non-government primary health facility – please specify _____ ☐ Private clinic ☐ Pharmacy ☐ Other shop selling medicines ☐ Sub-district/upazila/township hospital ☐ District hospital ☐ Provincial/divisional/state referral hospital ☐ Private hospital ☐ Other – please specify _____ ☐ None
3.4	Consider the last 20 women from this village who have given birth. How many had the delivery conducted by a skilled birth attendant*? <i>*A skilled birth attendant is an accredited health professional - such as a midwife, doctor or nurse - who has been educated and trained to proficiency in the skills needed to manage normal (i.e. uncomplicated) pregnancies, childbirth and the immediate postnatal period, and in the identification, management and referral of women and neonates for complications. Traditional birth attendants, whether trained or not, are not skilled birth attendants.</i>	_____ women
3.5	Consider 20 children in this village older than 1 year old. How many have had all the following vaccines? • BCG • 3 doses of DTP • 3 doses of measles • Polio	_____ children
SECTION 4: PUBLIC UTILITIES [To be collected by telephone or by visiting villages, best to talk to local authorities or villagers]		

4.1.1	What are the main sources of drinking water for the village (select all that apply)?	☐ Piped water ☐ Tube well ☐ Borehole ☐ Well ☐ Pool/pond/lake ☐ River ☐ Canal ☐ Stream ☐ Other – please specify _____
4.1.2	If piped water is available, for how many hours each day on average?	_____ hours
4.1.3	If piped water is not available to all households, where is the main waterpoint located?	☐ In the village ☐ Outside the village
4.1.4	<i>[Only show this question if the answer to 4.1.3 is 'Outside the village']</i> If outside the village, estimate approximate travel time to the waterpoint.	_____ minutes
4.1.5	Is water available throughout the year in the village?	☐ Yes ☐ No
4.2.1	What methods of communication are available in the village (select all that apply)?	☐ Radio ☐ Television ☐ Landline phone ☐ Mobile phone ☐ Internet ☐ Post office ☐ Other
4.2.2	<i>[Only show this question if 'Mobile phone' is selected in 4.2.1]</i> Is there mobile phone signal in the village?	☐ Yes, all of the time ☐ Yes, some of the time ☐ No
4.3.1	What type of energy supply is available in the village (select all that apply)?	☐ Mains power (national or international source)

		☐ Generator ☐ Solar power ☐ Firewood ☐ Charcoal ☐ Non-electric lamps/candles ☐ Other – please specify _____
4.3.2	If mains power is available, for how long each day on average?	_____ hours
4.4.1	What types of toilet are available in the village?	☐ Flush ☐ Improved pit latrine ☐ Traditional pit latrine ☐ Bucket ☐ Other – please specify _____
4.4.2	The number of households in this village was earlier estimated at <i>[number]</i> . How many of these households have either flush toilets or latrines?	_____ households
4.5.1	Is there a school(s) in the village or within 30 minutes' walk?	☐ Yes ☐ No
4.5.2	<i>[Only show this question if 'Yes' is selected in 4.5.1]</i> If yes, type of school(s) (select all that apply).	☐ Primary school ☐ Junior secondary or middle school ☐ Senior secondary or high school ☐ Combined junior and senior secondary (high) school ☐ Vocational or technical school ☐ Other – please specify _____
4.5.3	<i>[Only show this question if 'No' is selected in 4.5.1]</i> If no, how far is the nearest school from the village centre?	_____ km

Appendix 4.1 Observational study – Case Report Form (Village Health Worker/Village Malaria Worker) template

SEACTN Work Package A CRF – VHW	
Determining the incidence, causes and outcomes of rural febrile illness (RFI) in South and Southeast Asia, as part of the South and Southeast Asian Community-based Trials Network (SEACTN) Work Package A (WP-A) (Village Health Worker)	
Site Code: Staff ID: Only proceed for patients without scheduled appointments. Screening Number: Screening Date: Is the screening date today? ☐ YES ☐ NO (If NO) Select screening date: Has the patient been previously enrolled in this study for another instance of febrile illness? ☐ YES ☐ NO (If YES) Please type the participant number of his/her first enrollment below.	

DEMOGRAPHICS	
Is the patient's date of birth known? ☐ YES ☐ NO (If YES) Date of birth: (If NO) Age: years months days Sex: ☐ Male ☐ Female ☐ Other Pregnant: ☐ YES ☐ NO	

REASON FOR PRESENTATION

What is the main reason the patient visited the primary health centre today?

- ☐ Snake bite ☐ Trauma / accident
- ☐ Minor injury / wound dressing ☐ None of the above
- ☐ Child delivery

CRITICAL ILLNESS

Was the patient too unwell to be screened? ☐ YES ☐ NO

(If YES) What was the reason?

- ☐ Unconscious or lethargic ☐ Convulsions ☐ Haemorrhage (not obstetric)
- ☐ Difficulty breathing ☐ Uncontrollable pain ☐ Other, please specify: _____
- ☐ Obstetric problem ☐ Confused / disturbed mental state

(If YES) Was the patient referred? ☐ YES ☐ NO

(If YES) Where?

- ☐ Government health centre ☐ Government hospital ☐ Private clinic
- ☐ Private hospital ☐ Other

(If NO) Why?

- ☐ No transport / access ☐ Patient refusal ☐ Death ☐ Clinician decision not to refer ☐ Other

FEBRILE ILLNESS

Take the patient's axillary temperature and record the measurement to one decimal point.

_____.____°C OR _____.____°F

Did the patient have a fever in the last 24 hours? ☐ YES ☐ NO

ACUTE FEBRILE SYNDROMES

"Have you developed new or worsening of any of the following symptoms as part of this illness?"

Convulsions	☐ Yes ☐ No	Loose or frequent motions	☐ Yes ☐ No
Runny nose, nasal congestion or sore throat	☐ Yes ☐ No	(if YES) Blood in stools	☐ Yes ☐ No
Ear pain or discharge	☐ Yes ☐ No	Frequent urination or pain on urination	☐ Yes ☐ No
Tooth pain	☐ Yes ☐ No	Visible swelling or redness of one or more joints	☐ Yes ☐ No
Cough	☐ Yes ☐ No	Redness, discharge or pustules on area of skin	☐ Yes ☐ No
(if YES) Duration of cough (days)	_____	Diffuse rash	☐ Yes ☐ No
(if YES) Producing sputum (not saliva)	☐ Yes ☐ No	Eschar	☐ Yes ☐ No
(if YES) Coughing up blood	☐ Yes ☐ No	Unable to drink / feed	☐ Yes ☐ No
Shortness of breath or difficult breathing	☐ Yes ☐ No	Unable to walk	☐ Yes ☐ No
Wheeze or noisy breathing	☐ Yes ☐ No	Abnormally sleepy / lethargic / confused	☐ Yes ☐ No
Vomits everything	☐ Yes ☐ No	Other, please specify: _____	☐ Yes ☐ No
Loss of smell or taste	☐ Yes ☐ No		

"Has your child developed new or worsening of any of the following symptoms as part of this illness?"

Convulsions	☐ Yes ☐ No	Loose or frequent motions	☐ Yes ☐ No
Runny nose, nasal congestion or sore throat	☐ Yes ☐ No	(if YES) Blood in stools	☐ Yes ☐ No
Ear pain or discharge, swelling behind the ear or pulling at their ear	☐ Yes ☐ No	Visible swelling or redness of one or more joints	☐ Yes ☐ No
Tooth pain (not normal teething pains)	☐ Yes ☐ No	Redness, discharge or pustules on area of skin	☐ Yes ☐ No
Cough	☐ Yes ☐ No	Diffuse rash	☐ Yes ☐ No
(if YES) Duration of cough (days)	_____	Eschar	☐ Yes ☐ No
(if YES) Coughing up blood	☐ Yes ☐ No	Unable to drink / feed	☐ Yes ☐ No
Difficult breathing	☐ Yes ☐ No	Unable to sit / stand / walk when previously able	☐ Yes ☐ No
Vomits everything	☐ Yes ☐ No	Abnormally sleepy / lethargic	☐ Yes ☐ No
Pain / crying on urination or avoiding urination	☐ Yes ☐ No	Other, please specify: _____	_____
“Has your child had...”			
Convulsions	☐ Yes ☐ No	Redness, discharge or pustules on area of skin	☐ Yes ☐ No
Difficult breathing or turning blue	☐ Yes ☐ No	Yellowing of the eyes or skin	☐ Yes ☐ No
Vomits everything	☐ Yes ☐ No	Unable to drink / feed / reduced suckling	☐ Yes ☐ No
Loose motions	☐ Yes ☐ No	Abnormally sleepy / moves only when stimulated	☐ Yes ☐ No
Redness around or discharge from umbilicus	☐ Yes ☐ No	Other, please specify: _____	_____ –

NON-FEBRILE SYNDROMES

Duration of illness ☐ Less than or equal to 14 days ☐ More than 14 days

ACUTE NON-FEBRILE SYNDROMES

“Have you developed new or worsening of any of the following symptoms as part of this illness?”

Headache / migraine	☐	Intestinal worms	☐
Dizziness / vertigo	☐	Tiredness	☐
Abdominal pain	☐	Limb weakness	☐
Runny nose, nasal congestion or sore throat	☐	Dysuria	☐
Cough	☐	Skin problem (tinea / eczema)	☐
Shortness of breath or difficult breathing	☐	Other, please specify: _____	☐
Diarrhoea	☐		

“Has your child developed new or worsening of any of the following symptoms as part of this illness?”

Abdominal pain	☐	Intestinal worms	☐
Runny nose, nasal congestion or sore throat	☐	Skin problem (tinea / eczema)	☐
Difficult breathing	☐	Other, please specify: _____	☐
Diarrhoea	☐		

“Has your child had...”

Skin problem	☐	Abnormally sleepy / moves only when stimulated	☐
Watery / bloody stool	☐	Malnutrition	☐
Difficult breathing	☐	Yellowing of the eyes or skin	☐
Unable to drink / feed	☐	Other, please specify: _____	☐

CHRONIC NON-FEBRILE SYNDROMES

☐ Failure to thrive ☐ Fever ☐ Weight loss ☐ Gastro-oesophageal reflux

☐ Back pain	☐ Cough with blood	☐ Night sweats	☐ Other, please specify: _____
☐ Joint pain	☐ Cough without blood	☐ Fatigue	
☐ Headache	☐ Breathlessness	☐ Chronic rash or skin changes	

STUDY ELIGIBILITY		
Inclusion criteria (all should be “Yes”)	Yes	No
Axillary temperature at presentation ($\geq 37.5^{\circ}\text{C}$ (99.5°F) OR $< 35.5^{\circ}\text{C}$ (95.9°F)) OR history of fever in last 24h (<i>from above</i>)		
Willingness and ability to comply with study protocol for the study duration	☐	☐
Participant (or caretaker) is willing and able to give informed consent for participation in the study	☐	☐
Exclusion criteria (all should be “No”)	Yes	No
Currently enrolled in the study	☐	☐
Accident or trauma is the cause for presentation (<i>from above</i>)		
Presentation within 3 days after routine immunisations	☐	☐

ENROLMENT
Is the consent form signed? ☐ YES ☐ NO

D0 FEBRILE PATIENT

Participant no: |_|_|_|_|

CONTACT DETAILS

District: (District of VHW)

Village: (Village of VHW)

☐ Yes ☐ No

(If NO) Province: _____ District: _____ Village: _____

VITAL HEALTH MEASUREMENTS

Heart rate |_|_|_|beats per minute

No value was recorded. Please select a reason

- ☐ Patient refusal
- ☐ Patient condition
- ☐ Technical problem/equipment failure
- ☐ Other, please specify: _____

Respiratory rate |_|_|_|breaths per minute

No value was recorded. Please select a reason

- ☐ Patient refusal
- ☐ Patient condition
- ☐ Technical problem/equipment failure
- ☐ Other, please specify: _____

MUAC |_|_|_|mm

No value was recorded. Please select a reason

- ☐ Patient refusal
- ☐ Patient condition
- ☐ Technical problem/equipment failure
- ☐ Other, please specify: _____

Mental status	☐ Alert ☐ Voice ☐ Pain ☐ Unresponsive
During the vital health measurements was the patient: ☐ Calm ☐ Uncooperative	
HISTORY OF CURRENT ILLNESS	
Did the patient seek care prior to today for this illness? ☐ YES ☐ NO	
(If YES) From where?	☐ Traditional healer ☐ Village health worker (me) ☐ Village health worker (other) ☐ Government health centre ☐ Government hospital ☐ Private clinic ☐ Private hospital ☐ Pharmacy / Drug store ☐ Other
Type of medication received	☐ Oral ☐ Inhaled ☐ Topical ☐ Oxygen ☐ Nebulisers ☐ IV ☐ IM ☐ None (If Oral) List the oral medication(s) received, if known: _____
ENROLLED PATIENT REFERRAL	
Is the patient being referred to receive further healthcare? ☐ YES ☐ NO	
(If YES) Where?	
☐ Traditional healer ☐ Government health centre ☐ Government hospital ☐ Private clinic	☐ Private hospital ☐ Pharmacy / Drug store ☐ Other
ENROLMENT SAMPLES	
Dried Blood Spot collected? ☐ YES ☐ NO	
(If NO) What was the reason?	

(If YES) Time: [_H_][_H_] : [_M_][_M_]

Number of complete dried blood spots collected: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

Dried Blood Spot
(scan barcode)

Malaria RDT result ☐ Positive ☐ Negative ☐ Invalid ☐ Not done

(If Positive) Which malaria species? ☐ *P. falciparum* ☐ *P. vivax* ☐ Pan

D28 FOLLOW-UP

Site Code: |_|_|_|_|_| Participant Number: |_|_|_|_|_|

Staff ID: _____

FOLLOW-UP OUTCOME

Follow-up date: |_D_|_|D_|_|M_|_|M_|_|M_|_|/|_2_|_|0_|_|Y_|_|Y_|_|

Is the status of the patient known?

☐ Alive ☐ Dead ☐ Unknown or uncontactable ☐ Withdrawal from the study

(If Dead) Is the date of death known? ☐ Known ☐ Unknown

(If Known) Date of death

|_|_|-|_|_|_|_|-|_|_|_|_|

Place of death ☐ Home

☐ Healthcare facility. Name: _____

☐ Other, please specify: _____

(If Withdrawal) Reason: _____

☐ Check this box if the patient has withdrawn consent for his/her data to be used.

(If Unknown or uncontactable) Exit form

(If Alive) ☐ Follow-up done in person

☐ Follow-up done by telephone

ILLNESS OUTCOME

Have the patient's symptoms resolved? ☐ Yes ☐ No

If Yes: Estimate total duration of illness (days) |___|___|

If No: ☐ Same ☐ Worse ☐ Better

Has the patient sought care since enrolment? ☐ Yes ☐ No ☐ Unknown

☐ Traditional healer

☐ Private clinic

(If Yes)

☐ Village health worker (me)

☐ Private hospital (this one)

From where?

☐ Village health worker (other)

☐ Pharmacy / drug store

☐ Government health centre

☐ Other

☐ Government hospital

(If Yes) Sought care since enrolment for: ☐ Illness present at enrolment ☐ Different illness
☐ Both of the above

Has the patient received oral medication since enrolment? ☐ Yes ☐ No ☐ Unknown

(If Yes) From where?

☐ Traditional healer	☐ Private clinic
☐ Village health worker (me)	☐ Private hospital
☐ Village health worker (other)	☐ Pharmacy / Drug store
☐ Government health centre	☐ Other
☐ Government hospital	

List the oral medication(s) received, if known: _____

Has the patient been admitted overnight to a health facility since enrolment? ☐ Yes ☐ No ☐ Unknown

(If Yes) Number of nights spent in any health facility: |__| |__| |__| |__| |__|

Location: ☐ Government facility ☐ Private facility ☐ Other

Is the patient able to identify the approximate amount spent? ☐ Yes ☐ No

(If Yes) Approximate amount spent in local currency (number): |__| |__| |__| |__| |__| |__|

D28 FOLLOW-UP SAMPLES

Dried Blood Spot collected? ☐ Yes ☐ No

(If No) What was the reason?

- ☐ Patient refusal
- ☐ Inability to bleed patient
- ☐ Equipment not available
- ☐ Other, please specify: _____

(If Yes) Time: [__H__][__H__] : [__M__][__M__]

Number of complete dried blood spots collected: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

Dried Blood Spot (scan barcode) |__| |__| |__| |__| |__| |__| |__|

Appendix 4.2 Observational study – Case Report Form (Primary Health Centre) template

SEACTN Work Package A CRF – PHC	
Determining the incidence, causes and outcomes of rural febrile illness (RFI) in South and Southeast Asia, as part of the South and Southeast Asian Community-based Trials Network (SEACTN) Work Package A (WP-A) (Primary Health Centre)	
Site Code: Staff ID: Only proceed for patients without scheduled appointments. Screening Number: Screening Date: / / Is the screening date today? ☐ YES ☐ NO (If NO) Select screening date: Has the patient been previously enrolled in this study for another instance of febrile illness? ☐ YES ☐ NO (If YES) Please type the participant number of his/her first enrollment below.	

DEMOGRAPHICS	
Is the patient's date of birth known? ☐ YES ☐ NO (If YES) Date of birth: (If NO) Age: years months days Sex: ☐ Male ☐ Female ☐ Other Pregnant: ☐ YES ☐ NO	

REASON FOR PRESENTATION

What is the main reason the patient visited the primary health centre today?

- ☐ Snake bite ☐ Trauma / accident
- ☐ Minor injury / wound dressing ☐ None of the above
- ☐ Child delivery

CRITICAL ILLNESS

Was the patient too unwell to be screened? ☐ YES ☐ NO

(If YES) What was the reason?

- ☐ Unconscious or lethargic ☐ Convulsions ☐ Haemorrhage (not obstetric)
- ☐ Difficulty breathing ☐ Uncontrollable pain ☐ Other, please specify: _____
- ☐ Obstetric problem ☐ Confused / disturbed mental state

(If YES) Was the patient referred? ☐ YES ☐ NO

(If YES) Where?

- ☐ Government health centre ☐ Government hospital ☐ Private clinic
- ☐ Private hospital ☐ Other

(If NO) Why?

- ☐ No transport / access ☐ Patient refusal ☐ Death ☐ Clinician decision not to refer ☐ Other

FEBRILE ILLNESS

Take the patient's axillary temperature and record the measurement to one decimal point.

_____.____°C OR _____°F

Did the patient have a fever in the last 24 hours? ☐ YES ☐ NO

ACUTE FEBRILE SYNDROMES

"Have you developed new or worsening of any of the following symptoms as part of this illness?"

Convulsions	☐ Yes ☐ No	Loose or frequent motions	☐ Yes ☐ No
Runny nose, nasal congestion or sore throat	☐ Yes ☐ No	(if YES) Blood in stools	☐ Yes ☐ No
Ear pain or discharge	☐ Yes ☐ No	Frequent urination or pain on urination	☐ Yes ☐ No
Tooth pain	☐ Yes ☐ No	Visible swelling or redness of one or more joints	☐ Yes ☐ No
Cough	☐ Yes ☐ No	Redness, discharge or pustules on area of skin	☐ Yes ☐ No
(if YES) Duration of cough (days)	_____	Diffuse rash	☐ Yes ☐ No
(if YES) Producing sputum (not saliva)	☐ Yes ☐ No	Eschar	☐ Yes ☐ No
(if YES) Coughing up blood	☐ Yes ☐ No	Unable to drink / feed	☐ Yes ☐ No
Shortness of breath or difficult breathing	☐ Yes ☐ No	Unable to walk	☐ Yes ☐ No
Wheeze or noisy breathing	☐ Yes ☐ No	Abnormally sleepy / lethargic / confused	☐ Yes ☐ No
Vomits everything	☐ Yes ☐ No	Other, please specify: _____	☐ Yes ☐ No
Loss of smell or taste	☐ Yes ☐ No		

“Has your child developed new or worsening of any of the following symptoms as part of this illness?”			
Convulsions	☐ Yes ☐ No	Loose or frequent motions	☐ Yes ☐ No
Runny nose, nasal congestion or sore throat	☐ Yes ☐ No	(if YES) Blood in stools	☐ Yes ☐ No
Ear pain or discharge, swelling behind the ear or pulling at their ear	☐ Yes ☐ No	Visible swelling or redness of one or more joints	☐ Yes ☐ No
Tooth pain (not normal teething pains)	☐ Yes ☐ No	Redness, discharge or pustules on area of skin	☐ Yes ☐ No
Cough	☐ Yes ☐ No	Diffuse rash	☐ Yes ☐ No
(if YES) Duration of cough (days)	_____	Eschar	☐ Yes ☐ No
(if YES) Coughing up blood	☐ Yes ☐ No	Unable to drink / feed	☐ Yes ☐ No
Difficult breathing	☐ Yes ☐ No	Unable to sit / stand / walk when previously able	☐ Yes ☐ No
Vomits everything	☐ Yes ☐ No	Abnormally sleepy / lethargic	☐ Yes ☐ No
Pain / crying on urination or avoiding urination	☐ Yes ☐ No	Other, please specify: _____	_____
“Has your child had...”			
Convulsions	☐ Yes ☐ No	Redness, discharge or pustules on area of skin	☐ Yes ☐ No
Difficult breathing or turning blue	☐ Yes ☐ No	Yellowing of the eyes or skin	☐ Yes ☐ No
Vomits everything	☐ Yes ☐ No	Unable to drink / feed / reduced suckling	☐ Yes ☐ No
Loose motions	☐ Yes ☐ No	Abnormally sleepy / moves only when stimulated	☐ Yes ☐ No
Redness around or discharge from umbilicus	☐ Yes ☐ No	Other, please specify: _____	_____ —

DIAGNOSIS

How many days has the patient had these symptoms? _____

What do you think is wrong with the patient?

☐ Upper respiratory tract infection	☐ Eye infection	☐ Bone or joint infection
☐ Lower respiratory tract infection	☐ Diarrhoeal illness	☐ Brain or nervous system infection
☐ Urinary tract infection	☐ Other gastro-intestinal tract infection	☐ Fever of unknown source
☐ Sexually-transmitted infection	☐ Skin and soft tissue infection	☐ Other, please specify: _____
☐ Ear infection		

ANTIBIOTIC PRESCRIPTION

Was this patient prescribed antibiotics? ☐ YES ☐ NO

(If YES) Which antibiotics were prescribed? (Site-specific options as per example below)

☐ Amoxicillin	☐ Metronidazole
☐ Artemether/lumefantrine	☐ Penicillin
☐ Co-trimoxazole	☐ Other, please specify: _____

NON-FEBRILE SYNDROMES

Duration of illness ☐ Less than or equal to 14 days ☐ More than 14 days

ACUTE NON-FEBRILE SYNDROMES

“Have you developed new or worsening of any of the following symptoms as part of this illness?”

Headache / migraine	☐	Intestinal worms	☐
Dizziness / vertigo	☐	Tiredness	☐
Abdominal pain	☐	Limb weakness	☐
Runny nose, nasal congestion or sore throat	☐	Dysuria	☐
Cough	☐	Skin problem (tinea / eczema)	☐
Shortness of breath or difficult breathing	☐	Other, please specify: _____	☐
Diarrhoea	☐		

“Has your child developed new or worsening of any of the following symptoms as part of this illness?”

Abdominal pain	☐	Intestinal worms	☐
Runny nose, nasal congestion or sore throat	☐	Skin problem (tinea / eczema)	☐
Difficult breathing	☐	Other, please specify: _____	☐
Diarrhoea	☐		

“Has your child had...”

Skin problem	☐	Abnormally sleepy / moves only when stimulated	☐
Watery / bloody stool	☐	Malnutrition	☐
Difficult breathing	☐	Yellowing of the eyes or skin	☐
Unable to drink / feed	☐	Other, please specify: _____	☐

CHRONIC NON-FEBRILE SYNDROMES

☐ Failure to thrive ☐ Fever ☐ Weight loss ☐ Gastro-oesophageal reflux
☐ Back pain ☐ Cough with blood ☐ Night sweats ☐ Other, please specify: _____

☐ Joint pain	☐ Cough without blood	☐ Fatigue
☐ Headache	☐ Breathlessness	☐ Chronic rash or skin changes

STUDY ELIGIBILITY

Inclusion criteria (all should be “Yes”)	Yes	No
Axillary temperature at presentation ($\geq 37.5^{\circ}\text{C}$ (99.5°F) OR $< 35.5^{\circ}\text{C}$ (95.9°F)) OR history of fever in last 24h (<i>from above</i>)		
Willingness and ability to comply with study protocol for the study duration	☐	☐
Participant (or caretaker) is willing and able to give informed consent for participation in the study	☐	☐
Exclusion criteria (all should be “No”)	Yes	No
Currently enrolled in the study	☐	☐
Accident or trauma is the cause for presentation (<i>from above</i>)		
Presentation within 3 days after routine immunisations	☐	☐

ENROLMENT

Is the consent form signed? ☐ YES ☐ NO

D0 FEBRILE PATIENT

Participant no: |_|_|_|_|

CONTACT DETAILS

District: (District of PHC)

Village: (Village of PHC)

☐ Yes ☐ No

(If NO) Province: _____ District: _____ Village: _____

VITAL HEALTH MEASUREMENTS

Heart rate |_|_|_| beats per minute

No value was recorded. Please select a reason

- ☐ Patient refusal
☐ Patient condition
☐ Technical problem/equipment failure
☐ Other, please specify: _____

MUAC |_|_|_| mm

No value was recorded. Please select a reason

- ☐ Patient refusal
☐ Patient condition
☐ Technical problem/equipment failure
☐ Other, please specify: _____

Respiratory rate |_|_| breaths per minute

No value was recorded. Please select a reason

- ☐ Patient refusal
☐ Patient condition
☐ Technical problem/equipment failure
☐ Other, please specify: _____

Blood pressure |_|_|_| / |_|_|_| mmHg

No value was recorded. Please select a reason

- ☐ Patient refusal
☐ Patient condition
☐ Technical problem/equipment failure
☐ Other, please specify: _____

Mental status
☐ Alert ☐ Voice
☐ Pain ☐ Unresponsive

Height |_|_|_| cm

No value was recorded. Please select a reason

- ☐ Patient refusal
☐ Patient condition
☐ Technical problem/equipment failure
☐ Other, please specify: _____

Oxygen saturation |_|_| %

Weight |_|_| . |_|_| kg

No value was recorded. Please select a reason ☐ Patient refusal ☐ Patient condition ☐ Technical problem/equipment failure ☐ Other, please specify: _____	No value was recorded. Please select a reason ☐ Patient refusal ☐ Patient condition ☐ Technical problem/equipment failure ☐ Other, please specify: _____
During the vital health measurements was the patient: ☐ Calm ☐ Uncooperative	
HISTORY OF CURRENT ILLNESS	
Did the patient seek care prior to today for this illness? ☐ YES ☐ NO	
(If YES) From where?	☐ Traditional healer ☐ Private clinic ☐ Village health worker ☐ Private hospital ☐ Government health centre (this one) ☐ Pharmacy / Drug store ☐ Government health centre (other) ☐ Other ☐ Government hospital
Type of medication received	☐ Oral ☐ Inhaled ☐ Topical ☐ Oxygen ☐ Nebulisers ☐ IV ☐ IM ☐ None (If Oral) List the oral medication(s) received, if known: _____
ENROLLED PATIENT REFERRAL	
Is the patient being referred to receive further healthcare? ☐ YES ☐ NO	
(If YES) Where? ☐ Traditional healer ☐ Government health centre ☐ Government hospital ☐ Private clinic ☐ Private hospital ☐ Pharmacy / Drug store ☐ Other	
ENROLMENT SAMPLES	
Dried Blood Spot collected? ☐ YES ☐ NO	
(If NO) What was the reason? ☐ Patient refusal ☐ Inability to bleed patient ☐ Equipment not available ☐ Other, please specify: _____	

(If YES) Time: [_H_][_H_] : [_M_][_M_]

Number of complete dried blood spots collected: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

Dried Blood Spot
(scan barcode) | _ _ | _ _ | _ _ | _ _ | _ _ | _ _ | _ _ |

Malaria RDT result ☐ Positive ☐ Negative ☐ Invalid ☐ Not done

(If Positive) Which malaria species? ☐ *P. falciparum* ☐ *P. vivax* ☐ Pan

D28 FOLLOW-UP

Site Code: |_|_|_|_|_| Participant Number: |_|_|_|_|_|

Staff ID: _____

FOLLOW-UP OUTCOME

Follow-up date: |_D_|_|D_|_|M_|_|M_|_|M_|_|/|_2_|_|0_|_|Y_|_|Y_|_|

Is the status of the patient known?

☐ Alive ☐ Dead ☐ Unknown or uncontactable ☐ Withdrawal from the study

(If Dead) Is the date of death known? ☐ Known ☐ Unknown

(If Known) Date of death

|_|_|-|_|_|_|_|-|_|_|_|_|

Place of death ☐ Home

☐ Healthcare facility. Name: _____

☐ Other, please specify: _____

(If Withdrawal) Reason: _____

☐ Check this box if the patient has withdrawn consent for his/her data to be used.

(If Unknown or uncontactable) Exit form

(If Alive) ☐ Follow-up done in person

☐ Follow-up done by telephone

ILLNESS OUTCOME

Have the patient's symptoms resolved? ☐ Yes ☐ No

If Yes: Estimate total duration of illness (days) |___|___|

If No: ☐ Same ☐ Worse ☐ Better

Has the patient sought care since enrolment? ☐ Yes ☐ No ☐ Unknown

☐ Traditional healer

☐ Private clinic

(If Yes)

☐ Village health worker (me)

☐ Private hospital (this one)

From where?

☐ Village health worker (other)

☐ Pharmacy / drug store

☐ Government health centre

☐ Other

☐ Government hospital

(If Yes) Sought care since enrolment for: ☐ Illness present at enrolment ☐ Different illness
☐ Both of the above

Has the patient received oral medication since enrolment? ☐ Yes ☐ No ☐ Unknown

(If Yes) From where?

☐ Traditional healer	☐ Private clinic
☐ Village health worker (me)	☐ Private hospital
☐ Village health worker (other)	☐ Pharmacy / Drug store
☐ Government health centre	☐ Other
☐ Government hospital	

List the oral medication(s) received, if known: _____

Has the patient been admitted overnight to a health facility since enrolment? ☐ Yes ☐ No ☐ Unknown

(If Yes) Number of nights spent in any health facility: |__|__|__|__|__|

Location: ☐ Government facility ☐ Private facility ☐ Other

Is the patient able to identify the approximate amount spent? ☐ Yes ☐ No

(If Yes) Approximate amount spent in local currency (number): |__|__|__|__|__|__|

D28 FOLLOW-UP SAMPLES

Dried Blood Spot collected? ☐ Yes ☐ No

(If No) What was the reason?

- ☐ Patient refusal
- ☐ Inability to bleed patient
- ☐ Equipment not available
- ☐ Other, please specify: _____

(If Yes) Time: [H][H] : [M][M]

Number of complete dried blood spots collected: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

Dried Blood Spot (scan barcode) |__|__|__|__|__|__|__|__|

Appendix 4.3 Observational study – Standard Operating Procedures

This appendix begins on the next page.

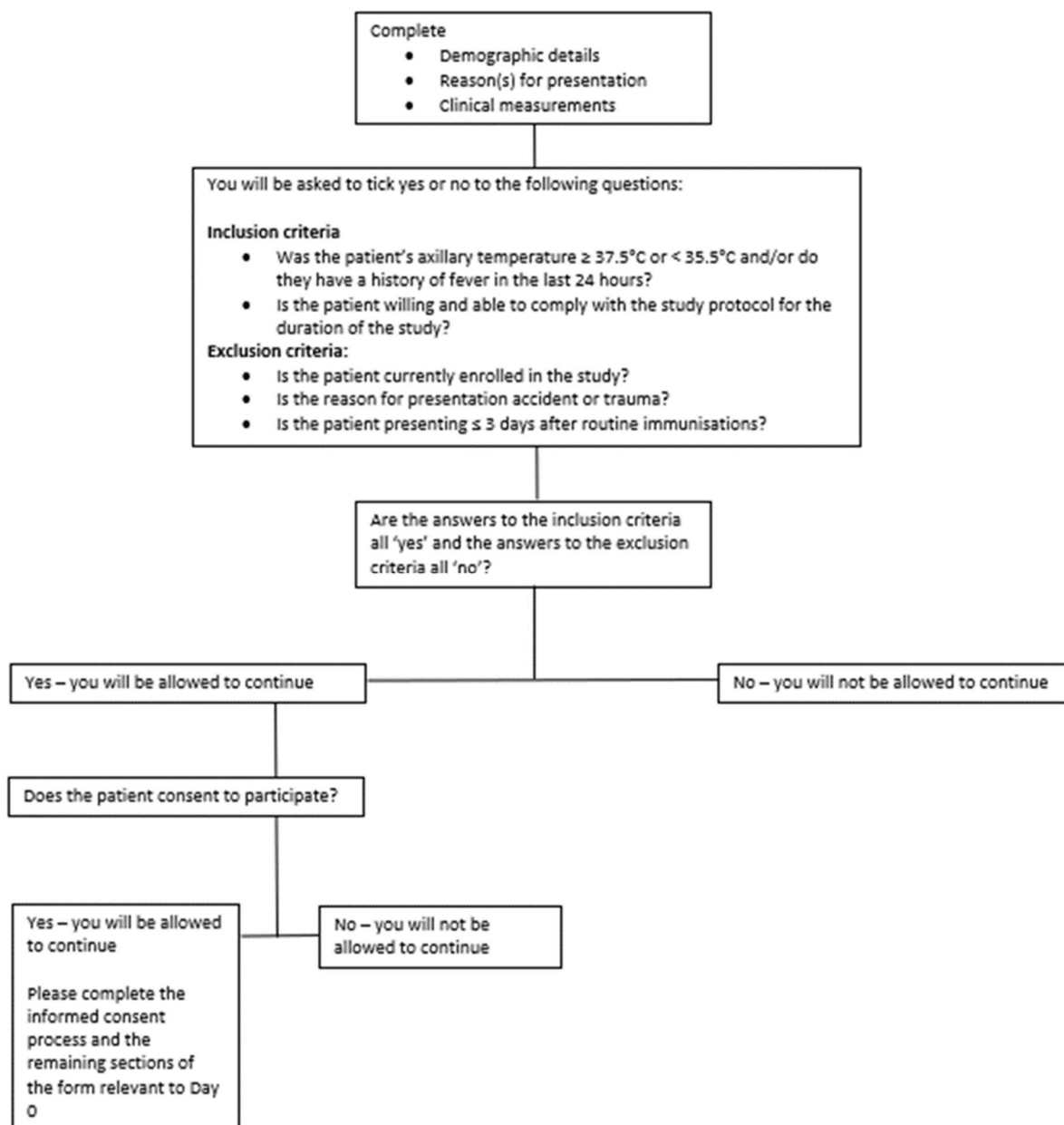
SEACTN Work Package-A

Standard Operating Procedure

Title:	Patient eligibility
Version:	1.0
Date:	20 July 2021

Procedure:

1. Follow the instructions on the CommCare app for checking patient eligibility as shown in the flowchart below.
2. The app will tell you if the patient is eligible based on the information about them you enter.
3. In the event the patient is not eligible, an error message will appear and you will not be able to proceed with the remainder of the form. You will have the opportunity to revisit the information entered in case you have entered it wrongly.



SEACTN Work Package-A

Standard Operating Procedure

Title:	Informed consent
Version:	1.0
Date:	21 April 2021

Abbreviations

GCP	Good Clinical Practice
ICF	Informed Consent Form
PIS	Patient Information Sheet
VHW	Village Health Worker
HCW	Health Care Worker

Background

SEACTN project aims to better understand febrile illness in rural areas of South and Southeast Asia. SEACTN Work Package-A is a prospective observational cohort study that will recruit patients of all ages with acute febrile illness attending village health workers or peripheral health facilities in rural Laos, Myanmar, and Bangladesh. The study aims to determine the incidence of febrile illness in rural communities, to determine aetiologies of community febrile illness by laboratory methods and to assess performance of host biomarkers in association with aetiology and outcomes.

Purpose and Scope

This document describes the procedures for seeking informed consent from potential participants and caretakers of potential participants.

Requirements

- Informed consent form
- Participant information sheet

This SOP is intended for research staff familiar with consenting patients for participation in the study and who have been authorised to do so by the Principal Investigator(s).

Procedures

Prior to the initiation of enrolment, community engagement or sensitization meetings with village leaders and local authority will be arranged to explain overall study objectives and activities. A waiver of consent or community consent as applicable in each site will be sought for collecting limited demographic data, reason for presenting from ALL patients seeking care at VHWs /HCWs during the initial screening. Only patients with an acute febrile illness will then be enrolled into the study.

Procedures for obtaining informed consent from potential participants:

1. In patients found to have an acute febrile illness during screening, informed consent should be obtained before proceeding with the **DO Febrile Patient Form** and blood sample collection.
2. If patient is a child, confirm that the caretaker is either the child's parent or a legally acceptable representative such as a close relation to the child, as per local guidelines.
3. Provide a brief summary of the study and explain that before providing a detailed explanation and seeking their consent for participation, you would like to determine whether the patient is eligible to participate.
4. Confirm eligibility by asking the patient or caretaker and consulting the patient's medical record.
5. If the patient is not eligible, thank the patient and/or caretaker and explain that you do not need to recruit their child to the study. Reassure the patient and/or caretaker that his/her or their child's clinical care will not be affected in any way.
6. If the patient is eligible, inform them that you would like to provide more information about the study, to help them decide if (s)he and/or their child should take part. Reassure the patient and/or caretaker that the routine clinical care will not be affected by their decision.
7. Confirm patient's age and choose the appropriate informed consent form(s) required for that age group.

Example table for Laos site (This table will be adjusted base on local legal requirements.)

Age	<12 years	12 to <15 years	15 years and over (adult)
Adult ICF for parents or LAR	X	X	
IAF		X	
Adult ICF for participants			X

8. Provide a summary of the study in simple language detailing the:
 - a. They are going to participate in "Research" study aims to better understand the incidence and causes of acute febrile illness in rural area in this region to improve its treatment in the future.
 - b. Collection of medical history, demographic data and follow-up processes today. Collection of outcome data one month later.

- c. Collection of blood sample (finger/heel prick) today and one month later.
 - d. Risks of discomfort during the collection of finger/heel prick (as well as the plan to minimise discomfort where possible by collection of routine clinical samples and research samples together);
 - e. Anticipated benefits of the study to the wider community;
 - f. Follow up arrangement and reimbursement of transportation if patient comes to the VHW.
9. Explain that if the patient and/or caretaker agrees to take part, they can change their mind at any time. Their participation is voluntary.
 10. Reassure them that their decision will not affect the care that the VHW will provide for them or their child.
 11. If the patient and/or caretaker is undecided, offer to answer any questions or clarify any misunderstandings.
 12. Explain that the patient and/or caretaker can take their time to decide.
 13. Use the Patient Information Sheet (PIS) to support your explanations and give the patient and/or caretaker a copy of the PIS for their records. If the patient and/or caretaker is illiterate, still give them a copy of the PIS and explain that they (or a family member) may want to refer to it at a later date.
 14. If the patient and/or caretaker refuses for their child to take part, thank them and assist them to return to routine steps of the clinic.
 15. If the patient and/or caretaker agrees for their child to take part, thank them and proceed with completion of the Informed Consent Form (ICF) and enrolment of the patient. The patients and/or caretaker must sign and date in the appropriate places of the consent form.
 16. If the patient and/or caretaker is illiterate, arrange for an impartial person to witness the consent process. The patient and/or caretaker will provide thumb print and the witness will counter-sign the ICF in the appropriate places.
 17. Give the patient and/or caretaker a copy of the signed ICF for their records. If no photocopy is available, sign on two forms or use carbon copy as appropriate. If subjects and/or caretaker refuse to keep a copy, document in the study file.

Update history

Version	Date	Summary of changes
0.1	Dec 2020	Draft created and circulated for inputs
1.0	21 Apr 2021	Version approved by PI (Prof Yoel Lubell)

SEACTN Work Package-A

Standard Operating Procedure

Title:	Measurement of blood pressure
Version:	1.0
Date:	14 July 2021

Materials and Equipment:

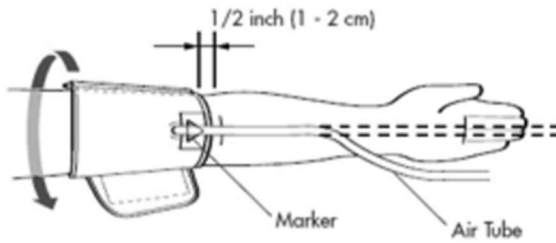
1. Automated sphygmomanometer and cuffs (OMRON HEM-7121)

Procedure:

1. Sit the patient upright with their upper arm positioned level with their heart and feet flat on the floor. Ensure the patient is relaxed.



2. Remove excess clothing that might interfere with the sphygmomanometer cuff or constrict blood flow in the arm.
3. Clean the sphygmomanometer cuff with an alcohol wipe and allow the alcohol to dry.
4. Choose the correct cuff size by wrapping it around the patient's arm and using the 'Index' line to ensure the patient's arm circumference falls within the 'Range' area. Choose a cuff of a different size if it does not.
5. Feel for the brachial pulse and place cuff so that the 'Artery' marker points to where the pulse is. If the brachial pulse is not palpable, place the cuff approximately where it should be felt, as in the picture.



6. Wrap the cuff snugly around arm.
7. Press the button on the sphygmomanometer to begin recording blood pressure.
8. Wait for the measurement to be completed and the reading displayed.



9. Enter the reading into the electronic case report form. If the measurement was not obtained, select the reason from the options provided.
10. Clean the sphygmomanometer cuff with an alcohol wipe. Allow the alcohol to dry before using it on the next patient.
11. Remove batteries from the sphygmomanometer at the end of the day to avoid damage from battery leaks.

Important note: Consider whether referral is required if the systolic blood pressure (first number) is <90 mmHg, or if the diastolic blood pressure (second number) is <40 or >140 mmHg.

SEACTN Work Package-A

Standard Operating Procedure

Title:	Measurement of mid-upper arm circumference
Version:	1.0
Date:	14 July 2021

Materials and equipment:

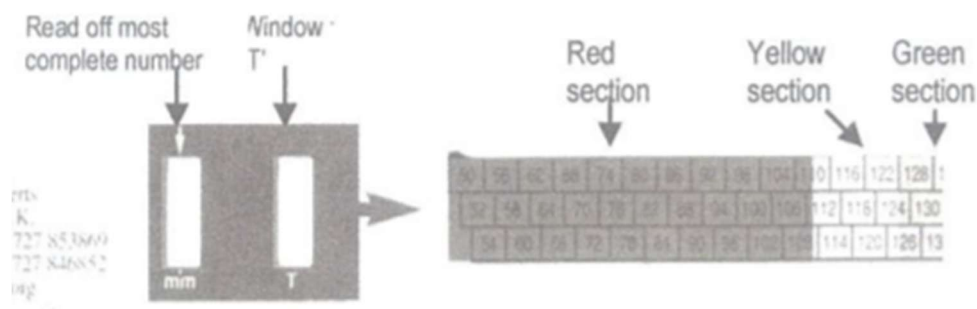
1. MUAC tape

Procedure:

1. If the tape is new, press out the black paper in the windows marked 'mm' and 'T'.
2. Place the tape round the middle of the limb left upper arm. The tape should be tight but not wrinkle the skin.



3. Pass the tail through the window marked 'T', then read the number which shows as the most complete in the window marked 'mm'.



For example, the correct reading in the picture below is 154 mm.



If the measurement was not obtained, select the reason from the options provided.

SEACTN Work Package-A

Standard Operating Procedure

Title:	Measurement of oxygen saturation
Version:	1.0
Date:	14 July 2021

Materials and Equipment:

1. Pulse oximeter and probes (adult, paediatric, and neonatal) (Lifebox)

Procedure:

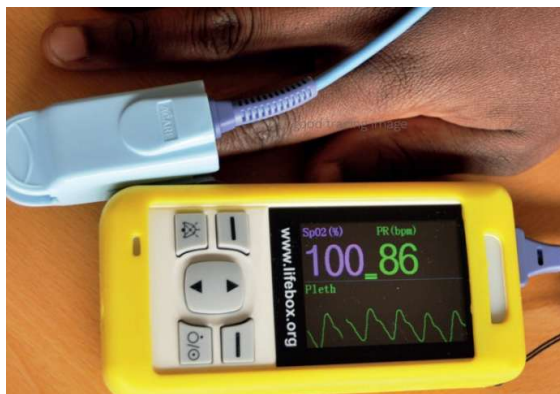
1. Ensure the patient is comfortable and relaxed.
2. Clean the probe with an alcohol wipe, ensuring that there is no visible dirt. Allow the alcohol to dry.



3.
 - a) Place the probe on a finger which has no varnish or pigment on the nail. The probe should not be too tight (this restricts circulation) or too loose (the probe may fall off, or light from other sources may be let in). It does not matter if the light source of the probe is on the nail or skin. Do not force the probe on to a finger which is too large for it, as this may damage the probe.
 - b) If all fingernails are varnished or pigmented, use an unvarnished and unpigmented toe instead or place the probe sideways as shown below.
 - c) If the finger is too small for the probe e.g., in small children, place it on a big toe instead, or use a neonatal probe.



4. Turn the probe on and check for a regular waveform like the one shown below. This may take 1-2 minutes. Tell the patient to stay still, as movement may result in an irregular waveform.



5. a) Once a regular waveform is observed, note the oxygen saturation.
6. b) A normal oxygen saturation is $\geq 95\%$. If you do not get a normal reading, check that the patient's fingers are warm, indicating adequate circulation, and repeat the measurement to be sure it is correct. If you are not sure that the probe is working correctly, test it on yourself.
7. Clean the probe with an alcohol wipe. Allow the alcohol to dry.
8. Record the oxygen saturation reading in the electronic case report form.
9. Remove batteries from the pulse oximeter at the end of the day to avoid damage from battery leaks.

Important note: Consider whether referral is required if the oxygen saturation is $< 90\%$.

SEACTN Work Package-A

Standard Operating Procedure

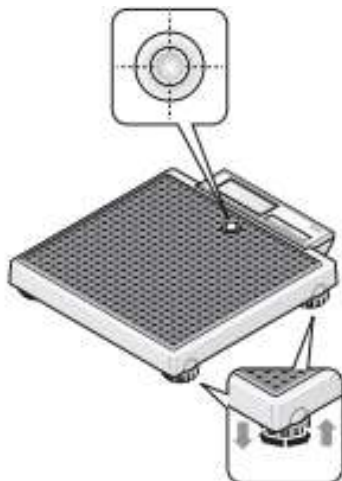
Title:	Measurement of weight
Version:	1.0
Date:	20 July 2021

Materials and Equipment:

1. Digital scales (SECA 876).

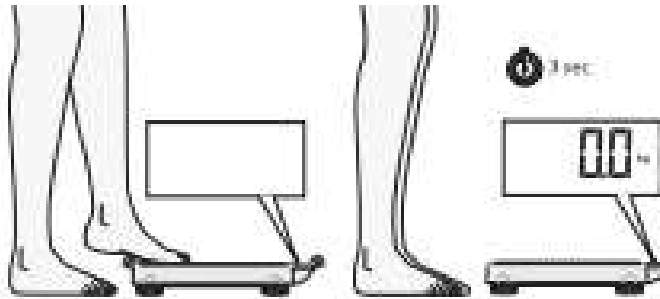
Procedure:

1. Instruct patient to remove footwear, headgear, and contents of their pockets. They should be in the minimum amount of clothing necessary to preserve modesty.
2. Place the scale on a firm surface and align it by turning the foot screws. Check it is aligned flat by observing the position of the circle, as shown below. The alignment of the base of the scale must be checked every time the scale is moved and corrected if required.

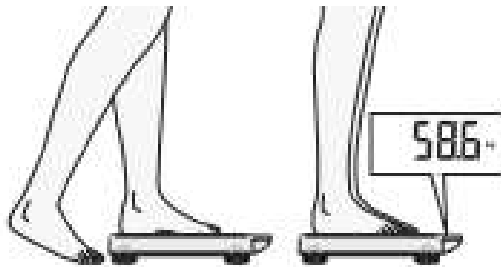


3. Ensure that only the feet of the scale are in contact with the ground.

4. Switch on the scales by gently touching the scales with one foot then stepping off for 3 seconds until the display shows '0.00'. Ensure there is no other load on the scales. If the scales do not start, you may need to replace the batteries.

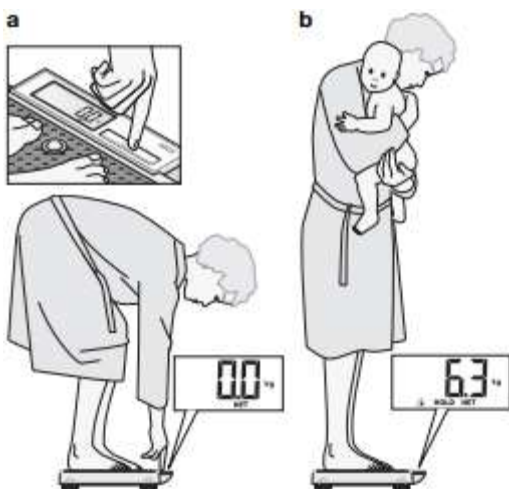


5. To weigh an adult or child who can stand on the scales independently, ask them to stand on the scales and read the measurement displayed.



6. To weigh a child or baby who cannot stand on the scales independently, follow the steps below:

- Ensure that there is no load on the scale.
- Ask the caregiver to stand on the scale.
- Press and hold the button until '0.00' appears on the display.
- Then hand the caregiver the child.
- The child's weight will be displayed.



7. If the measurement was not obtained, select the reason from the options provided.
8. The scales will automatically switch off if not in use for 20 seconds.

SEACTN Work Package-A

Standard Operating Procedure

Title:	Preparation of DBS
Version:	1.0
Date:	20 July 2021

Materials and Equipment:

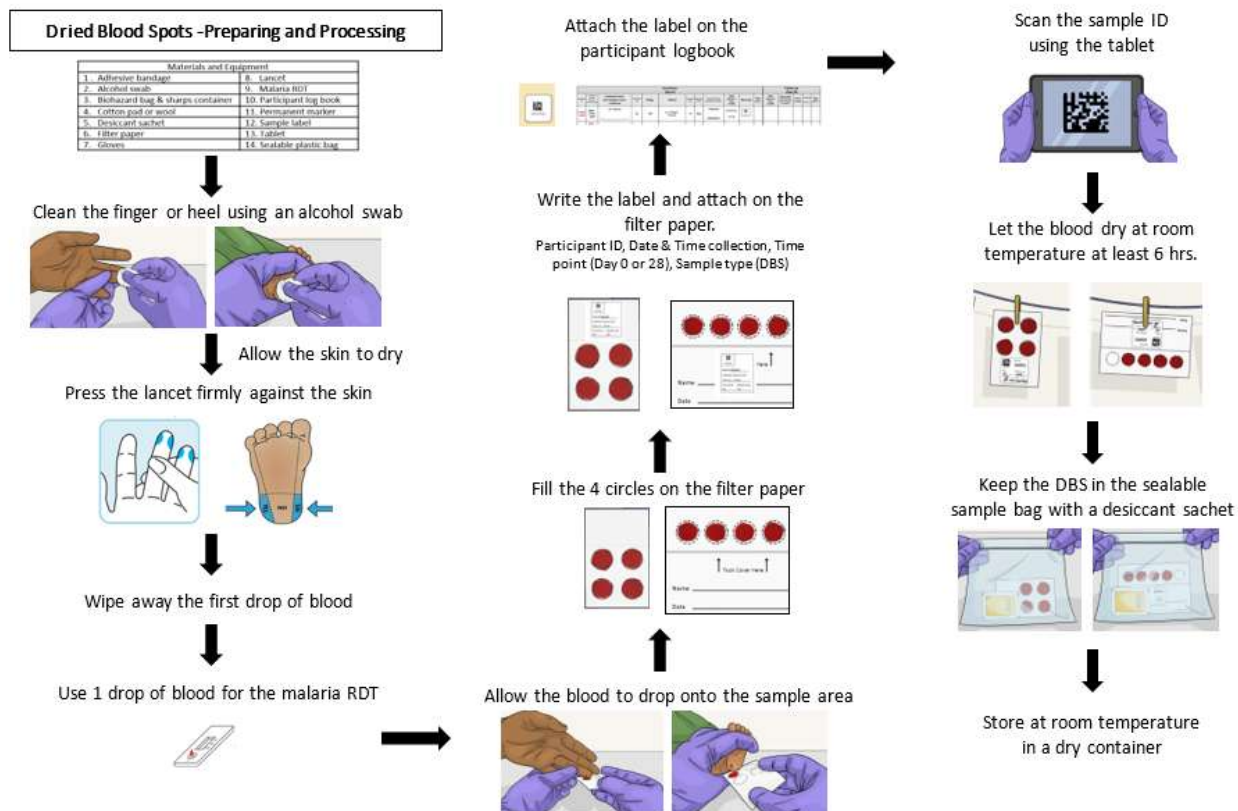
1. Adhesive bandage	7. Powder-free gloves
2. Alcohol swab	8. Lancet
3. Biohazard bag or Biohazard sharps container	9. Malaria Rapid Diagnostic Test (RDT)
4. Cotton pad or wool	10. Participant log book
5. Desiccant (Silica gel in a sachet)	11. Permanent marker
6. Filter paper (Standard Filter Paper or Whatman® 903 protein saver card)	12. Sample label
	13. Tablet
	14. Ziplock or sealable plastic bag

Procedure (Figure 1):

1. Disinfect, using an alcohol swab, the selected site on the finger or heel (for infant) and prick using a lancet.
2. Wipe off the first drop of blood with clean dry cotton wool because it may contain excess tissue fluids.
3. Apply 3-5 µL of blood (following the manufacturer's instructions) onto the malaria RDT.
4. Next, apply gentle pressure to the finger and allow a large drop of free-flowing blood to collect at the puncture site. DO NOT press the filter paper against the puncture site.
5. Drop of blood and allow a sufficient quantity of blood to soak through and completely fill or saturate a circle on the collection card (approximately 50 µL per circle).
6. Repeat until you have collected enough blood to fill the 4 circles on the blood collection card. If the participant is a child, collect as much blood as possible per spot.
7. Write the label with participant ID, date and time of collection, time point (Day 0 or 28) and sample type. Attach the labels on the filter paper and the participant log book. Also write the participant ID on the sealable sample bag using a permanent marker.
8. Let the spots air dry horizontally at least 6 hours or overnight.

Note: Spots should not be dried near an open window to prevent contact with sunlight, dust and flying insects during the drying procedure.

9. Keep the dried blood spots in the sealable sample bag with a desiccant sachet.
10. Place the sample bag in a cool and dry condition in temporary storage.
Note: Extreme temperatures (>37°C) in the presence of high humidity are not acceptable storage conditions.
11. Record the information on the participant log book or appropriate documentation.



SEACTN Work Package-A

Standard Operating Procedure

Title:	Follow-up and unscheduled visits
Version:	2.0
Date:	30 May 2023

Abbreviations

PI	Principal Investigator
SOP	Standard Operating Procedures
D1, D28, D42	Day 1, Day 28, Day 42
Hrs	Hours
LTFU	lost-to-follow-up

Background

SEACTN project aims to better understand febrile illness in rural areas of South and Southeast Asia. SEACTN Work Package-A is a prospective observational cohort study that will recruit patients of all ages with acute febrile illness attending village health workers or peripheral health facilities in rural Laos, Myanmar, and Bangladesh. The study aims to determine the incidence of febrile illness in rural communities, to determine aetiologies of community febrile illness by laboratory methods and to assess performance of host biomarkers in association with aetiology and outcomes.

Purpose and Scope

This document describes the timing, process and recording of follow-up and unscheduled visits.

Procedure

At Day 28 (D28), a follow up will be conducted to assess clinical recovery and when possible in person (via outreach or return to the study site) for collection of dried blood spots from finger/heel prick. Where face-to-face follow up is not possible, it can be conducted by telephone, SMS or note etc as appropriate. Window period allowed is +14 days, so follow up will occur no later than Day 42. If clarification is required, the study team will be consulted.

Follow-up aims to ascertain vital status, resolution/persistence of symptoms and any treatment sought/received since enrolment. Patients aged >28 days who will be followed up in person will undergo repeat finger/heel prick for dried blood spots to facilitate convalescent serology testing.

A face-to-face follow-up visit to the study site (or via community outreach) will be arranged for families that do not have access to a telephone or who reside in localities without reliable mobile telephone signal. Reimbursement for travel expenses will be provided to the participants who return to the clinic

for a face to face follow up, as deemed appropriate by the site PI (see Reimbursement SOP). Where feasible, outreach follow-up (e.g. home visits by study team) will be attempted for patients who are uncontactable on D28 by other means.

Attempts will be made to follow-up participants during the window period (+14 days or not later than Day 42), after which they will be declared lost-to-follow-up (LTFU) and further follow-up attempts will not be made. Data base will be completed as LTFU for that participant.

If a patient's symptoms resolve completely for ≥ 3 days (≥ 72 hours) and they then re-present during the follow-up period, this is counted as a new illness. The duration of illness relating to the presentation for which they were recruited into the study should not include the new illness.

In cases where a participant cannot be contacted at D42 and study staff have completed the database as LTFU, and a participant/friends/relatives later report the participant's status, study staff will record the outcomes in a participant log book (LTFU page).

Unscheduled visit

During D1- D27, if a participant returns to the clinic for any reasons, the visit either study related or non-study related will be determined as "unscheduled visit" and recorded in a study log book (unscheduled visit page). If the unscheduled visit is study related, reimbursement for travel and food will be provided.

The first visit that a participant makes to the clinic between D28-D42 will be considered the D28 follow up, and procedures for follow up will be made as described above, and recorded as a follow up visit. Participation in the study will be completed.

After completion of participation in the study (completion of follow up or LTFU), no more unscheduled visit will be recorded for that participant. If the participant returns later with febrile illness, this can be captured as a new episode, and the participant will be screened and enrolled as new enrolment.

Follow up	Procedures
Day 28 (+14 days or no later than Day 42)	Documentation of outcomes: vital status, persistence of symptoms, and the need for further care at other healthcare providers since enrolment Repeat finger/heel prick for dried blood spots in patients aged >28 days (for face-to-face meeting only)
Day 1 to Day 27	Unscheduled visit Record in a study log book (Unscheduled visit page)

An overview of planned data collection at baseline assessment and subsequent visits is provided in the Annex.

Update history

Version	Date	Summary of changes
0.1	1 December 2020	Document created and circulated for inputs
1.0	21 Apr 2021	Version approved by PI (Prof Yoel Lubell)
2.0	30 May 2023	Updated to clarify procedure for reckoning duration of illness

Annex

Procedures	Visits		
	D0	D28 (+14 days)	D 28 Follow up/call /SMS (+14 days)
Informed consent	X		
Demographics	X		
Contact details	X		
Medical history	X		
Vital signs	X		
Malaria rapid diagnostic test (mRDT)	X		
Dried blood spot	X	X (face-to-face follow up)	
Outcome data		X	X

SEACTN Work Package-A

Standard Operating Procedure

Title:	Protocol deviation
Version:	1.0
Date:	21 Apr 2021

Abbreviations

PI	Principal Investigator
IRB	Institutional Review Board

Background

SEACTN project aims to better understand febrile illness in rural areas of South and Southeast Asia. The SEACTN Work Package-A is a prospective observational cohort study that will recruit patients of all ages with acute febrile illness attending village health workers or peripheral health facilities in rural Laos, Myanmar, and Bangladesh. The study aims to determine the incidence of febrile illness in rural communities, to determine aetiologies of community febrile illness by laboratory methods and to assess performance of host biomarkers in association with aetiology and outcomes.

Purpose and Scope

This document describes the procedures for recording deviations from the approved study protocol.

Requirements

Protocol Deviation form

Procedure

Country (Site) Principal Investigators (PI) should be notified about all protocol deviations. They are responsible for accurate and timely completion the Protocol Deviation form, and will determine on a case by case basis which deviations require upward reporting to IRBs. By default, any protocol deviation that results in an adverse event to the participant should be reported to the local ethics board and to the study sponsor focal point by the country PI.

1. Date of deviation	Enter the date directly in the following format (DD/MM/YYYY).
2. Date deviation identified	Enter the date directly in the following format (DD/MM/YYYY).

3. Deviation description	Write a brief description of the deviation.
4. Deviation identified by:	Name the team member that identified the deviation.
5. Type of deviation identified	Select the type of deviation from the following list: 1. Consent procedures 2. Inclusion/exclusion criteria 3. Laboratory assessments/procedures 4. Study procedures 5. Visit schedule/interval 6. Other, specify
6. Did the protocol deviation result in an Adverse Event (AE)?	State whether the protocol deviation resulted in an AE by checking Yes or No. If Yes, provide description and report to PI.
7. Did the subject continue in the study?	Specify whether the subject continued in the study by checking Yes or No. If No, provide clarification.
8. Does the deviation meet IRB reporting requirements?	Specify whether the deviation met IRB reporting requirements by checking Yes or No.
9. Date the deviation was reported to the IRB (if applicable):	If Yes was checked for Question 8, enter the date the deviation was reported to the IRB in the following format (DD/MM/YYYY).

Update history

Version	Date	Summary of changes
0.1	1 December 2020	Document created and circulated for inputs
1.0	21 April 2021	Version approved by PI (Prof Yoel Lubell)

Protocol Deviation Form: SEACTN WP-A

PI Name:

Site:

Subject ID:

1. Date of deviation:
2. Date deviation identified:
3. Deviation description:
4. Deviation identified by:
5. Type of deviation identified:
6. Did the protocol deviation result in an AE?
 - ☐ Yes
 - ☐ No
 Comments/Clarification:
7. Did the subject continue in the study?
 - ☐ Yes
 - ☐ No
 Explain:
8. Does the deviation meet IRB reporting requirements (any deviation resulting in an AE should be reported to local IRB and country PI)?
 - ☐ Yes
 - ☐ No
 Comments/Clarification:
9. Date the deviation was reported to the IRB (if applicable):
10. Action taken to resolve this deviation (if any):
11. Deviation impact (check all that apply):
 - ☐ Study Validity
 - ☐ Safety
 - ☐ No Impact
 - ☐ Outcome Measures
 - ☐ Other, specify:

Investigator Signature: _____ Date: _____

SEACTN Work Package-A

Standard Operating Procedure

Title:	Unanticipated problem
Version:	1.0
Date:	21 Apr 2021

Abbreviations

UP	Unanticipated Problem
IRB	Institutional Review Board
ID	Identification

Background

SEACTN project aims to better understand febrile illness in rural areas of South and Southeast Asia. SEACTN Work Package-A is a prospective observational cohort study that will recruit patients of all ages with acute febrile illness attending village health workers or peripheral health facilities in rural Laos, Myanmar, and Bangladesh. The study aims to determine the incidence of febrile illness in rural communities, to determine aetiologies of community febrile illness by laboratory methods and to assess performance of host biomarkers in association with aetiology and outcomes.

Purpose and Scope

The purpose of this document is to describe the process for recording unanticipated problems (UP) and any action that is taken.

Requirements

1. Unanticipated Problem form

Procedures

Information to be collected if UP occurs is as follows.

1. Date UP identified	Enter the date that the UP was identified.
2. Identify UP	Describe the incident, experience, or outcome.
3. The event was unanticipated in terms of nature, severity or frequency	Check Yes or No. If No, the event is not an unanticipated problem. Reconsider the reporting mechanism; this is not the correct form.

4. The event is related or possibly related to participation in the research	Check Yes or No. If No, the event is not an unanticipated problem. Reconsider the reporting mechanism; this is not the correct form.
5. The event suggests that the research places participants or others at a greater risk of harm than was previously known or recognised.	Check Yes or No. If No, the event is not an unanticipated problem. Reconsider the reporting mechanism; this is not the correct form.
6. Briefly describe the UP	Briefly describe the incident, experience, or outcome with the date the event occurred and/or was discovered. Describe harm or potential harm to participant(s). Indicate if event is resolved and whether affected participant(s) remain in the study. If >1 participant was affected, list their IDs here if needed due to limited space in the header ID box. Additional pages or documents may be attached with investigator signature and date.
7. What action was taken with the study as a result of the UP?	Record action(s) taken (if known) using the categories listed; use "Other" to describe an action not listed. If no action was taken, provide rationale.
8. Additional comments	Enter any additional comments, actions or repercussions not covered.
8. Statement of Investigator and Signature	Investigator signs/dates the form to verify review & agreement with the assessment. Record person who completed the form & date completed.

Update history

Version	Date	Summary of changes
0.1	1 December 2020	Document created and circulated for inputs
1.0	21 April 2021	Version approved by PI (Prof Yoel Lubell)

WP-A: Unanticipated Problem (UP) Form

PI Name/Site: _____ Participant(s) ID: _____

1. Date Unanticipated Problem (UP) identified: _____ (DD/MMM/YYYY)
2. Identify UP: _____
3. The event was unexpected in terms of nature, severity, or frequency: Yes/No
4. The event is related or possibly related to participation in the research: Yes/No
5. The event suggests that the research places participants or others at a greater risk of harm than previously known or recognized: Yes/No

If the answers to items 3-5 above are ALL Yes, report the event as an Unanticipated Problem to PI (and IRB if applicable). If any answer is No to items 3-5 above, do not use this form to report the event.

6. Briefly describe the UP (Attach additional pages or supplementary information as necessary. Include incident date, discovery date, describe harm or potential harm to participant(s), whether incident is resolved, & whether participant(s) remains on study.):

7. What action was taken with the study as a result of the UP? (Check all that apply.)

- ☐ Revision of protocol to eliminate apparent immediate hazards to participants
- ☐ Notification of currently enrolled participants
- ☐ Modification of inclusion or exclusion criteria to mitigate newly identified risks

- ☐ Suspension of research procedures in currently enrolled participants
- ☐ Implementation of additional procedures for monitoring participants
- ☐ Provision of additional information about newly recognized risks to previously enrolled participants
- ☐ Modification of consent documents to include a description of newly recognized risks (site and/or study wide)
- ☐ Other: _____
- ☐ Suspension of enrolment of new participants
- ☐ No action taken; rationale: _____

8. Additional comments: _____

Statement of Investigator: I have personally reviewed this report and agree with the above assessment.

Investigator Signature _____

Date _____
(DD/MMM/YYYY)

Name of Person Completing Form _____

Date _____
(DD/MMM/YYYY)

SEACTN Work Package-A

Standard Operating Procedure

Title:	Site follow-up visit reimbursement
Version:	1.0
Date:	21 April 2021

Abbreviations

D28	Day 28 (after enrolment)
PI	Principal Investigator

Background

SEACTN project aims to better understand febrile illness in rural areas of South and Southeast Asia. SEACTN workplan-A is a prospective observational cohort study that will recruit patients of all ages with acute febrile illness attending village health workers or peripheral health facilities in rural Laos, Myanmar, and Bangladesh. The study aims to determine the incidence of febrile illness in rural communities, to determine aetiologies of community febrile illness by laboratory methods and to assess performance of host biomarkers in association with aetiology and outcomes.

Purpose and Scope

This document describes the process for reimbursement of patients or caretakers who return to the study site for follow up on D28 or any unscheduled study related visit.

Requirements

1. Reimbursement receipt/payment
2. Reimbursement summary table

Procedure

1. Individual study sites will determine a standard amount to reimburse patients or caretakers who return (with children) to the study site for a follow up visit, or unscheduled visits that are related to the study.
2. This rate will be determined in advance by the study country PI and informed to the sponsors in advance of study initiation.
3. Study site research staff will record specific reimbursements one-by-one on a receipt/payment slip (see example below) completed at the time of the reimbursement, not later. A copy can be given to the patients or caretaker upon request and the original retained at the study site for financial review.

4. Study site research staff will ensure that the caretaker understands and agrees to the reimbursement at the time of recruitment during the consent process.
5. Study site research staff will record all reimbursements on a reimbursement summary table (see example below).
6. The table and slips will be made available to financial monitors on request.
7. The site coordinator will review the reimbursement table on a regular basis to ensure accuracy and to ensure the totals are within the budget allocation
8. If the reimbursement totals exceed the allocated reimbursement budget, the site coordinator will immediately alert the country PI.

Update history

Version	Date	Summary of changes
0.1	1 Dec 2020	Document created and circulated for inputs
1.0	21 Apr 2021	Version approved by PI (Prof Yoel Lubell)

RECEIPT / PAYMENT Protocol: SEACTN WP-A

Date:.....// 20.....

Received from

The sum of

..... (Amount

On account of

Authorize By:

Paid By :

Received By :

Signature :

Signature :

Protocol: SEACTN WP-A

Site:

Date (DD/MM/YYYY)	Study subject UID	Indication of compensation (D28, other follow-up day)	Staff who recorded/paid expense	Completed receipt given to caretaker Y/N	Amount

Appendix 4.4 Observational study – Algorithmic diagnosis rules expert panel

Name	Position	Medical specialty
Rusheng Chew	Clinical Researcher, University of Oxford and Mahidol Oxford Tropical Medicine Research Unit and Visiting Senior Specialist, Alice Springs Hospital, Australia	Adult Infectious Diseases and Respiratory Medicine
Nicholas Day	Professor of Tropical Medicine, University of Oxford and Mahidol Oxford Tropical Medicine Research Unit and Honorary Consultant Physician, John Radcliffe Hospital, UK	Adult Infectious Diseases and General (Internal) Medicine
Arjun Chandna	Clinical Researcher, University of Oxford and Mahidol Oxford Tropical Medicine Research Unit and Specialty Registrar, University College London Hospitals, UK	Adult Infectious Diseases and General (Internal) Medicine
James Callery	Clinical Researcher, University of Oxford and Mahidol Oxford Tropical Medicine Research Unit and Locum General Practitioner, UK	General Practice
Enitan Carrol	Professor of Paediatric Infection, University of Liverpool and Honorary Consultant in Paediatric Infectious Diseases and Immunology, Alder Hey Children's Hospital, UK	Paediatrics and Paediatric Infectious Diseases

Appendix 4.5 Observational study – Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	NA	
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	NA	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	72	4.1, para. 1–2
Objectives	3	State specific objectives, including any prespecified hypotheses	72–73	4.1, para. 3
Methods				
Study design	4	Present key elements of study design early in the paper	75	4.2.2, para. 1–3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	73–74, 86	4.2.1, para. 1 – 2, Fig. 4.1, Table 4.6
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control	75	4.2.2, para. 2–3

		selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i>—Give the eligibility criteria, and the sources and methods of selection of participants <i>(b) Cohort study</i>—For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i>—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	75–82	4.2.3 and sub-sections, Tables 4.2–4.4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	75–76	4.2.3, para. 1–2
Bias	9	Describe any efforts to address potential sources of bias	75	4.2.2, para. 1
Study size	10	Explain how the study size was arrived at	75	4.2.2, para. 1

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	84	4.2.4, para. 1
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	84	4.2.4, para. 1
		(b) Describe any methods used to examine subgroups and interactions		
		(c) Explain how missing data were addressed		
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed		
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed		
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy		
		(e) Describe any sensitivity analyses		
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	85	Fig. 4.2
		(b) Give reasons for non-participation at each stage		
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	91	Table 4.8
		(b) Indicate number of participants with missing data for each variable of interest		

		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	101–102	Table 4.10
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	94–111	4.3.2, 4.3.3, 4.3.4, Table 4.10, Fig 4.5–4.11
		(b) Report category boundaries when continuous variables were categorized		
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA	
Discussion				
Key results	18	Summarise key results with reference to study objectives	111–112	4.4.1, para. 1–3
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	115	4.4.3, para. 3
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	112–114	4.4.2, para. 1–5
Generalisability	21	Discuss the generalisability (external validity) of the study results	114	4.4.3, para. 1
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	37	2.3, para. 1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Appendix 5.1 Systematic review – Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)

2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Appendix 1b (in published manuscript)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Eligibility criteria
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Search strategy, Table 5.1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Table 5.1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Study selection
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Data extraction
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Eligibility criteria
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Tables 5.2 – 5.4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Quality assessment
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Tables 5.2 – 5.4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Data analysis and synthesis of results
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary	NA

Section and Topic	Item #	Checklist item	Location where item is reported
		statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Data analysis and synthesis of results, Tables 5.2 – 5.4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Data analysis and synthesis of results
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Quality assessment, Data analysis and synthesis of results
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 5.1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Appendix 5.3
Study characteristics	17	Cite each included study and present its characteristics.	Tables 5.2 – 5.4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure 5.2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Tables 5.2 – 5.4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Impact of pulse oximetry on diagnosis, Impact of pulse oximetry on clinical management, Impact of pulse oximetry on patient outcomes
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Figure 5.2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Impact of pulse oximetry on diagnosis, Impact of pulse oximetry on clinical management, Impact of pulse oximetry on patient outcomes
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion, para. 1
	23b	Discuss any limitations of the evidence included in the review.	Discussion, para. 4
	23c	Discuss any limitations of the review processes used.	Discussion, para. 4
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion, para. 2-3
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Protocol and registration
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Protocol and registration
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Protocol and registration
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Acknowledgements, Role of funding sources (in published manuscript)
Competing interests	26	Declare any competing interests of review authors.	Competing interests (in published manuscript)
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data availability (in published manuscript)

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>

Appendix 5.2 Systematic review – Technical Advisory Panel members

Name	Position	Email
Mike English	Professor of International Child Health, University of Oxford	menglish@kemri-wellcome.org
Jennifer Daily	Independent consultant in <i>in vitro</i> diagnostics and global health markets; formerly Manager – Diagnostics Access Initiatives, CHAI (Clinton Health Access Initiative)	jenniferanndaily@gmail.com
Arjen Dondorp	Professor of Tropical Medicine, University of Oxford	arjen@tropmedres.ac
David Bell	Independent consultant in global health, diagnostics, and infectious disease; formerly Head of Program – Malaria and Acute Febrile Syndrome, FIND (Foundation for Innovative New Diagnostics)	bell00david@gmail.com

Appendix 5.3 Systematic review – Authors and practitioners proposed by Technical Advisory Panel

Authors – for publication list searches	Practitioners – for grey literature recommendations
Amy Sarah Ginsburg Karin Källander Kevin Baker Quique Bassat Mark Ansermino	Yasir bin Nisar Martin Willi Weber Mike Ruffo Cindy McWhorter Ann Detjen Iain Wilson Smita Kumar Rasa Izadnegahdar Felix Lam

Appendix 5.4 Systematic review – List of rejected studies at full-text review stage and reasons for rejection

No.	Study reference	Reason for rejection
1	Tanen DA, Trocinski DR. The use of pulse oximetry to exclude pneumonia in children. <i>Am J Emerg Med</i> . 2002;6:521-3.	High-income country setting
2	Starr N, Rebollo D, Asemu YM, et al. Pulse oximetry in low-resource settings during the COVID-19 pandemic. <i>Lancet Glob Health</i> . 2020;8:e1121-2.	Peri-operative setting
3	Enoch AJ, English M, Clinical Information Network, McGivern G, Shepperd S. Variability in the use of pulse oximeters with children in Kenyan hospitals: A mixed-methods analysis. <i>PLoS Med</i> . 2019;16:e1002987.	Participants not in target population
4	Cummings MJ, Goldberg E, Mwaka S, et al. A complex intervention to improve implementation of World Health Organization guidelines for diagnosis of severe illness in low-income settings: a quasi-experimental study from Uganda. <i>Implement Sci</i> . 2017;12:126.	Participants not in target population
5	Tolla HS, Asemere YA, Belete AB, et al. (2018) Use of pulse oximetry for diagnosis of hypoxemia and monitoring of children with pneumonia: A descriptive study from Ethiopia. <i>Am J Trop Med Hyg</i> . 2018;99:409.	No valid comparator group
6	Floyd J, Wu L, Burgess DH, Izadnegahdar R, Mukanga D, Ghani AC. Evaluating the impact of pulse oximetry on childhood pneumonia mortality in resource-poor settings. <i>Nature</i> . 2015;528:S53-9.	Modelling study
7	Rees CA, Basnet S, Gentile A, et al. An analysis of clinical predictive values for radiographic pneumonia in children. <i>BMJ Global Health</i> . 2020;5:e002708.	Modelling study
8	McCollum ED, King C, Colbourn T, et al. Pulse oximetry in paediatric primary care in low-income and middle-income countries. <i>Lancet Respir Med</i> . 2019;7:1001-2.	Opinion
9	Matata L, Baker K, Mucunguzi A, Posada M, Habte T, Kallander K. Acceptability of selected respiratory rate counters and pulse oximeters for use by frontline health workers in the detection of pneumonia symptoms in children in sub-Saharan Africa and Southeast Asia. <i>Am J Trop Med Hyg</i> . 2015;93(4 Suppl):543.	Abstract with no results
10	Baker K, Mucunguzi A, Matata L, Posada M, Habte T, Kallander K. Accuracy of selected devices for the detection of pneumonia symptoms – results from laboratory testing and field evaluations of respiratory rate counters and pulse oximeters with frontline health workers in sub-Saharan Africa	Abstract with no results

	and Southeast Asia. <i>Am J Trop Med Hyg.</i> 2015;93(4 Suppl):543.	
11	Hamid MA, Chandna A, Siddiqui S, Fayyaz J. Pulse oximetry: A reliable and cost effective screening tool in children with pneumonia for developing countries. <i>J Pak Med Assoc.</i> 2016;66:1015-8.	Narrative review
12	Herbert LJ, Wilson IH. Pulse oximetry in low-resource settings. <i>Breathe.</i> 2012;9:90-7.	Narrative review
13	Duke T, Subhi R, Peel D, Frey B. Pulse oximetry: Technnology to reduce child mortality in developing countries. <i>Ann Trop Paediatr.</i> 2009;29:165-75.	Narrative review

Appendix 5.5 Systematic review – Data extraction template

GENERAL INFORMATION	
Extraction date	
Citation	
Publication type	
ELIGIBILITY	
Eligibility criteria met	
Type of study	
Participants	
Intervention	
Comparison	
Outcome measures	
METHODS	
Aim	
Design	
Unit of allocation	
Start date	
End date	
Duration of participation	

Ethical approval needed/obtained	
PARTICIPANTS	
Population	
Setting	
Inclusion criteria	
Exclusion criteria	
Method of recruitment	
Informed consent	
Total population at start	
Clusters	
Baseline imbalances	
Withdrawals and exclusions	
Demographics	
GROUPS	
Intervention and comparison	
Description of intervention	
Treatment duration	
Timing	
Delivery	
Providers	

Co-intervention	
Economic information	
Resource requirements	
Integrity of delivery	
Compliance	
RELEVANT OUTCOMES	
Outcome name	
Time points measured	
Time points reported	
Outcome definition	
Person measuring/reporting	
Outcome validated	
Imputation of missing data	
Assumed risk estimate	
Power	
OTHER	
Funding sources	
Conflicts of interest	
DATA AND ANALYSIS	
Results	

Any other results	
Missing participants	
Unit of analysis	
Statistical methods and appropriateness	
Reanalysis required	
Reanalysis possible	
CONCLUSIONS	
Key findings	
Correspondence required	

Adapted from: Cochrane Effective Practice and Organisation of Care (EPOC). Data collection form: Intervention review – Randomised trials and non-randomised trials. London, UK: The Cochrane Collaboration; 2017.

Appendix 5.6 Cost-effectiveness analysis of pulse oximetry – Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist

	Item	Guidance for Reporting	Reported in section
TITLE			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Title (in published manuscript)
ABSTRACT			
Abstract	2	Provide a structured summary that highlights context, key methods, results and alternative analyses.	Abstract (in published manuscript)
INTRODUCTION			
Background and objectives	3	Give the context for the study, the study question and its practical relevance for decision making in policy or practice.	Introduction
METHODS			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	NA
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Study design and participants; Table 5.5
Setting and location	6	Provide relevant contextual information that may influence findings.	Setting
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Base case
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Base case
Time horizon	9	State the time horizon for the study and why appropriate.	Base case
Discount rate	10	Report the discount rate(s) and reason chosen.	Base case
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Base case
Measurement of	12	Describe how outcomes used to capture	Study design and participants; Base

outcomes		benefit(s) and harm(s) were measured.	case; Table 5.6
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Study design and participants; Base case; Table 5.6
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Base case; Table 5.6
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Base case
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Base case
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Assumptions
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for sub-groups.	Sensitivity analyses
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	NA
Characterizing uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	Sensitivity analyses
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (e.g., clinicians or payers) in the design of the study.	NA
RESULTS			
Study parameters	22	Report all analytic inputs (e.g., values, ranges, references) including uncertainty or distributional assumptions.	Table 5.6
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Cost-effectiveness of pulse oximetry in children <5 years old; Cost-effectiveness of extending pulse oximetry to all patients
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if	Sensitivity analyses, Table

		applicable.	5.7
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	NA
DISCUSSION			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could impact patients, policy, or practice.	Discussion
OTHER RELEVANT INFORMATION			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Declarations (in published manuscript)
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Declarations (in published manuscript)

Appendix 6.1 Delphi survey – questionnaire

A. Introduction

1. Thank you for participating in this survey. Our objective is to obtain expert consensus on analytes which should be included as targets in hypothetical multiplex lateral flow rapid diagnostic tests for use at the point of care in rural areas of your region. The consensus opinion will facilitate future development of such tests.

You have been selected to participate based on your expertise in healthcare in the tropics. We also seek to understand your views on the use of such rapid tests.

The survey will be run over two rounds, or fewer if consensus is reached earlier. Your responses are confidential and other participants will not be informed of your identity. The link you have used to access this survey is unique to you, so please do not share it.

2. This round closes at **1700 Indochina Time (GMT +7)** on **[date]**.

[Second round only] You will be able to view an anonymised summary of the responses to each question from the previous round before you answer the same questions in this round.

3. Each round of this survey should take approximately **20-30** minutes to complete. Your responses will be saved as you progress through the survey. If you cannot complete the round in one sitting, you will be able to return to where you left off by clicking the link you used to access the survey.

[First round, and second round if respondent did not participate in first round] B.

About you

4. **[One option only to be selected]** Please select the option that best describes your professional role.
 - Clinician
 - Clinician researcher
 - Non-clinician researcher
5. **[One option only to be selected]** What is your specialty or area of expertise?
 - Options for clinicians and clinician researchers:
 - Clinical infectious diseases
 - Clinical microbiology
 - Clinical infectious diseases and clinical microbiology
 - Internal medicine
 - General practice
 - Other (please state)
 - Options for non-clinician researchers:

- Epidemiology
- Microbiology
- Other (please state)

6. **[One option only to be selected]** How many years of experience do you have in your specialty or area of expertise?
- 0 to 5
 - >5 to 10
 - >10 to 15
 - ≥15 to 20
 - >20

C. Survey questions

7. You have been selected for your expertise in healthcare in **[country]**, which is in **[region]**. For the purposes of this study, **[region]** comprises of **[list of countries in region]**.

You will now be asked to answer four short scenario-based questions. When answering the questions, please include the following in your considerations, basing them on your regional context:

- disease epidemiology;
- disease severity and clinical outcomes;
- availability of directed treatment in the setting in which the diagnosis is made;
- health services delivery in your region;
- expected performance characteristics and clinical utility of each analyte or biomarker;
- the different roles of primary and secondary healthcare facilities e.g., it may be more useful to rule out high-consequence diseases in primary care, whereas it may be more useful to rule in high-consequence diseases in secondary care.

8. **Scenario 1:** You are asked to assist in the development of a multiplex lateral flow rapid diagnostic test for **year-round** point-of-care use in **children (age >28 days to <15 years)** in **[region]** **presenting** with acute (≤ 14 days) non-malarial fever to **rural primary healthcare facilities** e.g., **mobile village health workers, rural health centres, and general practitioners**. The test substrate is fingerprick blood.

Which targets would you include in this rapid diagnostic test?

Please rank **seven** targets, with 1 being most important and 7 least important. A pathogen-analyte pair counts as one target, and you are allowed to select more than one analyte per pathogen. If you wish to rank a pathogen, analyte, or biomarker which is not included in the list, please choose 'Other' and enter the relevant information as free text.

[Second round only] Before you answer, here is a summary of the results to this question from the last round. **[Display summarised results from first round]**

Item type	Item	Analyte
Bacterium	<i>Staphylococcus aureus</i>	- Antigen - Other (please state)
	<i>Rickettsia</i> spp.	- IgM - IgG - Antigen - Other (please state)
	<i>Orientia tsutsugamushi</i>	- IgM - IgG - Antigen - Other (please state)
	<i>Salmonella</i> spp. (typhoidal)	- Antigen - Other (please state)
	<i>Salmonella</i> spp. (non-typhoidal)	- Antigen - Other (please state)
	<i>Leptospira</i> spp.	- IgM - IgG - Antigen - Other (please state)
	<i>Burkholderia pseudomallei</i>	- Antigen - Other (please state)
	<i>Brucella</i> spp.	- IgM - IgG - Antigen - Other (please state)
	Other (please state)	Other (please state)
	Other (please state)	Other (please state)
	Other (please state)	Other (please state)
Virus	Dengue	- NS1 antigen - IgM - IgG - Other (please state)
	Chikungunya	- Antigen - IgM - IgG - Other (please state)

		• Zika	• Antigen • IgM • IgG • Other (please state)
		• Japanese encephalitis	• Antigen • IgM • IgG • Other (please state)
		• HIV	• Antigen • IgG • Other (please state)
		• Hepatitis B	• Surface antigen • Other (please state)
		• Hepatitis A	• IgM • IgG • Other (please state)
		• Hepatitis E	• IgM • IgG • Other (please state)
		• Other (please state)	• Other (please state)
		• Other (please state)	• Other (please state)
		• Other (please state)	• Other (please state)
	Parasite	• <i>Schistosoma</i> spp.	• Antigen • IgM • IgG • Other (please state)
		• <i>Leishmania</i> spp.	• Antigen • IgM • IgG • Other (please state)
		• Other (please state)	• Other (please state)
		• Other (please state)	• Other (please state)
		• Other (please state)	• Other (please state)
	Host biomarker	• Angiopoietin-1 (Ang-1)	
		• Angiopoietin-2 (Ang-2)	
		• Chitinase-3-like protein-1 (CHI3L1)	

		• C-X-C motif chemokine-10 (CXCL-10)	
		• C-reactive protein (CRP)	
		• E-selectin	
		• Ferritin	
		• Glucose	
		• Haemoglobin (Hb)	
		• Interferon-γ induced protein-10 (IP-10)	
		• Interleukin-6 (IL-6)	
		• Interleukin-8 (IL-8)	
		• Interleukin-10 (IL-10)	
		• Interleukin-17A (IL-17A)	
		• Interleukin-18 (IL-18)	
		• Lactate	
		• Mid-regional pro-adrenomedullin (MR-proADM)	
		• Procalcitonin (PCT)	
		• Soluble CD-14 (sCD-14)	
		• Soluble fms-like tyrosine kinase-1 (sFlt-1)	
		• Soluble fms-like tyrosine kinase -2 (s-Flt-2)	
		• Soluble intercellular adhesion molecule-1 (sICAM-1)	
		• Soluble tumour necrosis factor receptor-1 (sTNFR-1)	

		• Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1)	
		• Soluble vascular adhesion molecule-1 (sVCAM-1)	
		• Tumour necrosis factor-α (TNF-α)	
		• Other (please state)	
		• Other (please state)	
		• Other (please state)	

[First round only, response compulsory] To help develop consensus, please provide brief reasons for your rankings. Aggregate feedback will be shared with other participants in the next round, but you will not be identifiable.

[Display if biomarkers selected] You have ranked host biomarker(s). Please select a reason for each from the following list:

- To differentiate between viral and non-viral infection
- As a marker of disease severity
- Both of the above
- Other (please state)

[Display list of selected biomarkers with a drop-down menu with these options next to each biomarker]

9. Assume this multiplex lateral flow rapid diagnostic test has a clinical sensitivity of 75% and a clinical specificity of 90% for the diseases you have selected. How helpful do you think it would be in clinical decision-making for **children (age >28 days to <15 years)** in **[region]** **presenting to rural primary healthcare facilities** with acute (≤ 14 days) non-malarial fever?

[Second round only] Before you answer, here is a summary of the results to this question from the last round. **[Display summarised results from first round]**

- Unhelpful
- Neither helpful nor unhelpful
- Helpful

10. If this multiplex lateral flow diagnostic test were helpful in aiding clinical decision-making, would you incorporate it into an electronic algorithm-based clinical decision support tool for treating **children (age >28 days and <15 years) presenting to rural primary healthcare facilities in [country]** with acute (< 14 days) non-malarial fever?

[Second round only] Before you answer, here is a summary of the results to this question from the last round. **[Display summarised results from first round – by country for the participant's region]**

- Yes
- No

11. **Scenario 2:** You are asked to assist in the development of a multiplex lateral flow rapid diagnostic test for **year-round** point-of-care use in **adults (age ≥15 years)** in **[region]** **presenting** with acute (≤14 days) non-malarial fever to **rural primary healthcare facilities** e.g., **mobile village health workers, rural health centres, and general practitioners**. The test substrate is fingerprick blood.

Which targets would you include in this rapid diagnostic test?

Please rank **seven** targets, with 1 being most important and 7 least important. A pathogen-analyte pair counts as one target, and you are allowed to select more than one analyte per pathogen. If you wish to rank a pathogen, analyte, or biomarker which is not included in the list, please choose 'Other' and enter the relevant information as free text.

[Second round only] Before you answer, here is a summary of the results to this question from the last round. **[Display summarised results from first round]**

[Use table from Question 8]

[First round only, response compulsory] To help develop consensus, please provide brief reasons for your rankings. Aggregate feedback will be shared with other participants in the next round, but you will not be identifiable.

[Display if biomarkers selected] You have ranked host biomarker(s). Please select a reason for each from the following list:

- To differentiate between viral and non-viral infection
- As a marker of disease severity
- Both of the above
- Other (please state)

[Display list of selected biomarkers with a drop-down menu with these options next to each biomarker]

12. Assume this multiplex lateral flow rapid diagnostic test has a clinical sensitivity of 75% and a clinical specificity of 90% for the diseases you have selected. How helpful do you think it would be in clinical decision-making for **adults (age ≥15years)** in **[region]** **presenting** to **rural primary healthcare facilities** with acute (≤14 days) non-malarial fever?

[Second round only] Before you answer, here is a summary of the results to this question from the last round. **[Display summarised results from first round]**

- Unhelpful
- Neither helpful nor unhelpful
- Helpful

13. If this multiplex lateral flow diagnostic test were helpful in aiding clinical decision-making, would you incorporate it into an electronic algorithm-based clinical decision support tool or guideline for treating **adults (age ≥15 years) presenting to rural primary healthcare facilities in [country]** with acute (≤14 days) non-malarial fever?

[Second round only] Before you answer, here is a summary of the results to this question from the last round. **[Display summarised results from first round – by country for the participant's region]**

- Yes
- No

14. **Scenario 3:** You are asked to assist in the development of a multiplex lateral flow rapid diagnostic test for **year-round** point-of-care use in **children (age >28 days to <15 years)** in **[region]** admitted with acute (≤14 days) non-malarial fever to **rural secondary healthcare facilities** e.g., **district or rural hospitals**. The test substrate is fingerprick blood.

Which targets would you include in this rapid diagnostic test?

Please rank **seven** targets, with 1 being most important and 7 least important. A pathogen-analyte pair counts as one target, and you are allowed to select more than one analyte per pathogen. If you wish to rank a pathogen, analyte, or biomarker which is not included in the list, please choose 'Other' and enter the relevant information as free text.

[Second round only] Before you answer, here is a summary of the results to this question from the last round. **[Display summarised results from first round]**

[Use table from Question 8]

[First round only, response compulsory] To help develop consensus, please provide brief reasons for your rankings. Aggregate feedback will be shared with other participants in the next round, but you will not be identifiable.

[Display if biomarkers selected] You have ranked host biomarker(s). Please select a reason for each from the following list:

- To differentiate between viral and non-viral infection
- As a marker of disease severity
- Both of the above

- Other (please state)

[Display list of selected biomarkers with a drop-down menu with these options next to each biomarker]

15. Assume this multiplex lateral flow rapid diagnostic test has a clinical sensitivity of 75% and a clinical specificity of 90% for the diseases you have selected. How helpful do you think this multiplex lateral flow rapid diagnostic test would be in clinical decision-making for **children (age >28 days to <15 years)** in **[region]** admitted to **rural secondary healthcare facilities** with acute (≤ 14 days) non-malarial fever?

[Second round only] Before you answer, here is a summary of the results to this question from the last round. **[Display summarised results from first round]**

- Unhelpful
- Neither helpful nor unhelpful
- Helpful

16. If this multiplex lateral flow diagnostic test were helpful in aiding clinical decision-making, would you incorporate it into an electronic algorithm-based clinical decision support tool or guideline for treating **children (age >28 days and <15 years)** admitted to **rural secondary healthcare facilities in [country]** with acute (≤ 14 days) non-malarial fever?

[Second round only] Before you answer, here is a summary of the results to this question from the last round. **[Display summarised results from first round – by country for the participant's region]**

- Yes
- No

17. **Scenario 4:** You are asked to assist in the development of a multiplex lateral flow rapid diagnostic test for **year-round** point-of-care use in **adults (age ≥ 15 years)** in **[region]** admitted with acute (≤ 14 days) non-malarial fever to **rural secondary healthcare facilities** e.g., **district or rural hospitals**. The test substrate is fingerprick blood.

Which targets would you include in this rapid diagnostic test?

Please rank **seven** targets, with 1 being most important and 7 least important. A pathogen-analyte pair counts as one target, and you are allowed to select more than one analyte per pathogen. If you wish to rank a pathogen, analyte, or biomarker which is not included in the list, please choose 'Other' and enter the relevant information as free text.

[Second round only] Before you answer, here is a summary of the results to this question from the last round. **[Display summarised results from first round]**

[Use table from Question 8]

[First round only, response compulsory] To help develop consensus, please provide brief reasons for your rankings. Aggregate feedback will be shared with other participants in the next round, but you will not be identifiable.

[Display if biomarkers selected] You have ranked host biomarker(s). Please select a reason for each from the following list:

- To differentiate between viral and non-viral infection
- As a marker of disease severity
- Both of the above
- Other (please state)

[Display list of selected biomarkers with a drop-down menu with these options next to each biomarker]

18. Assume this multiplex lateral flow rapid diagnostic test has a clinical sensitivity of 75% and a clinical specificity of 90% for the diseases you have selected. How helpful do you think this multiplex lateral flow rapid diagnostic test would be in clinical decision-making for **adults (age ≥15 years) in [region] admitted to rural secondary healthcare facilities** with acute (≤14days) non-malarial fever?

[Second round only] Before you answer, here is a summary of the results to this question from the last round. **[Display summarised results from first round]**

- Unhelpful
- Neither helpful nor unhelpful
- Helpful

19. If this multiplex lateral flow diagnostic test were helpful in aiding clinical decision-making, would you incorporate it into an electronic algorithm-based clinical decision support tool or guideline for treating **adults (age ≥15 years) admitted to rural secondary healthcare facilities in [country]** with acute (≤14 days) non-malarial fever?

[Second round only] Before you answer, here is a summary of the results to this question from the last round. **[Display summarised results from first round – by country for the participant's region]**

- Yes
- No

20. Which aetiologies do you think contribute the most towards the current annual incidence of acute (≤14 days) febrile illness **across all age groups in [region]**? Please rank **five in descending order of perceived annual incidence** i.e., 1 having the highest perceived annual incidence and 5 having the least. If aetiologies you feel

should be included are not listed, please state them under 'Other' in the relevant categories.

[Second round only] Before you answer, here is a summary of the results to this question from the last round. **[Display summarised results from first round]**

Item type	Item
Bacterium or fungus	• <i>Staphylococcus aureus</i>
	• <i>Rickettsia</i> spp.
	• <i>Orientia tsutsugamushi</i>
	• <i>Salmonella</i> spp. (typhoidal)
	• <i>Salmonella</i> spp. (non-typhoidal)
	• <i>Leptospira</i> spp.
	• <i>Burkholderia pseudomallei</i>
	• <i>Streptococcus pneumoniae</i>
	• <i>Streptococcus pyogenes</i>
	• <i>Brucella</i> spp.
	• <i>Mycobacterium tuberculosis</i>
	• <i>Talaromyces</i> spp.
	• Other (please state)
	• Other (please state)
	• Other (please state)
Virus	• Dengue
	• Chikungunya
	• Zika
	• Japanese encephalitis
	• HIV
	• Hepatitis B
	• Hepatitis A

		• Hepatitis E	
		• Enteroviruses	
		• Other (please state)	
		• Other (please state)	
		• Other (please state)	
	Parasite	• <i>Schistosoma</i> spp.	
		• <i>Leishmania</i> spp.	
		• <i>Plasmodium</i> spp.	
		• Pathogenic amoebae	
		• <i>Wuchereria bancrofti</i>	
		• <i>Brugia</i> spp.	
		• Other (please state)	
		• Other (please state)	
		• Other (please state)	
	Non-infectious	• Non-infectious aetiologies e.g., autoimmune diseases	

D. Comments on survey questions and structure

21. **[First round only]** We are keen to improve the survey for the final round. Please provide any feedback you might have on the questions, structure, or any other aspect of the survey.

E. Thank you and next steps

22. **[First round only]** Thank you for completing this round of the survey. We will send you an email with your personalised link to the next round when it commences on **[date]**.

[Second round only] Thank you for completing the final round of the survey.

Would you like to receive a copy of the published results?

- Yes

- No

Many thanks again for your time, it is much appreciated.

Appendix 6.2 Delphi survey – list of participants

Mainland Southeast Asia panel

Name	Position	Country	Round 1	Round 2
Yoke Fun Chan	Professor of Microbiology, University of Malaya	Malaysia	✓	✓
Hock Hin Chua	Clinician-researcher and Infectious Diseases Physician, Sarawak General Hospital	Malaysia	✓	✓
Adeeba Kamarulzaman	Professor of Medicine and Infectious Diseases, University of Malaya	Malaysia	✓	✓
Joon Wah Mak	Professor of Pathology, International Medical University	Malaysia	✓	✓
Timothy William	Clinician-researcher and Infectious Diseases Physician, Queen Elizabeth Hospital	Malaysia	✓	✓
Muhamad Yazli Yuhana	Clinician-researcher and Infectious Diseases Physician, MARA University of Technology	Malaysia		✓
Direk Limmathurotsakul	Associate Professor of Tropical Hygiene, Mahidol University	Thailand	✓	✓
Stuart Blacksell	Professor of Tropical Microbiology, University of Oxford	Thailand		✓
Punnee Pitisuttithum	Professor of Clinical Tropical Medicine, Mahidol University	Thailand		✓
Pratap Singhasivanon	Associate Professor of Tropical Hygiene, Mahidol University	Thailand	✓	✓
Jittima Dhitavat	Associate Professor of Clinical Tropical Medicine, Mahidol University	Thailand		✓
Mayfong Mayxay	Professor, University of Health Sciences	Laos	✓	✓
Elizabeth Ashley	Professor of Tropical Medicine, University of Oxford	Laos	✓	✓
Paul Newton	Professor of Tropical Medicine, University of Oxford	Laos	✓	✓
Koukeo Phommasone	Deputy Head of Microbiology Department, Mahosot Hospital	Laos	✓	✓
David Dance	Clinical Microbiologist, Lao-Oxford-Mahosot Hospital Wellcome Research Unit	Laos	✓	✓
Claudia Turner	Clinician-researcher, paediatrician, and Chief Executive Officer, Angkor Hospital for Children	Cambodia	✓	✓

Sotharith Bory	Head of Internal Medicine and Infectious Diseases Departments, Calmette Hospital	Cambodia	✓	✓
Paul Turner	Professor of Paediatric Microbiology, University of Oxford	Cambodia	✓	✓
John Crump	Professor of Medicine, Pathology, and Global Health, University of Otago	Myanmar	✓	✓
Frank Smithuis	Professor of Tropical Medicine, University of Oxford	Myanmar	✓	
Myo Swe	Clinician-researcher, Myanmar Oxford Clinical Research Unit	Myanmar		✓
François Nosten	Professor of Tropical Medicine, University of Oxford	Myanmar	✓	✓
Aung Pyae Phy	Senior Research Clinician, Shoklo Malaria Research Unit	Myanmar	✓	✓

Maritime Southeast Asia panel

Name	Position	Country	Round 1	Round 2
Jemelyn García	Clinician-researcher and Infectious Diseases Physician, Research Institute for Tropical Medicine	Philippines	✓	
Jaime Montoya	Professor, University of the Philippines	Philippines		✓
Josh Francis	Principal Research Fellow, Menzies School of Health Research	Timor-Leste	✓	✓
Charlotte Hall	Physician, Bairo Pite Clinic	Timor-Leste	✓	✓
Lois Hong-Rajaraman	Clinical Director, Associação Maluk Timor	Timor-Leste		✓
Clare Nourse	Professor of Paediatrics, University of Queensland	Timor-Leste	✓	✓
Erni Juwita Nelwan	Professor, University of Indonesia	Indonesia	✓	✓
Ric Price	Professor of Global Health, Menzies School of Health Research	Indonesia		✓
Kartika Saraswati	Research Physician, Oxford University Clinical Research Unit Indonesia	Indonesia	✓	✓

South Asia panel

Name	Position	Country	Round 1	Round 2
Razia Fatima	National Coordinator, Common Management Unit for TB, HIV/AIDS, and Malaria	Pakistan		✓
Summiya Nizamuddin	Medical Microbiologist, Shaukat Khanum Memorial Cancer Hospital and Research Center	Pakistan	✓	✓
Naseem Salahuddin	Head of Infectious Diseases Department, The Indus Hospital	Pakistan	✓	✓
Faisal Sultan	Infectious Diseases Physician, Shaukat Khanum Memorial Cancer Hospital and Research Center	Pakistan	✓	✓
Bushra Jamil	Medical Microbiologist, Aga Khan University Hospital	Pakistan	✓	✓
Christopher Parry	Honorary Clinical Fellow, Liverpool School of Tropical Medicine	Nepal	✓	✓
Abhilasha Karkey	Medical Microbiologist, Oxford University Clinical Research Unit Nepal	Nepal		✓
Bipin Adhikari	Clinical Researcher, Mahidol Oxford Tropical Medicine Research Unit	Nepal	✓	✓
Anup Bastola	Chief Consultant Tropical Medicine, Ministry of Health	Nepal	✓	✓
Firdausi Qadri	Medical Microbiologist, International Centre for Diarrhoeal Disease and Research, Bangladesh	Bangladesh	✓	✓
Mohammad Abul Faiz	Former Director-General of Health Services, Ministry of Health and Family Welfare	Bangladesh	✓	✓
Subhash Hira	Affiliate Professor of Global Health, University of Washington	India	✓	✓
Priscilla Rupali	Senior Professor and Head of Infectious Diseases Department, Christian Medical College	India	✓	✓

Appendix 6.3 Cost-effectiveness analysis of multiplex lateral flow rapid diagnostic test - Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist

	Item	Guidance for Reporting	Reported in section
TITLE			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Title (in published manuscript)
ABSTRACT			
Abstract	2	Provide a structured summary that highlights context, key methods, results and alternative analyses.	Abstract (in published manuscript)
INTRODUCTION			
Background and objectives	3	Give the context for the study, the study question and its practical relevance for decision making in policy or practice.	Introduction
METHODS			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	NA
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Study design and participants; Table 6.2
Setting and location	6	Provide relevant contextual information that may influence findings.	Setting
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Base case
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Base case
Time horizon	9	State the time horizon for the study and why appropriate.	Base case
Discount rate	10	Report the discount rate(s) and reason chosen.	Base case
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Base case

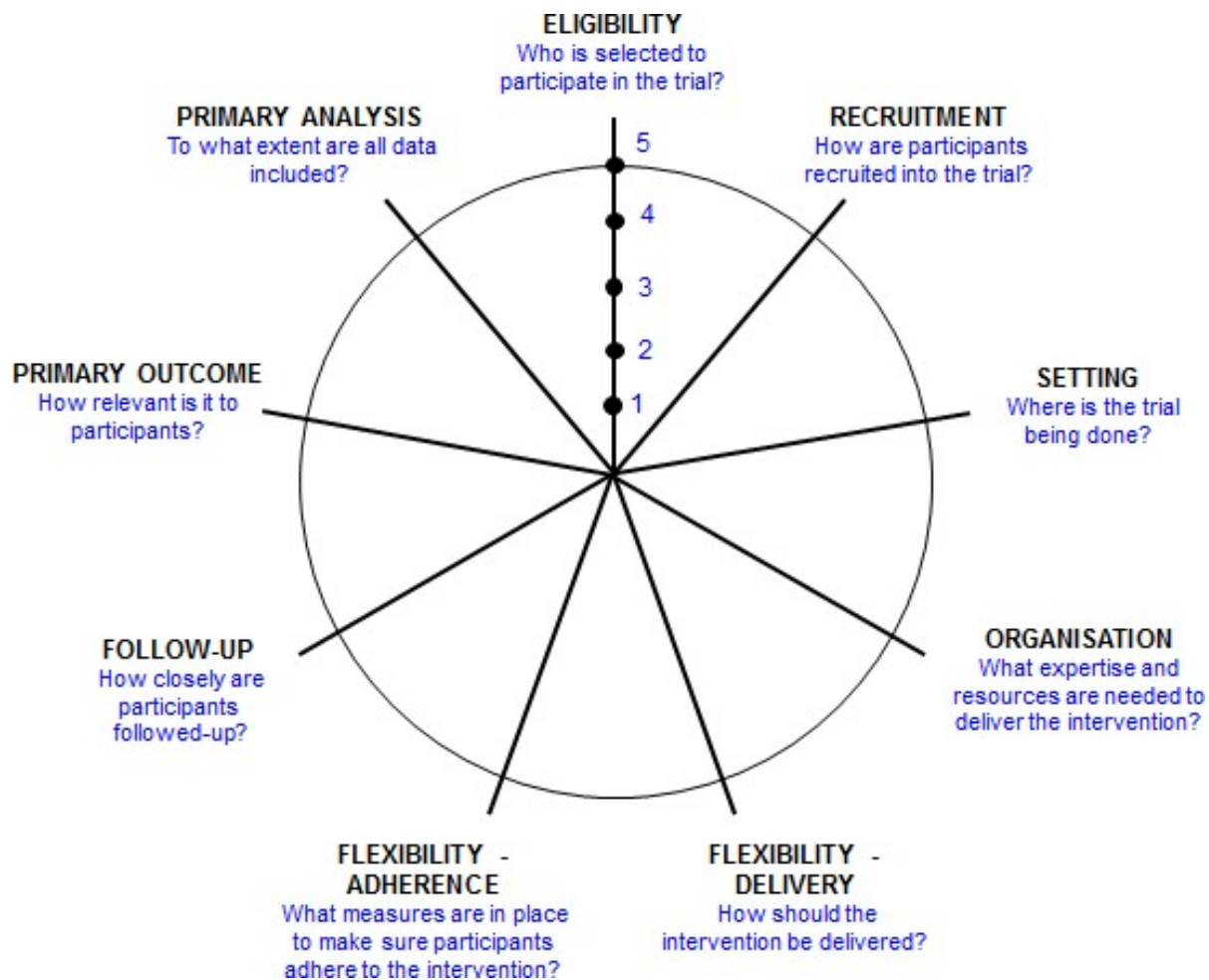
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Study design and participants; Base case; Table 6.2; Table 6.3
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Study design and participants; Base case; Table 6.2
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Base case; Table 6.2
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Base case
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Base case
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Assumptions
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for sub-groups.	Sensitivity and scenario analyses
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	NA
Characterizing uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	Sensitivity and scenario analyses
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (e.g., clinicians or payers) in the design of the study.	NA
RESULTS			
Study parameters	22	Report all analytic inputs (e.g., values, ranges, references) including uncertainty or distributional assumptions.	Table 6.2
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Base case; Table 6.5
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if	Sensitivity and scenario analyses, Table 6.6; Figure

		applicable.	6.7; Figure 6.8
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	NA
DISCUSSION			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could impact patients, policy, or practice.	Discussion
OTHER RELEVANT INFORMATION			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Declarations (in published manuscript)
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Declarations (in published manuscript)

Appendix 7.1 Cluster-randomised trial of an electronic clinical decision support tool – PRAgmatic EXplanatory Continuum Indicator Summary (PRECIS)-2 toolkit

Domain		Score	Rationale
1	Eligibility Criteria	5	The goal of the intervention is for it to be incorporated as part of routine care for patients with acute febrile illness in rural South and Southeast Asian primary health centres, therefore all patients who present with acute fever will be eligible. The only exception is neonates, for whom fever necessitates referral to secondary care as per well-established guidance.
2	Recruitment Path	4	Patients will be pragmatically recruited as they present to study facilities, with written consent waivers sought from the relevant ethics committees. Healthcare workers will, however, receive compensation for the time taken to enroll and follow up patients, at sites where this is necessary to the successful running of the trial. This may involve per capita payment for each recruited patient.
3	Setting	5	The trial and usual care settings are identical i.e., rural South and Southeast Asian primary health centres.
4	Organisation intervention	5	The trial uses identical organization to usual care, in that the same healthcare workers who normally work at the primary health centres involved in the trial will be those using the intervention (or continuing with the current standard of care if working at a primary health centre in the control arm).
5	Flex of experimental intervention – Delivery	5	While healthcare workers in the intervention arm are recommended to follow the recommendations of the EDAM app, there is no compulsion to do so and their clinical judgement will remain paramount.
6	Flex of experimental intervention – Adherence	5	While healthcare workers in the intervention arm are recommended to follow the recommendations of the EDAM app, there is no compulsion to do so and their clinical judgement will remain paramount.
7	Follow up	3	Not all patients would be routinely followed up, but because some of the secondary outcomes involve events which occur at later time points e.g., recovery at day 7, telephone follow-up is necessary. This follow-up method was chosen to ensure that

			the nature of follow up is well-balanced between pragmatic and explanatory.
8	Outcome	5	The primary outcome is the proportion of patients prescribed antibiotics. This is of importance to the participants (patients), as well as healthcare workers and the wider health system.
9	Analysis	5	An intention-to-treat approach will be taken for the analysis of the primary outcome, although a per protocol analysis will also be performed in parallel.



Appendix 7.2 Cluster-randomised trial of an electronic clinical decision support tool – Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist

Section/item	Item No	Description	Location
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title (in published manuscript)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Methods > Trial registration
	2b	All items from the World Health Organization Trial Registration Data Set	Throughout chapter and in trial registration document
Protocol version	3	Date and version identifier	In protocol submitted as Supplementary Information for published manuscript
Funding	4	Sources and types of financial, material, and other support	Methods > Funding
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Authors and affiliations (in published manuscript)
	5b	Name and contact information for the trial sponsor	Methods > Ethical approval; trial registration document

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Methods > Funding
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Methods > Safety considerations
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction, para. 1-4
	6b	Explanation for choice of comparators	Introduction, para. 1-4
Objectives	7	Specific objectives or hypotheses	Introduction, para. 5
Trial design	8	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)	Introduction, para. 5; Methods > Design
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Methods > Setting
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	Methods > Participant characteristics

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Methods > Description of intervention
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	Methods > Description of intervention; Methods > Description of other study procedures and follow-up
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Methods > Description of intervention
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Methods > Outcome measures
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Methods > Description of intervention; Methods > Description of other study procedures and follow-up
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Methods > Sample size calculations

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Methods > Setting
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Methods > Design
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Methods > Design
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Methods > Design
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Methods > Description of intervention; Methods > Data management; Methods > Data quality assurance

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Methods > Description of other study procedures and follow-up
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Methods > Data management; Methods > Data quality assurance
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Methods > Description of statistical analyses
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	Methods > Description of statistical analyses
	20c	Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	Methods > Description of statistical analyses; Methods > Participant characteristics
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Methods > Data quality assurance; Methods > Safety considerations
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Methods > Safety considerations

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Methods > Safety considerations
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Methods > Safety considerations
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Methods > Ethical approval
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Methods > Ethical approval
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	NA
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Methods > Data management
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Conflict of interest declaration
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Methods > Data management
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Methods > Dissemination
	31b	Authorship eligibility guidelines and any intended use of professional writers	Methods > Dissemination
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Methods > Data management
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA