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Acute febrile illness, antibiotic use, and the role of diagnostics to target treatment in India

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Abstract

Holloway, B. 2022. Acute febrile illness, antibiotic use, and the role of diagnostics to target treatment in India. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1819. 145 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-1439-6.

Aim: This thesis examined the causes of acute febrile illness (AFI), the current use of antibiotics and diagnostics, and evaluated the diagnostic accuracy of C-Reactive Protein (CRP) to differentiate bacterial from non-bacterial causes of AFI in children and adult outpatients at R.D. Gardi Medical College hospital, in Ujjain, India.

Methods: A prospective cross-sectional study of children and adult outpatients with fever ≥37.5°C, or history of fever in the past 48 hours, and no signs of severe illness. Patient history, physical examination, culture, rapid diagnostic tests, and follow-up after one week was performed for all patients. Whole blood and urine were collected from all patients, and symptom based nasopharyngeal throat swabs, stool, and skin/ear/joint/aspirate specimens. Fever was classified as bacterial or non-bacterial based on microbiology and laboratory results together with an expert panel review. Data on antibiotic use before, during, and after enrolment was described by Anatomical Therapeutic Chemical classification and AWaRe categories. Serum CRP levels were measured and the performance characteristics for CRP to differentiate between bacterial and non-bacterial AFI were calculated. The area under the receiver operating curve (AUC), sensitivity, specificity, positive and negative predictive values, and likelihood ratios were estimated using 10, 20, 40, 60 and 80 mg/L thresholds. A rapid ethnographic qualitative study on the utilization of diagnostics was conducted using unstructured observations, structured observations and 43 semi-structured interviews. Interview data were analyzed using inductive thematic analysis.

Results: Of 1000 outpatients, 24.4% were categorized as bacterial; 71.8% non-bacterial; and 3.8% an undetermined cause of fever. Throughout the course of AFI, 41.0% of patients received one or more antibiotics. The leading contributors to total antibiotic volume were macrolides. 'Watch' antibiotics accounted for 72.3%, 52.7%, and 32.6% of encounters before, during and after the outpatient visit. The overall median CRP was low but higher in the group classified as bacterial compared to non-bacterial (3.6 mg/L vs. 2.7 mg/L, $p<0.0001$, respectively). The AUC was low at 0.60 (95% CI 0.56 - 0.65). Caregivers trusted and understood the importance of diagnostics, but their acceptance wavered depending on the severity of illness and preference to treat their child directly with medicines. Caregivers struggled to get tests done and return for follow-up due to costs, delays in testing, further complicated by travel time, distance and competing priorities.

Conclusion: This thesis highlights the challenges in determining the cause of AFI. Over,under, and inappropriate use of antibiotics throughout the course of AFI are of major concern.The organization of diagnostic services, together with direct and indirect costs, hinder caregiversfrom utilizing diagnostics. CRP is too weak as a single indicator of bacterial infection to safelysupport physicians in making treatment decisions for febrile outpatients in India.

Keywords: fever, acute febrile illness, fever, infectious disease, diagnostics, c-reactive protein, antibiotics, antibiotic resistance

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“Beyond mountains there are mountains”
— Haitian proverb

As you solve one problem, another problem presents itself,
and so, you go on, and try to solve that one too.

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Holloway B, Mathur A, Purohit M, Sharma A, Pradhan R, Hemwani K, Bergström A, Mårtensson A, Hildenwall H, Pathak A. (2022) Classification of non-severe acute febrile illness as bacterial or non-bacterial: A prospective observational study of children and adult outpatients presenting at a rural, tertiary-teaching hospital in Ujjain, India. *Submitted manuscript.*

II. Holloway B, Chandrasekar H, Purohit M, Sharma A, KC A, Fernandez-Carballo B.L, Dittrich S, Hildenwall H, Bergström A. (2022) Antibiotic use before, during and after seeking care for acute febrile illness at a hospital outpatient department: a cross-sectional study from rural India. *Submitted manuscript.*

III. Holloway B, Mathur A, Pathak A, Bergström A. (2020). Utilisation of diagnostics in India: a rapid ethnographic study exploring context and behaviour. *BMJ Open*, 10:e041087.

IV. Holloway B, Mathur A, Sharma A, Pradhan R, Hemwani K, Fernandez-Carballo BL, Bergström A, Hildenwall H, Purohit M. (2022). Performance characteristics of C-reactive protein to distinguish bacterial from non-bacterial causes of acute febrile illness in India. *In manuscript.*

Contents

Abbreviations

ABR	Antibiotic resistance
AFI	Acute febrile illness
AMR	Antimicrobial resistance
ATC	Anatomical Therapeutic Chemical
AUC	Area under the receiver operating curve
AWaRe	Access, Watch, Reserve
BFF-Dx	Biomarkers for Fever Diagnostics
CI	Confidence intervals
COM-B	Capability, Opportunity, Motivation – Behavior
CRF	Case report forms
CRP	C-reactive protein
FDCs	Fixed dose combination
FIND	Foundation for Innovative New Diagnostics
IQR	Interquartile range
LMICs	Low- and middle-income countries
LR-	Likelihood ratio negative
LR+	Likelihood ratio positive
NPV	Negative predictive value
OPD	Outpatient department
PCR	Polymerase chain reaction
POCT	Point of care tests
PPV	Positive predictive value
RD	Ruxmaniben Deepchand
RDT	Rapid diagnostic test
WHO	World Health Organization
UN	United Nations

1. Introduction

1.1 Antibiotics

Antibiotics are essential for basic and modern healthcare. They are important medicines for preventing and treating bacterial infections in humans and animals. Since the introduction of penicillin for the treatment of bacterial infections in the 1940s, antibiotics have made countless medical procedures possible and have saved countless lives (1). Antibiotics have become the cornerstones supporting essential and modern medicine. Figure 1[1], illustrates a select few of the medical conditions and procedures that rely on the effectiveness of antibiotics.

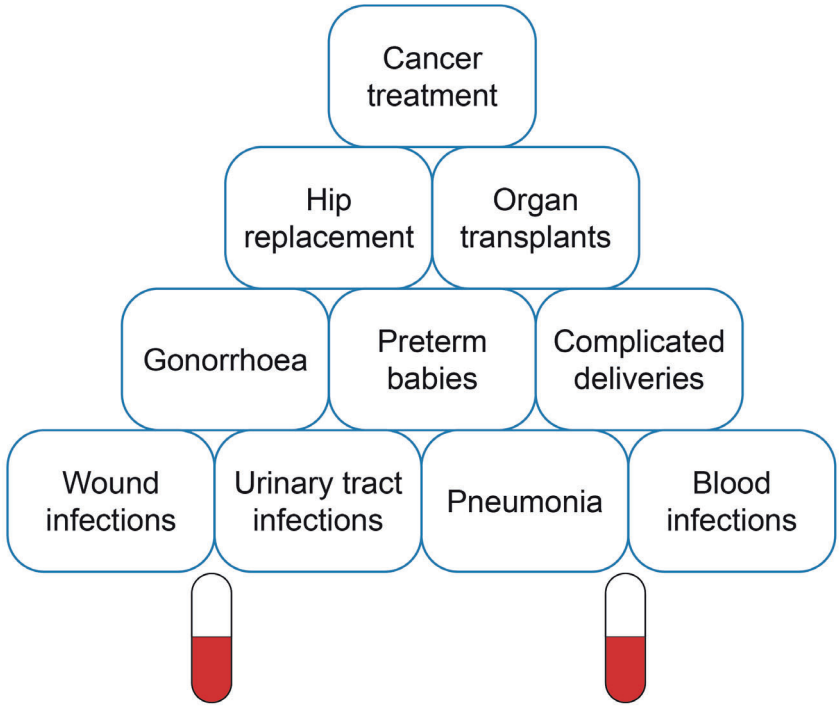

Figure 1: The antibiotic pyramid shows just some of the many types of diseases and surgical procedures which rely on effective antibiotics.

[1] Adapted from the ReAct Toolbox

While antibiotics are medicines directed towards preventing and treating bacteria, antimicrobials are directed towards all microorganisms, including bacteria, viruses (e.g. HIV), parasites (e.g. malaria), and fungi (e.g. Candida) as displayed in Figure 22 (2). Antimicrobials include antibiotics, and therefore antimicrobial resistance (AMR) also includes antibiotic resistance (ABR). The terms ABR and AMR are often used interchangeably, however in many cases where the broader term is used, the focus is actually on ABR. This thesis focuses solely on antibiotics and ABR; however, may refer to literature where the broader terms antimicrobials or AMR are used. For example, the United Nations (UN) and the World Health Organization (WHO), predominantly focus on antibiotics and ABR in their work but generally use the overarching term AMR, to ensure resistance to other antimicrobials is not excluded (3,4).

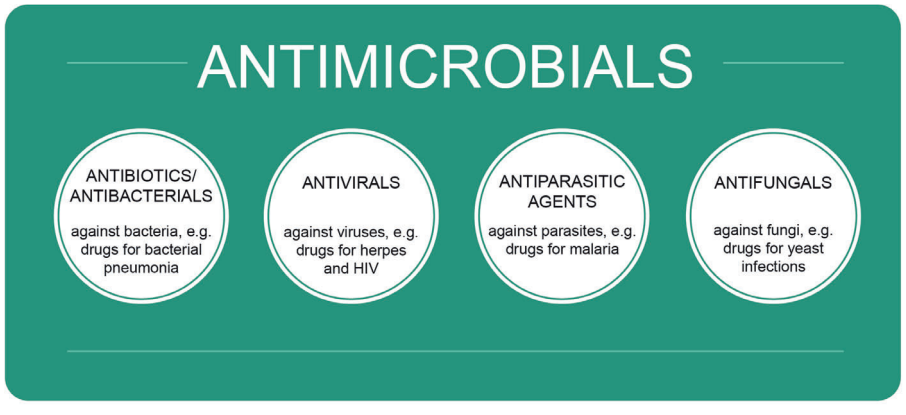

Figure 2. Types of antimicrobials and the microorganisms they are active against.

Antibiotics are powerful medicines which disrupt essential processes or structures in the bacterial cell, slowing down bacterial growth or killing the bacterium (2). There are several different classes of antibiotics, all of which inhibit vital functions of the bacteria, acting on one of three main targets i) the bacterial cell wall or membranes; ii) the production of the bacterial DNA and RNA; iii) the production of the ribosome and associated proteins (2). Antibiotics that focus on a wide spectrum of bacteria are known as broad-spectrum antibiotics, while those which are only active against certain strains of bacteria are called narrow-spectrum antibiotics (2). Broad-spectrum antibiotics have the benefit that they can inhibit a wider range of bacteria, however this comes at the expense of having a negative effect on non-disease causing bacteria (2). These antibiotics are often the go-to drugs when the target bacteria is unknown, to cover all the bases (2).

[2] Adapted from the ReAct Toolbox

1.2 Antibiotic resistance

All use of antibiotics promotes the development of ABR. The use of antibiotics when not clinically indicated, or the use of the wrong antibiotic for the wrong indication, is accelerating the development of ABR, compromising the treatment of infectious diseases, and undermining the ability to prevent and treat infections. As ABR erodes antibiotic efficiency, these valuable cornerstones have started to crumble and the "pyramid of health" (Figure 1) risks to fall with them (2). To slow the process, the right drugs must be used for the right reasons, and when possible, treatment options should be targeted at antibiotic/bacteria combinations least likely to build resistance.

ABR occurs when the bacteria develop the ability to protect themselves against the effects of the drug. Clinically speaking, ABR means that a bacterium can grow in the antibiotic concentration used during standard therapy. Consequently, using that antibiotic to treat an infection will likely lead to a treatment failure (2). Resistance can occur due to random mutations in the bacterial DNA or when the bacteria receive resistance genes from other bacteria nearby, also known as horizontal gene transfer (2).

In the early days of antibiotic use, many new antibiotics were being developed. As ABR began to emerge, one antibiotic that stopped working was replaced with another treatment option. No genuinely novel classes of antibiotics have reached the market since 1987. Since then, very little innovation has taken place in the field, and as a result, few novel antibiotic classes are under research and development (5–7). Consequently, the antibiotic pipeline has been to drying up over time, leaving a discovery void. A timeline of the discovery of the major antibiotic classes up until 2010 is featured in Figure 3[3] (2), and adapted from ReAct/Silver (2011) (8). Ten years on, a new analysis of the pipeline for antibiotics concludes that the breadth and novelty of the antibiotic pipeline is still insufficient to meet the growing threat of ABR (9).

[3] Adapted from the ReAct Toolbox / Silver 2010

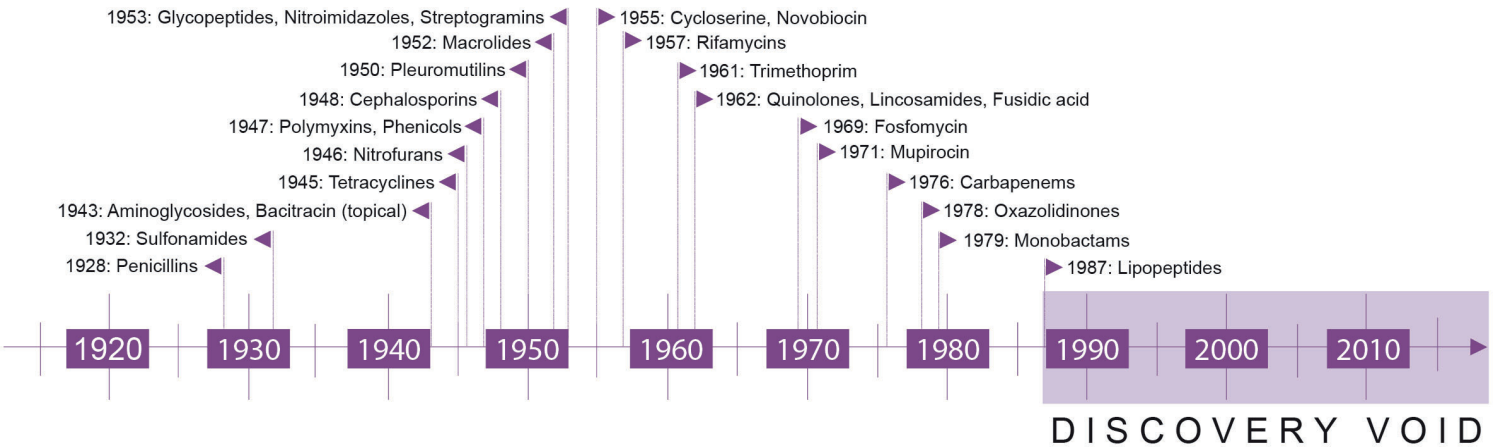

Figure 3: Timeline of the discovery of different antibiotic classes in clinical use. “The discovery void” refers to the period from 1987 until today, as the last antibiotic class that has been successfully introduced as treatment was discovered in 1987.

1.3 Access versus excess use of antibiotics

Equally important to reducing the overuse of antibiotics is ensuring access to these essential medicines for those in need; this is known as the "Access vs. Excess dilemma" (10). A study of antibiotic consumption from 2000-20015 found an alarming 65% rise in antibiotic use across the globe (11). The increase was predominantly driven by increased use in low- and middle-income countries (LMICs), and attributed to rising living standards. While increased access to antibiotics is beneficial, it must be ensured that the right drugs are being used for the right reasons.

An estimated 80-90% of human antibiotic use occurs in outpatient settings (12). In healthcare centers or outpatient clinics, when patients present with symptoms suggestive of infection, healthcare providers are faced with the dilemma of whether to prescribe antibiotics or not. Studies suggest that healthcare providers tend to be cautious and prescribe antibiotics even if symptoms are suggestive of viral etiology (13–15). Reasons driving inappropriate antibiotic use include a lack of knowledge on their correct use and negative effects, patient pressure to be given an antibiotic, a desire to please the patient so they come back in the future, perverse financial incentives which link doctors pay to the number of prescriptions given, a lack of guidelines to assist clinical management, the absence of diagnostic tools, wanting to cover all the bases regardless even if a bacterial infection is unlikely in fear of missing to treat a potentially life-threatening condition (16–22). In LMICs, these fears are real as patients may not be able to return for care if the illness persists or deteriorates given logistic and financial barriers.

Limited access to antibiotics in many LMICs compromises health and productivity (10,23,24). Access to antibiotics varies globally and on the country level, and is dependent on a country's regulatory framework and health system (1,25,26). Global collaboration is needed to ensure universal access to effective antibiotics (1,25,26). Regulations to control the distribution and use of antibiotics, such as limiting the sale of antibiotics to prescription only, may seem like a simple solution. Still, such laws risk cutting off access to antibiotics for parts of the population, particularly rural populations that lack access to prescribers (27). To support access to medicines at the country level, the WHO Model List of Essential Medicines was developed. The list provides countries guidance on the minimum medicine needs for a basic healthcare system. The drugs on the list are for use in priority health conditions of public health relevance are selected based on evidence of efficacy and safety as well as cost-effectiveness (28).

1.4 The global burden of antibiotic resistance

ABR is one of the greatest threats to health and sustainable development (3,29–31). The recent Global Burden of Antibiotic Resistance study revealed that the most comprehensive data to date estimate that 1.27 million deaths globally were attributable to AMR in 2019 (32). This is significantly greater than previous estimates from the 2014 *Review on Antimicrobial Resistance* which suggested 700,000 deaths attributable to AMR (33). Moreover, the new data suggests an estimated 4.95 million deaths were found to be associated with drug-resistant infections in 2019 alone (32). The long-awaited, compelling evidence presents a complete picture of the spread of ABR across the globe. Findings affirm that ABR is not a future problem; it is already a leading cause of death worldwide with a magnitude of infectious diseases such as malaria and HIV (32).

The burden of ABR strikes hardest on LMICs, with the highest attributable date rates from resistant pathogens found in sub-Saharan Africa (27.3/100,000 deaths attributable to AMR and 98.9/100,000 associated with AMR) and South Asia (21.5/100,000 attributable and 76.8/100,000 associated deaths) (32). In resource-limited settings, high rates of infectious diseases, weak healthcare infrastructure, and lack of access to clean water and sanitation, extensive use of broad-spectrum antibiotics, and poor access to second- and third-line antibiotics needed to treat resistant infections, promote the rapid development and spread of resistant infections (34,35). The report echoes another recent paper that highlighted serious gaps in the AMR data in many low-income settings, including data on the underlying causes of infections, patient outcomes and resistance, amongst others, and emphasizes the need for diagnostic capacity and data collection in the countries affected the most to improve understanding and facilitate the response to ABR (32).

1.5 The global response to antibiotic resistance

Addressing the problem of ABR is a complex challenge needing harmonized multisectoral action on a global scale (36). Initial global efforts to address the issue were organized by the WHO starting with scientific working groups already back in 1994, the first global strategy in 2001 (37), and a implementation workshop as early as 2002 (38). Over the following 15 years, uptake on the issue was slow, collective action failed to take hold, and it became clear that ABR must be approached from numerous angles by various stakeholders to get the momentum deserved (25,26,36,39,40).

In an effort to frame the issue and structure the action needed, the WHO joined together with the Food and Agriculture Organization and World Organization for Animal Health to create what is known as the Tripartite collaboration (41). In 2015, the WHO, together with the Tripartite, released the

Global Action Plan on ABR (4), which was adopted at the 68th World Health Assembly by all the WHO member states. The Global Action Plan outlines five strategic objectives as seen below in Figure 4[4]. As part of it, all countries committed to developing national action plans on AMR to support and coordinate actions needed at the national level. Slowly countries have been developing national action plans, but their implementation, especially in LMICs, has been limited and challenging (42–44).

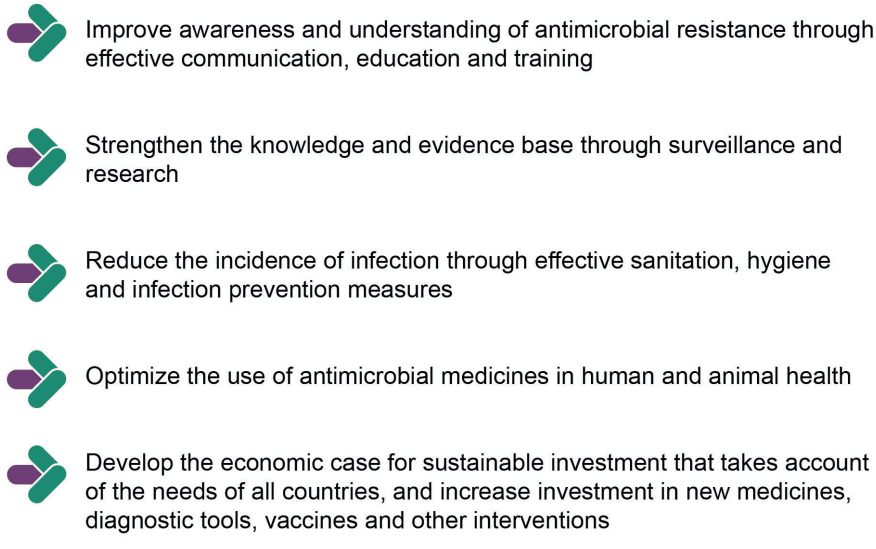

Figure 4. The five strategic objectives of the Global Action Plan on Antimicrobial resistance.

In 2016, the issue of ABR made it to the level of the UN General Assembly. This was a historic moment as only the fourth time ever that a health topic received attention from the highest global governing body. Heads of States committed to a broad multisectoral approach to addressing AMR with the signing of the UN political declaration on AMR (30). As a result, the UN Secretary convened the Interagency Coordination Group (45) on AMR, which was tasked with preparing recommendations to the UN Secretary General (3). An outcome of the recommendations was the establishment of a One Health Global Leaders Group on Antimicrobial Resistance in 2020 to work together for political momentum, leadership and action on AMR, which was established in 2017 (46). Most recently, to keep up the momentum and regain focus on ABR amid the COVID-19 pandemic, the High-Level Interactive Dialogue

[4] Adapted from the Global Action Plan on Antimicrobial Resistance 2015

on AMR was held in November 2021, and 113 member states and 39 supporting organizations signed onto a Call to Action on ABR (47).

In addition to the global governance on AMR through the UN, Tripartite collaboration, and actions taken at the country level, several civil society organizations and public-private partnerships have mobilized to support the response to ABR. Two key organizations, ReAct – Action on Antibiotic Resistance (48) and CDDEP (Center for Disease Dynamics, Economics and Policy) (49) have driven the response to ABR, focusing on LMICs, for over 15 years. As the profile of ABR has risen, it has become more and more apparent for the need for global collective action, and the number of players in the ABR field has grown exponentially during the last five to seven years. Several research hubs or university centers on ABR have opened, a few new small civil society organizations focusing predominately on ABR have emerged, and many of the large already established civil society organizations working in global health, animal, environmental, policy arenas have placed ABR on their agendas.

One of those organizations is the Foundation for Innovative New Diagnostics (FIND). The global alliance for diagnostics, FIND, is an international nonprofit organization that enables the development and delivery of much-needed diagnostic tests that meet the needs of lower-income countries (50). FIND facilitates the connection of countries and communities, decision-makers, healthcare providers, funders and developers to catalyze diagnostic innovation to make testing an integral part of primary care to combat diseases that disproportionately affect vulnerable populations (50). As diagnostics play an essential role in aiding treatment decisions, in response to the problem of ABR, and to support global goals to eradicate malaria, FIND decided to focus on malaria and acute febrile syndrome as part of their 2015-2020 strategy (51). FIND's webpage describes their goal to "build access to AMR testing and surveillance to safeguard drugs and reduce mortality" and focus on "preventing AMR development and mortality through developing and improving diagnostic systems" (52). In 2015, FIND, together with the WHO, ReAct, and Médecins Sans Frontières (Doctors without Borders), convened a group of global health and diagnostic experts to map the needs for diagnostics for ABR focusing on LMICs (53). The outcome of this meeting, together with additional underlying formative work (54,55) led to the development of one of FIND's several priority projects, Biomarkers for Fever Diagnostics (BFF-Dx) (56). The project includes a large multi-center clinical trial to study the performance of promising biomarker diagnostic tests that can differentiate between bacterial and non-bacterial causes of fever in resource-limited settings.

The work of this thesis is a consequence of a collaboration between Uppsala University and FIND along the lines of the BFF-Dx project together with the research group's collaborator RD Gardi Medical College in India.

1.6 Monitoring antibiotic use

Knowledge about antibiotic use is key to understanding the areas in need of attention and assisting in developing context-appropriate interventions to improve antibiotic use. Antibiotic use can be quantitatively measured as the number of antibiotics sold, prescribed, dispensed or consumed, and it can be done at the national, regional, community, household or provider level. The two most common ways of measuring antibiotic use are in terms of quantity and appropriateness of prescribing, that is to say, if the right antibiotic is being used for the right indication in the right dose for the right duration at the right time. It is also essential to monitor the availability of antibiotics via medicine prices, availability and affordability (57).

What is considered appropriate may differ from one context to the next depending on disease and resistance patterns and prescribing and clinical guidelines. Evaluations on the appropriateness of prescribing may also be useful to investigate the reasons why antibiotics are being prescribed and if patients take their antibiotics accordingly. Traditionally Knowledge, Attitudes, Beliefs and Practices surveys have been used to look at the "how" and "why" of antibiotic use (58–63). In recent years, more qualitative methods have been employed as the social sciences have engaged in the topic of ABR, bringing fresh approaches and new perspectives to the study of antimicrobials in society (64–69).

Studies of antibiotic use in LMICs have mainly focused on hospitals (70) or wholesales-based estimates (71). Efforts to improve antibiotic use have focused mainly on secondary or tertiary care hospitals (72) and have predominately been in the public sector (73). Health services in LMICs are increasingly delivered through mixed public and private providers (74), with up to 80% of healthcare sought outside of formal healthcare facilities at private clinics, pharmacies, or from informal providers or drug sellers (75–77). Despite this, antibiotic use across the diversity of healthcare providers and informal markets is not systematically monitored.

The most widely used classification system for drugs in humans is the Anatomical Therapeutic Chemical (ATC) classification system (78), coordinated by the WHO Collaborating Center for Drug Statistics Methodology (79). The ATC system organizes drugs into different groups by the organ or system on which they act and their characteristics (80). In an effort to make a standardized unit for comparison, drugs are given a Defined Daily Dose (DDD) which is the assumed average maintenance dose per day for the main indication for a drug in adults. Together the ATCs and DDDs create a standardized system for of drug utilization metrics which allows for the comparison of drug utilization over time and across settings.

As a complement to the ATC system and in an effort to specifically support the monitoring and reporting of antibiotic use, in 2017 the WHO introduced the AWaRe classification system (28). By categorizing antibiotics into

'Access', 'Watch' and 'Reserve' groups, the AWaRe system is intended to support evaluation, benchmarking and target setting in local and national contexts. The classifications are based on their use as first-, second- or last-choice treatment options, the spectrum of activity, and susceptibility to induce resistance in organisms. AWaRe was endorsed by the G20 Health Ministers in 2018 (81), and in 2019, the WHO updated the list and began listing many antibiotics whose use is not evidence-based, as 'Not recommended' (82).

1.7 Acute febrile illness in low- and middle-income countries

Fever is the single most common symptom of infection and one of the most common reasons for seeking healthcare by outpatients in LMICs (83). Acute febrile illness (AFI) is commonly characterized as an abrupt-onset illness lasting less than two weeks, with many potential simultaneous symptoms (84). In low-income countries, the wide range of diseases responsible for causing AFI, including respiratory tract infections, diarrheal disease, and vector-borne diseases, cause one-third of all morbidity and one-fourth of all mortality (85). In addition to infectious causes, AFI can also be a symptom of malignancy, surgical, causes, rheumatic disease, or inflammation amongst others.

There is no universal set of definitions for the different types of febrile illness (86), and several terms and definitions are found in the literature. Non-malarial fever refers to causes of fever either in non-malaria endemic regions or settings afflicted by malaria but for whom the included patients have negative diagnostic tests for malaria (87). Some studies include all fevers with any associated symptom, while others are limited to "undifferentiated". The term 'undifferentiated' is usually intended to mean fevers with no focus of infection/localizing symptom, however, patients rarely present with fever alone, it may be accompanied with headache, chills, and myalgia (87), and later, specific organs may be involved (84).

Most research on AFI has applied a study-specific temperature cut-off to define fever. Since intermittent fever is present with several fever-causing infections, and a proportion of patients may take antipyretics before seeking care, excluding patients with complaints of fever but without a measurable temperature could overlook a significant part of the febrile population and decrease the sensitivity to diagnose some infections. Furthermore, in resource-limited settings, it is unlikely that patients or their caregivers have thermometers at home, and they are also often unavailable in some peripheral health centers (88,89). Consequently, fever epidemiology studies in LMICs often use a cut-off of an axillary temperature ≥37.5°C and/or history of fever in the preceding days as reported by the patient or caregiver. This approach is supported

by the fact that in malaria endemic settings, caregivers have been found to have a fairly high sensitivity to detect fever (90–94).

In an effort to align definitions and support the comparison of results, this thesis uses a definition of AFI that is aligned with the FIND BFF-Dx project (56,95) and its underlying formative work (54,55). Therefore, for this thesis, AFI is intended to cover all potential non-severe causes of fever by outpatients in LMICs.

1.8 Establishing the cause of acute febrile illness

Identifying the underlying cause of fever is particularly challenging for healthcare providers in resource-limited outpatient settings. Diagnosis is often based on a patient's medical history and clinical examination, but the non-specific clinical presentation of fever could be caused by many potential etiologies (96–98). A definitive disease diagnosis is difficult to confirm as the availability of rapid diagnostic tests (RDTs) is limited (87,96,97,99), and laboratory facilities for identifying microorganisms are often lacking (96–99). Poor febrile illness diagnosis in LMICs results in higher morbidity, mortality, wasted resources and increased ABR as illustrated in Figure 5[5] (100).

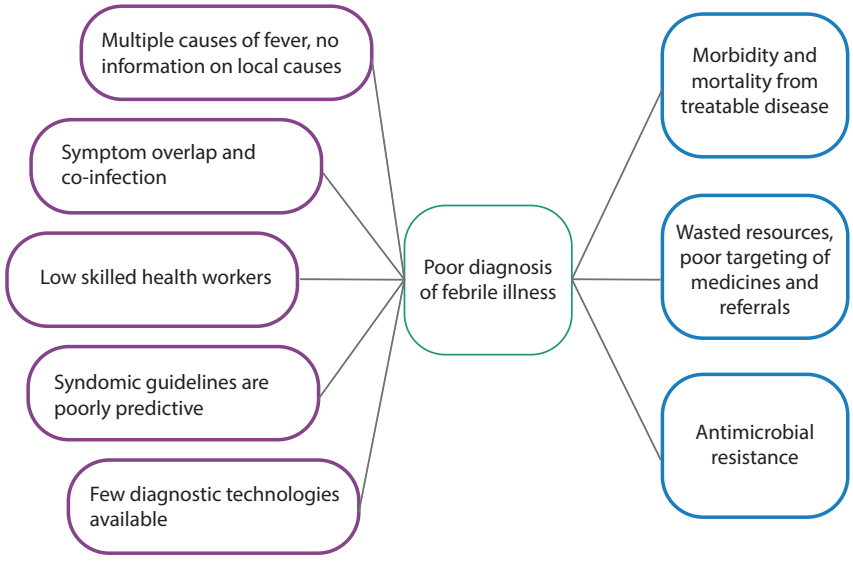

Figure 5. Factors contributing to poor febrile illness diagnosis in low-resource settings and their effects.

[5] Adapted from Unitaid - Fever diagnostic technology landscape 2018

In research settings, even with a comprehensive panel of microbiological tests, a large proportion of fevers will remain undiagnosed (101–104). Challenges are associated with choosing which pathogens to test for based on the study population, local epidemiology, and seasonality as well as which diagnostic approach to use based on time of presentation, sample type, and direct versus indirect testing (55). Molecular methods such as polymerase chain reaction (PCR) have high specificity and sensitivity but the identification of an organism does not necessarily mean it is the cause of infection, yet possibly an earlier infection (105). When it comes to serological tests, interpreting results can be challenging as positive results can be caused by subclinical or previous infection and cross-reactivity. Either a fourfold rise of titer in the convalescence sample or a high acute-phase titer is needed to confirm the diagnosis.

In the absence of a gold standard for identifying the cause of fever, great variation can be seen in the methods used to establish the cause of fever (106). In a comprehensive review from 2016, almost 20% of the 60 included studies, determined the cause of fever based solely on microbiological data, a few studies relied only on clinical assessment and many studies combined microbiology and laboratory data with clinical assessment (106). To overcome the challenges and find a harmonized approach that would allow for comparison between different studies, Escadafel et al (2017) suggest a combination of clinical and microbiological data reviewed by an independent panel to establish the cause of fever in LMIC settings (55).

1.9 Causes of acute febrile illness

Minimal data is routinely collected on the diagnosis and causes of fever in outpatients in LMICs. There are no routinely reported indicators, except for malaria, where national programs capture the proportion of suspected cases who are tested through routine household surveys. The only data for other AFI causes is derived from studies or special surveys (100). Recent reviews of the limited evidence describe the traditional pathogen- or disease-specific approach to understanding the causes of fever, such as focusing on typhoid or respiratory tract infection. Little research has been done at the symptom level, particularly for outpatients making it challenging to comprehend the cause and proper management of febrile illness (87,99). The lack of consensus definitions, sampling frames, and protocols makes it challenging to interpret and compare results of the limited evidence.

Traditionally, in malaria endemic areas, malaria was seen as a common cause of febrile illness, however, with the development and roll-out of the malaria RDT a better understanding of the real malaria incidence has evolved. RDT positive cases have helped to guide targeted treatment for malaria, however, in the case of a negative test, the lack of reliable tools to distinguish other

fever causes has contributed to increased antibiotic use (107). In many parts of the world, there is sparse evidence on non-malarial causes of fever (108).

Of the existing studies from Southeast Asia and several African countries, the data have shown that viruses like dengue or chikungunya, and not bacterial infections, are the causative agents of a large proportion of AFI cases (101,102,104). In Asia, dengue, influenza and Japanese encephalitis virus were common viral causes of non-malarial fever, while typhus and leptospirosis were main contributors of bacterial causes (101,104). Many of these infections are self-limiting and do not respond to antibiotic treatment. Patients who are unnecessarily exposed to antibiotics receive limited benefit at the expense of additional cost and fueling the problem of ABR. To reduce the indiscriminate use of antibiotics and stem the emerging crisis of ABR, an accurate diagnostic for AFIs is essential.

1.10 Fever diagnostic tools

To guide the appropriate use of antibiotics for AFI, diagnostic tests that identify patients with bacterial infections, and provide clinicians with timely, actionable results are needed (33). Several barriers exist to uptake and appropriate use of diagnostics in LMICs. Specific pathogen detection is challenging and complicated by the ever-changing epidemiology of fever, as seen with the rapid global spread of the COVID pandemic. Pathogen-specific testing, which requires sophisticated laboratory facilities, is often not adapted for LMICs with weak healthcare systems which lack funds, laboratory capacity, and sufficiently trained staff (109–112). Furthermore, traditional microbiological laboratory methods have long turn-around times that are not suited for patients who suffer from long waiting times, and travel distances together coupled with high out-of-pocket expenditures for direct and indirect costs of diagnosis, care, and treatment (109–112). Also, these traditional methods are not the most reliable as microbes can be missed.

Point of care tests (POCT) are tests that are performed at or near the patient with a fast turnaround time and can help guide patient management decisions within the same clinical encounter (113,114). There are no specific requirements of characteristics to be a POCT, but the WHO has suggested a set of characteristics for POCTs to meet the needs of low-resource settings with the ‘ASSURED’ (Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free) criteria (115,116). Recently an update was proposed with the ‘REASSURED’ criteria, adding Real-time connectivity and Ease of specimen collection to the list (117).

POCTs would be especially useful in resource-limited settings where delays in diagnostic testing can lead to high loss-to-follow-up rates (118). To address this need, there is an increasing amount of research on POCTs that measure host biomarkers to aid in differentiating between bacterial and other

causes of AFI (106,119). Host biomarkers can be detected from tissue or biological fluid and can be clinical biometric data, biochemical or genetic markers. Biomarkers which circulate in the blood at levels that can be measured in a small sample, can be detected using laboratory methods or simple devices such as a lateral flow assay. During an infection, host biomarkers of fever are differentially elevated in response to a variety of pathogens. As a result, host biomarkers are not restricted to specific pathogens and may be detectable in almost any clinical setting globally. Host biomarkers have long been proposed as a tool to differentiate bacterial from non-bacterial infections (120).

In 2015, an expert working group was convened by the WHO, Médecins Sans Frontières, ReAct and FIND on diagnostics to discriminate bacterial from other infectious causes of fever (53). A Delphi process of three rounds of input was used to obtain an expert consensus from a consortium of global health and diagnostic experts for characteristics of a test to differentiate bacterial from non-bacterial infections. The work resulted in an agreement that a biomarker test to differentiate bacterial from non-bacterial causes of infections in LMICs was of very high priority (54). A target product profile was published, establishing a priority intended use population of non-malarial, non-severe outpatients in low-resources settings (54). The main desirable characteristics of the test were: suitable for use at the community level, with limited infrastructure, minimal training, rapid turnaround time, >90–95% sensitivity, >80–90% specificity, and a price <5.00 USD, but optimally <1.00 United States dollar (54).

Several fever biomarkers have been studied, and in a review of studies from 2010-2015 the following were identified as the highest performing host biomarkers with statistically significant findings in the literature[6]: C-reactive protein (CRP), Heparin-binding protein, CRP + IP-10 + TRAIL, lactate, Procalcitonin + 10-Gene classifier, PMN counts, 48-Gene classifier, CD35 + CD32 +CD88 +MHC1, MxA, and IL-4 (106). Of them, CRP is currently the most validated biomarker in the available literature that is available in the form of a POCT, and potentially economically feasible for use in LMICs to aid in determining the need for antibiotic prescription (54,106).

[6]CD, Cluster of differentiation; HBP, Heparin-binding protein; IL, interleukin; IP-10, IFN gamma-inducible protein 10/CXC motif chemokine 10 (CXCL10); MHC, Major histocompatibility complex; MxA, Myxovirus resistance protein 1; PMN, Polymorphonuclear leukocyte; TRAIL, TNF-related apoptosis-inducing ligand

1.11 C-reactive protein as a diagnostic tool for acute febrile illness

CRP is an acute-phase protein synthesized by the liver, which is found in blood plasma. Its concentration rises in response to inflammation and levels can peak after 36 to 50 hours making its interpretation difficult in the first 24 hours of illness. CRP has long been used in high-income country settings to aid in determining if an infection is of bacterial etiology despite its varying performance characteristics ([n=36 studies]: sensitivity 62-100%, specificity 26-100%) (106,121,122). CRP is not often used in resource-limited settings to differentiate between bacterial and non-bacterial infections. Differences in disease prevalence, microbiological causes, and comorbidities may cause the diagnostic characteristics of tests used in high-income settings to not apply to LMICs (123). There is insufficient published evidence on its diagnostic performance in febrile patients in LMICs, including India. A few evaluations have examined CRP's utility with non-severe febrile illness in LMICs, including Malawi, Mozambique, Tanzania, and Southeast Asia (124–127). While the results varied between populations, the performance of CRP was particularly poor in subjects with malaria, HIV and malnutrition (54,124,125).

Despite the shortcomings of CRP to differentiate the cause of illness in LMICs, researchers have begun to test its utility to contribute to guiding antibiotic prescription in outpatient settings in several countries in Southeast Asia (128,129) and as part of an electronic clinical algorithm in Tanzania (130). In 2016, a study from primary healthcare in Vietnam showed CRP testing reduced antibiotic use by 14% for non-severe acute respiratory tract infection without compromising patients' recovery (128). In the study, doctors were advised that adults 16–65 years with a CRP <20 mg/L should not receive antibiotics, and those >100 mg/L should generally receive antibiotics. Limitations from this study include that no specific recommendation was given between the distant thresholds, values for children were simply adjusted to half those for adults, and cut-offs were based on previous studies from Europe and Russia (128). A study in Thailand and Myanmar that tested CRP thresholds of 20 mg/L and 40 mg/L in febrile patients, found a cut-off of 40 mg/L giving a modest but significant reduction in antibiotic prescribing (129). The cut-offs were chosen based on the literature (124,131) including studies from Southeast Asia (125,132), and one from Thailand that had evaluated 20 and 40 mg/L CRP for the identification of bacterial infections (sensitivity of 92% for 20 mg/L and 86% for 40 mg/L) (133).

Evidence on the positive impact on antibiotic prescribing despite the varied performance characteristics has left the use of CRP polarized in the global health community (134). Several studies are ongoing to generate further evidence for CRP in LMICs (95,135). The utility of CRP testing has not been clarified in India, a country with high levels of antibiotic use and resistance

(35) and where fever is the most common symptom of patients presenting to primary care (83).

1.12 Implementation of diagnostic tools

Diagnostics are one of the tools which could transform the way antibiotics are prescribed in healthcare (33). However, for a diagnostic to impact prescribing, it is not enough to ensure its utility in a defined population and site of use (106), the contextual dynamics surrounding the use of diagnostics must also be understood (136). For successful implementation, the needs of end-users, both patients and healthcare providers, must also be taken into consideration (54).

In 2019 the WHO held a technical consultation on in vitro diagnostics for AMR. In the related meeting report, the WHO emphasized the importance of promoting research and development of new diagnostics tools and that it is also imperative to promote access to and better use of existing tools (137). They acknowledged diagnostics will face barriers to adoption and that available tools will not be implemented successfully without efforts on many fronts, especially in LMICs (137). In wait for the arrival of new technologies, the global health diagnostic community can prepare by studying the utilization of existing tools. Lessons learned can inform the ongoing development of new technologies, appropriate interventions and implementation strategies targeted at LMICs. It is important to note that implementation strategies are not "one size fits all", and must be tailored to the specific context.

The use of diagnostics into sustainable clinical practice are reliant on the complex challenge of changing behavior (138). For successful implementation to occur, a new desired behavior should start and most often, a previous behavior should cease for both providers and patients. In recent years there have been several calls to involve expertise from the social and behavioral sciences to support antimicrobial stewardship and implementation of its related interventions (138–143). These disciplines can provide comprehensive approaches to examine the wide-ranging contextual, organizational, and interpersonal factors which influence why people behave in the way they do, in relation to particular innovations (138).

Lorencatto et al (2018) describe four key elements in the process of developing and evaluating complex behavior change interventions: i) defining the desired behavior and understanding the current behavior in context; ii) using a theory driven, systematic approach to design interventions; iii) examining implementation options; and iv) learning through evidence synthesis and reporting (138). There is a growing body of literature on implementation theories and frameworks that support this process which can be used alone or combined with others (144–152). These approaches can often be applied for the design, evaluation, or guide through all parts of an implementation project or

research question. In light of the expanding evidence base, guidance has also emerged on how to choose theories, models and frameworks that are most appropriate for a project's needs and research question (153–158).

Efforts have begun to examine how human behavior and decision making affects antibiotic use practices (140,159–162). The WHO regional office for Europe has recently published a series of materials to guide the implementation of antibiotic stewardship programs (163,164). The Tailoring Antimicrobial Programs Toolbox aims to support antibiotic stewardship working groups to address drivers of and barriers to AMR. It follows a traditional five-step project management process which is focused on analyzing the context, prioritizing desired behaviors and building strategies and interventions.

Another approach gaining attention to help address ABR is the Behaviour Change Wheel (144,159,160,165,166). The Behaviour Change Wheel is a theory-driven, systematic and evidence-based approach for design and evaluation of behavior change interventions and policies (144). By setting out a systematic effort to understand the target behavior and tailoring the implementation by linking this understanding to techniques known to change behavior, the Behaviour Change Wheel provides a scientific approach to designing interventions that are most likely to be effective (144). The Behaviour Change Wheel is accompanied by a robust guide with step by step guidance through the three stages in the behavior change intervention design process: i) understand the behavior; ii) identify intervention options; iii) identify content and implementation strategies (167). The first stage of the Behaviour Change Wheel uses the 'Capability, Opportunity, Motivation and Behavior' (COM-B) model to identify the needs of a target population and enhance the choice of appropriate interventions and tailored implementation strategies. COM-B posits that capability, opportunity and motivation are needed to perform a specific desired behavior (Figure 6) (144).

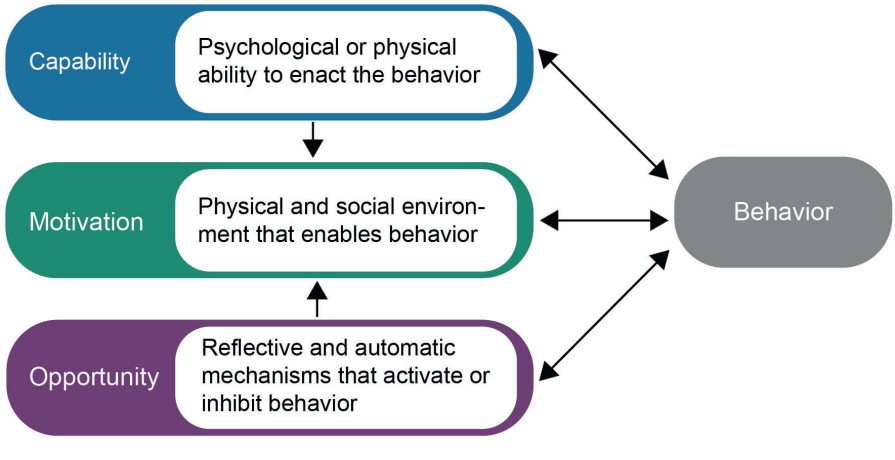

Figure 6. The COM-B system, a model for understanding behavior.

1.13 Study rationale

In resource-limited settings, the burden of infectious disease and ABR is high, and the impact of ABR strikes hardest on the poor. In order to slow the development and spread of ABR, there is an urgent need to optimize antibiotic use. The Global Action Plan on Antimicrobial resistance, the overarching steering document describing actions needed to address ABR, emphasizes the importance to increase the evidence base on how optimize the use of antibiotics to slow the development and spread of ABR (4). LMICs especially need support to secure access to effective antibiotics while ensuring limiting excess use.

The majority of antibiotic use is concentrated in outpatient settings. Fever is one of the main reasons for seeking care and antibiotic use. However, determining the cause of AFI is challenging and even in high-income research settings. To successfully address the management and treatment of AFI and use of antibiotics, we need to know and understand the state and deficiencies in the current management and treatment for AFI.

Determining the underlying cause of AFI is challenging due to myriad of pathogens causing fever, overlapping symptoms, and a lack of diagnostic tools. One of the tools which could transform the way antibiotics are prescribed in healthcare are diagnostics which support physicians to determine the cause of illness and make treatment decisions (33). Until these tools are developed and adapted to resource-limited settings, up-to-date local epidemiological data can support targeted antibiotic prescribing.

Antibiotic use not only has a role in the development and spread of resistance but also has an impact on clinical, microbiological and laboratory assessments conducted for patient management and care. It is important to understand how antibiotics are being used by patients throughout the course of febrile illness, not just those prescribed in formal outpatient settings but also explore the antibiotics procured from the wide spectrum of providers where they are available and frequently obtained in resource-limited setting.

As novel diagnostic platforms are being developed and legacy technologies tested in LMICs, as tools to address ABR, it is essential to ensure the needs of their end-users are taken into consideration (111,168). To support the use of currently available diagnostics, and adoption of any forthcoming diagnostic tools into sustainable clinical practice, the contextual, organizational and interpersonal factors which influence the current state of utilization of diagnostics must be understood.

CRP testing may be beneficial to improve antibiotic use for AFI, but the evidence of its diagnostic performance to differentiate between bacterial and non-bacterial causes of illness has varied across resource-limited settings. The utility of CRP to support diagnosis and treatment decisions in non-severe febrile outpatients in LMICs must be established.

2. Aims and objectives

The overall aim of the PhD project is to understand the causes of AFI, the current use of antibiotics and diagnostics, and to evaluate the diagnostic accuracy of CRP to differentiate bacterial from non-bacterial causes of AFI in outpatients at RD Gardi Medical College hospital, in Ujjain, India.

The specific objectives for each study are:

- To classify the cause of non-severe AFI as bacterial or non-bacterial in children and adults.
- To estimate and compare antibiotic use throughout the course of AFI among children and adults.
- To investigate the utilization of diagnostics by caregivers of sick children attending the pediatric OPD.
- To evaluate the performance characteristics of CRP to differentiate between bacterial and non-bacterial causes of AFI in children and adults.

3. Methods

3.1 Study setting

The studies included in this thesis were conducted at the tertiary-teaching hospital attached to Ruxmaniben Deepchand (RD) Gardi Medical College in the state of Madhya Pradesh, India. Paper I,II,IV took place at both the pediatric and general medicine outpatient departments (OPD) while Paper III took place solely at the pediatric OPD.

3.1.1 Country profile

India, the world's second-most populous country, is the world's largest consumer of antibiotics based on total volume (35). A point prevalence study of antibiotic prescription conducted in 2017 across multiple tertiary care hospitals in India, found 57% of patients receiving antimicrobials (169). In comparison, the 2015 Global-Point Prevalence Study performed across 53 countries found the prevalence of antimicrobial prescribing 34% (70). While the global study found regional differences of 48% in East and South Asia and 30% in European hospitals (70), prescribing practices are clearly higher in India compared to many other countries (169). A study from 2011 from Ujjain, India, found 66% of outpatients with a suspected infectious etiology were prescribed antibiotics, of which, 34% were for upper respiratory tract infections, a condition often caused by viruses where antibiotics have no effect (13). A later study at the same hospitals in 2015 found that broad-spectrum antibiotics were frequently prescribed for inpatients for unindicated conditions such as viral and enteric fever (15). While there is no comprehensive country-wide data on prescribing practices, medical audit data on antibiotic prescribing in the private sector in India 2013-2014 found high antibiotic prescription rates for infections generally of viral origin and self-limiting in nature (170).

India has become a hotspot for the development of ABR (35). A meta-analysis of 82 research papers from India, 2000-15, found that ABR was common among pediatric bloodstream infections. High rates of resistance were seen to the WHO recommended first-line antibiotics (*Staphylococcus aureus*/methicillin 50%, erythromycin 53%, cefotaxime 57%, co-trimoxazole 58%; *Klebsiella pneumoniae*/ampicillin 96%, gentamicin 75%; *Escherichia coli*/ampicillin 93%; gentamicin 56%) (171). The overall burden from ABR is challenging to measure (35), however, it is estimated that 58,000 neonatal

deaths each year can be attributed to drug resistant sepsis in India alone (1). The health and economic burden of resistance in India, as in other LMICs, can be devastating to patients and health budgets, where resources are already constrained and limited health insurance coverage leads to high out of pocket expenditure (34).

The Indian healthcare system is comprised of governmental healthcare facilities, private clinics, teaching hospitals, and informal providers (172). The urban public healthcare centers of Ujjain are comprised of a district hospital, community health center, and civil dispensaries. A second community health center, 20 primary healthcare centers, and 175 sub-centers are dispersed throughout the rural areas. The public health infrastructure is complemented by a few large private hospitals and outpatient clinics spread throughout the urban areas. The majority of allopathic doctors practice in urban settings (173) leaving the majority of services in rural areas to be provided informal healthcare providers (174–176).

3.1.2 Local profile

Madhya Pradesh is in the north-central part of the subcontinent and is one of the poorer states in India. The 2018 UN Development Program's Multidimensional Poverty Index is an indicator of poverty which takes into consideration various deprivations experienced by people within the areas of health, education and standard of living. The index ranked Madhya Pradesh the fourth poorest among all Indian states, noting that one-third of the state's population lives under poverty (177). Ujjain district is situated in the western part of the state and has a population of about approximately 2 million inhabitants, around 61% of whom live in rural areas, and with agriculture as the main source of income (178). The semi-rural city of Ujjain is the administrative center of the district and hosts a population of approximately 700,000 inhabitants (179).

The climate of Ujjain is tropical, with a rainy season occurring from June to September, characterized by the simultaneous occurrence of many fever causing diseases (i.e., respiratory tract infection, diarrhea, dengue, malaria, etc.). The burden of malaria has steadily declined across India (180). In Ujjain, the annual parasite index, which is the number of confirmed malaria cases per 1,000 individuals under surveillance, was much lower than the country average in 2018 (0.03 vs. 0.32, respectively) (180,181). Childhood mortality and morbidity attributable to *Streptococcus pneumoniae, Haemophilus influenzae* type b, and rotavirus have also declined in India since 2000, partially due to vaccine program implementation (182).

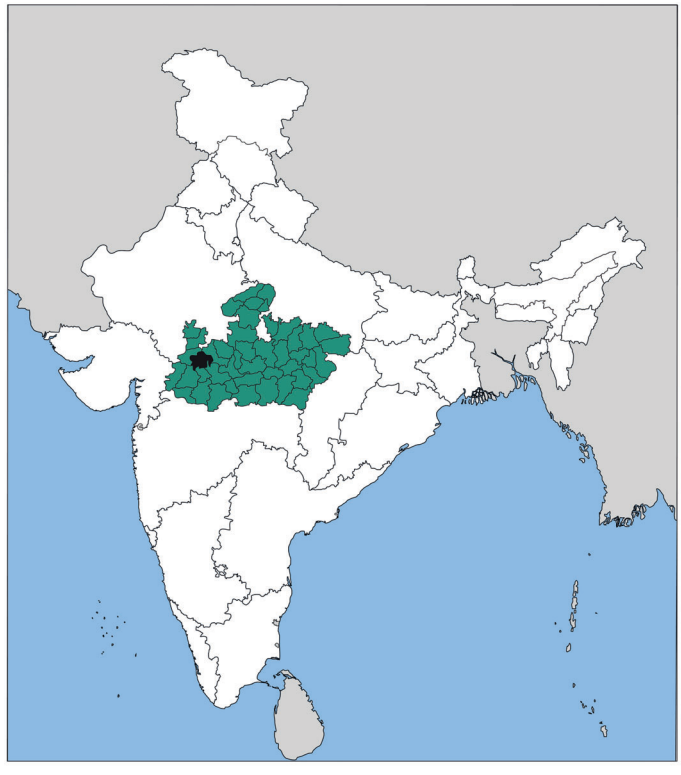

Figure 7. Map of India (white), Madhya Pradesh (green) and the Ujjain district (black).

3.1.3 Study hospital

The hospital connected to RD Gardi Medical College, is located about five kilometers from the city of Ujjain in a village called Surasa and caters to a rural population from the nearly 450 surrounding villages in the 200 km catchment area. The patient population is comprised of predominately agriculture day laborers who earn a daily wage of about 150 Indian Rupees or 2 United States dollars.

The 570-bed tertiary-teaching hospital is managed by the non-profit organization Ujjain Charitable Trust Hospital and Research Centre. The OPDs are open Monday-Saturday from 9:00-13:00 and 14:00-17:00 and staffed with resident physicians attending on a rotating schedule of two days per week.

Approximately 50 patients are seen per day at both the pediatric and medicine OPDs. Most patients come for basic primary care, without referral. It is usually the first contact they have with a formal healthcare provider for the presenting illness. However, many patients have already visited an informal healthcare provider before their hospital visit (176).

Upper respiratory tract infections, diarrhea, and fever are the most common presenting symptoms. At the charitable hospital, there is no charge for patient consultation, symptomatic therapy, i.e., cough syrup and paracetamol, and selected medicines to treat common illnesses, i.e., antibiotics and anthelmintics. In some cases, doctors prescribe medications that are not on the hospital formulary, these medications are paid for out of pocket. Regardless of whether patients receive a prescription, almost any medication can be obtained from a private pharmacy or drug retailer outside of the hospital.

3.2 Study design

This thesis is comprised of both qualitative and quantitative research. A large quantitative, prospective, cross-sectional study was conducted to investigate the causes of fever, use of antibiotics, and utility of CRP as a diagnostic tool for febrile children and adults (Papers I, II, IV). In addition, a qualitative rapid ethnographic study on the use of diagnostics for sick children was used to provide an in-depth understanding of the social, cultural and behavioral aspects of care-seeking, care and treatment of childhood illness, and use of diagnostics by patients/caregivers and providers the study setting (Paper III).

3.3 Study participants

This thesis focused on patients/caregivers seeking care at the pediatric and medicine OPDs. For all studies, patients were first treated by a resident physician according to routine care. After patient consultation was complete, patients were screened for eligibility. For the quantitative work (Papers I, II, IV), consecutive patients (children were aged 2 months - 17 years, and adults were aged 18-65 years) were screened for AFI and recruited to the study. AFI was defined as an axillary temperature ≥37.5°C measured electronically at initial evaluation or a reported history of fever in the previous 48 hours, a duration of fever ≤14 days, and no signs of severe illness. For the qualitative semi-structured interviews (Paper III), caregivers of sick children presenting to the pediatric department who had been sent for one or more diagnostic tests were invited to participate.

3.4 Sample size

Papers I, II, and the observations of Paper III were exploratory in nature and which precluded a sample size calculation. Therefore the sample size for the cross-sectional study was calculated for the objective of Paper IV and was based on the target product profile which identified an acceptable level of

sensitivity and desired sensitivity of ≥90% for a diagnostic assay to differentiate between bacterial and non-bacterial infections (54). The calculation aimed at getting a sufficient number of patients to get accurate estimates of the sensitivity of CRP and was made under the assumption that approximately 10% of patients with fever would have bacterial infections. With a 90% sensitivity, 95% confidence, the desired interval width of 0.2, the minimum sample size required was 440 patients, this was doubled to include both 500 pediatric and 500 adult patients to allow for conducting sub-group analyses. For community controls, a sample size of 100 children and 100 adults was considered sufficient to obtain a representative sample of CRP levels in the community. For the semi-structured interviews of Paper III, interviews were conducted until saturation was reached, i.e., the team agreed no new information emerged which resulted in 43 semi-structured interviews.

3.5 Data collection methods

Cross-sectional study

For the quantitative studies (Papers I, II, IV), patients presenting to the pediatric and medicine OPDs were recruited to the study from June to September 2019.

3.5.1 Patient enrollment

Patients were first clinically managed according to routine practice by a resident physician. For the purposes of this study, the resident physician made a free text description of a presumptive diagnosis based on the patient's history and a clinical examination, based on standard clinical practice without any use of diagnostic tests. Once the consultation was finished, a study nurse screened patients for fever and assessed them for inclusion. Patients/caregivers of minors who were eligible for enrollment were directed to a separate room where a they were provided with oral and written information about the study in Hindi or English. Afterwards, a study clinician obtained informed consent. The study clinician then took patient history and performed a clinical examination guided by standardized case report forms (CRF) (Appendix 1). This was done solely for the purposes of the study and was independent from the patient consultation done as part of standard practice. Clinical data was recorded including: symptoms, prior reported antipyretic, antibiotic, and antimalarial use for the current AFI episode, examination findings, as well as vital signs. The presumptive diagnosis and antibiotic prescription by the resident physician as part of routine care were collected from the patient's outpatient record.

3.5.2 Follow-up

One week after enrollment, patients were requested to return to the OPDs for follow-up. Patients/caregivers who did not report for follow-up by day seven were called by phone each day until they could be reached. During follow-up, the study clinician recorded the time to resolution of illness, if symptoms had worsened and if any further care or treatment was received. Details on any medicines received were noted together with if treatment modification was done by a formal/informal provider, or self-medication. For reported antibiotic use before and after the outpatient visit, patients/caregivers were asked to name the antibiotics. Patients who brought their medicines with them were asked to show the medicines or their packages or send a picture via text message. Study activities did not interfere with the treatment of AFI or antibiotic prescription as part of routine practice. Laboratory results which may have had an influence patient management and care were provided to both the patients and the resident physician.

3.5.3 Sample collection and processing

A standard panel of tests was performed for all enrolled patients. Whole blood and a urine sample were collected for each study participant. Additional symptom-based stool, throat swab, and skin/ear/joint/aspirate samples were taken based on criteria outlined in Figure 8, based on a participant's clinical presentation. A study nurse was responsible to coordinate the collection of samples.

A study phlebotomist collected venous blood, 15 ml for adults and 7 ml for children under aseptic precautions in three tubes: one EDTA (2 ml adult, 2 ml child), one plain (3 ml adult, 2 ml child) and a blood culture bottle (10 ml adult, 1-3 ml child). Directly after collection, the blood samples were inoculated in an aerobic blood culture bottle (Blood Culture FA Plus Bottle (adult patients), Blood Culture PF Plus Bottle (for pediatric patients), bioMérieux, USA). Patients or their caregivers were responsible for collecting the urine sample using the 'clean catch' method and stool samples using a clean, dry bedpan following instructions to avoid contamination. The study clinician swabbed the posterior oropharynx using a sterile cotton swab, touching the possible infected area but avoiding touching the tongue, uvula, or lips.

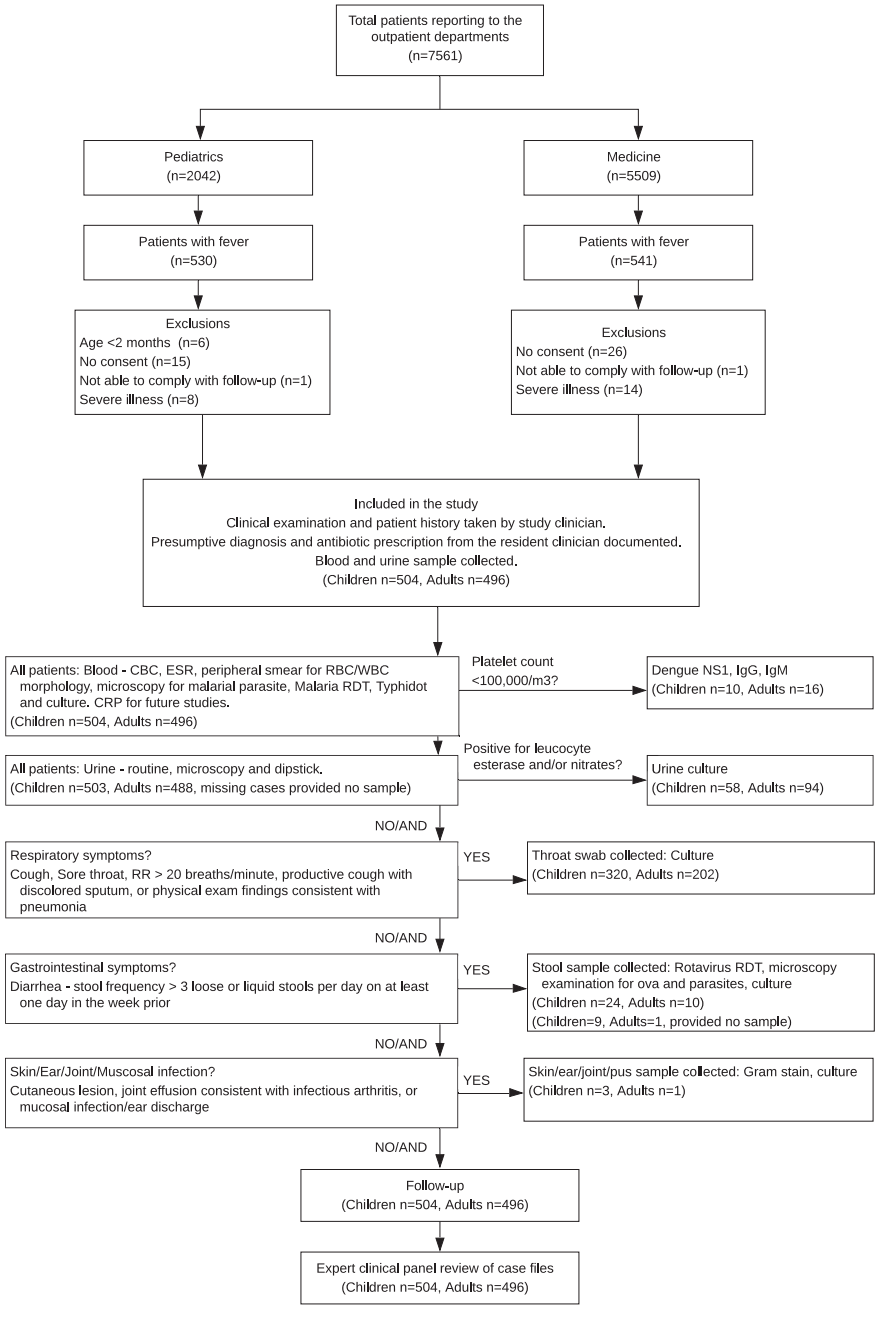

Figure 8. Flow chart of patients through the study and investigations performed. NB: If subjects had more than one symptom, they underwent investigation for each.

Rapid ethnographic study

For the qualitative work (Paper III), structured and unstructured observations were conducted together with semi-structured interviews during the period October to December 2018.

3.5.4 Unstructured observations

The unstructured observations were focused on the interactions between the caregivers and physicians as they assessed the children, tried to determine the cause of illness, ordered diagnostics and prescribed medication, during initial and follow-up visits. Time was also spent exploring the pathways patients/caregivers take through the hospital, to become familiar with the logistics caregivers must endure to complete the tests, receive results and follow-up. Discussions were held directly in English with physicians, nurses, pharmacists, laboratory technicians and orderlies. During patient consultation, a research assistant interpreted from Hindi to English.

3.5.5 Structured observations

Structured observations (183,184) of the utilization of diagnostics were done for the month of December 2018. The observations focused on routine tests such as blood, urine, and stool tests, as well as x-rays, ultrasound, electrocardiogram, and electroencephalogram. Any non-routine diagnostics or tests which were considerably more expensive, such as magnetic resonance imaging, were excluded. When patients were ordered one or more diagnostic test, the time from patient consultation to eventual follow-up and types of tests ordered was documented by a research assistant into a data entry log. In cases where patients/caregivers did not return for follow-up, the registration logbooks at the separate testing rooms were reviewed to assess if patients/caregivers had done the tests.

3.5.6 Semi-structured interviews

Semi-structured interviews were conducted with caregivers of children who had been sent for diagnostics. A semi-structured topic guide (Appendix 2) was prepared by the PhD student to help the interviewer explore concepts related to the care seeking behavior and the utilization of diagnostics. The guide was based on the literature and findings from the observations. It was written in English, then translated from English to Hindi, piloted and modified as necessary before starting the interviews. Participants were purposely sampled for the interviews. The structured observations were used to identify caregivers of children who had been sent for diagnostic testing. The interviews were conducted in Hindi, led by a research assistant with medical and public health training. Interviews were audio recorded and the PhD student observed and

took notes during the interviews. Interviews were done in two rounds. The first round (n=30) recruited caregivers directly after patients were sent for diagnostics but before the tests were done. These interviews were conducted in private rooms at the hospital close to the pediatric OPD.

The second round of interviews (n=13), recruited caregivers who had not returned to the OPD for follow-up, five or more days after the initial visit. These caregivers were contacted by phone, then interviewed at the caregivers' homes at a time of their convenience. An updated version of the interview guide was created, piloted and used accordingly. The second version included additional questions to explore why they had not done the tests and/or not returned for follow-up. Interviews continued until saturation was reached (185), i.e. the team agreed no new information emerged.

3.6 Laboratory methods

All laboratory analyses were performed in the Central Research Laboratory of RD Gardi Medical College following local standard operating procedures and manufacturer's instructions. For all patients, complete blood count, erythrocyte sedimentation rate, and peripheral smear examination including malaria parasite staining, malaria RDT, typhoid RDT, and dengue RDT (if platelet count was <100,000/m^3) were conducted. Plasma was separated to quantify CRP (Turbodyne CRP UV; Tulip Diagnostics Pvt Ltd, India). The assay has an effective range of 3-400 mg/L. Blood culture bottles were incubated in an automated blood culture system and bacterial identification was done using the automated Vitec 2 system (bioMérieux, France). Cases identified as potential contaminants by standard laboratory methods, were excluded from the analysis. Urine samples underwent a routine examination, if the dipstick was positive for leukocyte esterase and/or nitrates, urine culture was performed. Culture was conducted for throat swabs. Stool samples had culture, microscopy and rotavirus RDT performed. Gram stain and culture were performed on ear and joint aspirate samples. Bacterial identification for urine, throat, stool and ear/joint samples was done according to the Clinical and Laboratory Standards Institute (2019) recommendations (186). The manufacturer's reported test specifications are provided in the appendices (Appendix 3).

3.7 Fever classification: bacterial or non-bacterial

The cause of fever was established in a two-step process as illustrated in Figure 9, and described in full in Paper I, following the BFF-Dx methodology (95). First, a laboratory classification was established based on positive microbiological and laboratory results following pre-established case definition criteria (Appendix 4). Cases without a laboratory classification had their case

files reviewed and classified by an expert clinical panel of three physicians. Separate panels were used for children and adult patients. Case files included patient history, clinical examination findings, details on patient-reported antipyretic, antibiotic and antimalaria use prior to seeking care, as well as results from a complete blood count and erythrocyte sedimentation rate (Appendix 5). Each clinical panel member reviewed all summary case files and classified them into one of the three overarching categories, bacterial, non-bacterial or indeterminate cause of fever, using the provided patient classification process guidelines (Appendix 6).

Patients with a unanimous classification by the expert panel were assigned the appropriate classification, "unanimous clinical panel classification". The panel discussed indeterminate and non-unanimous cases as a whole until the panel members came to a "reassessment panel classification". The unanimous and reassessment panel classifications were combined into the "aggregate clinical panel classification". The laboratory and aggregate clinical panel classifications were combined to establish the "final classification". Aware of the challenges in establishing the cause of fever, even with laboratory testing and expert clinical review, the performance of CRP was investigated throughout the different phases of the classification process ranging from more confirmed (i.e., laboratory classification) to less confirmed (i.e., clinical panel classifications). CRP values were not used in the laboratory classification or provided to the clinical panel members.

After this process, a post-hoc quality check was done on all cases categorized by the laboratory classification. First cases with a positive typhoid RDT were reviewed together with culture positive for *Salmonella* which identified that some blood culture-positive cases were RDT negative. Recognizing the sub-optimal performance of typhoid diagnostics (187), it was decided to refine the case definition for typhoid to exclude the RDT results and rely solely on blood culture-positive cases for *Salmonella.* Therefore, all culture negative but RDT positive cases had their classification removed and were sent for review by the clinical panel.

Following this, two clinicians from the author group reviewed all the bacterial isolates identified by bacterial culture and highlighted those that were less likely to cause the fever. *Escherichia coli* from the stool and throat swabs, and *Klebsiella pneumoniae* isolated from the stool, were judged less likely to be the causative pathogen of fever. *Pseudomonas aeruginosa* and *Sphingomonas paucimobilis,* which were isolated from throat samples were considered to be commensals. Finally, *Salmonella enterica* ssp isolated from the urine was considered a contaminant. Each of these cases had their classification removed and were designated as undetermined. Ideally, these cases should have also been reviewed by the clinical panel, however, at the time, all clinical panel members were busy responding to the COVID-19 pandemic.

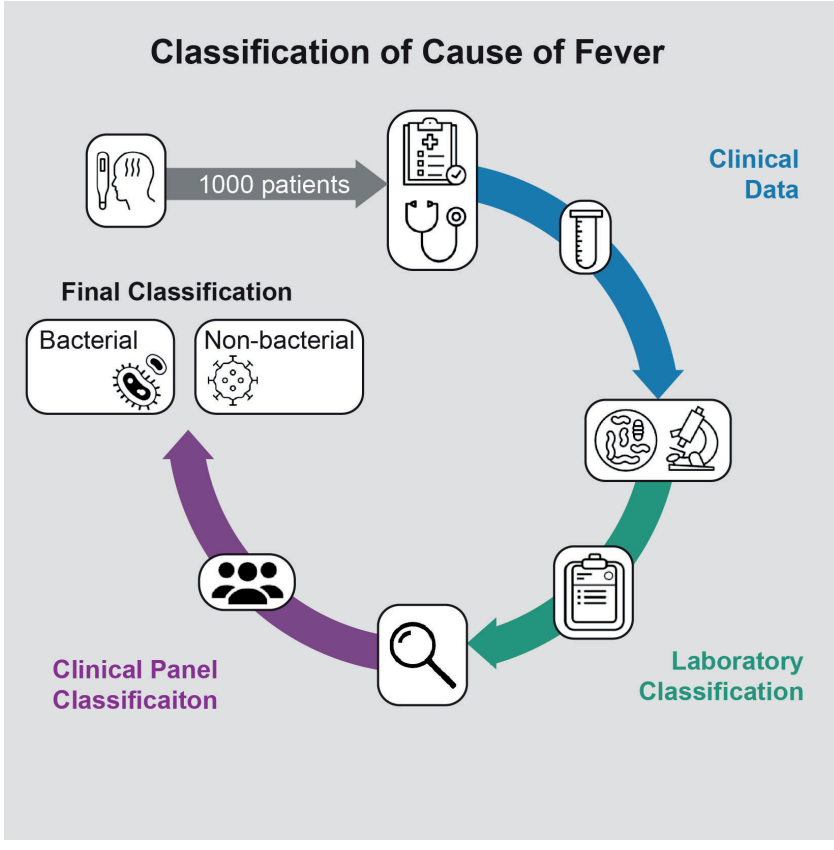

Figure 9. Process to classify the cause of fever as bacterial or non-bacterial

3.8 Measuring antibiotic use

Any antibiotics in the classes J01-antibacterial agents for systemic use, A07-intestinal antibiotics, and orally administered metronidazole (P01AB01) were considered (80). Data on antibiotic use (Paper II) were collected before, during, and after an outpatient visit. Antibiotic prescription during the outpatient visit was also described in relation to the presumptive diagnosis provided by the resident physician. Data were grouped according to ATC classification 4th level in Defined Daily Doses (DDDs) and AWaRe category (82) in antibiotic encounters. An encounter was defined as a patient receiving one or more antibiotics at any of the three-time points (i.e., a patient can have a maximum of three encounters). For encounters with more than one antibiotic, the AWaRe classification was based on a higher restricted antibiotic, i.e. an encounter with both a 'Watch' and 'Reserve' antibiotic would be classified as 'Reserve' (188). DDDs were calculated using dosage, frequency, duration of the prescribed antibiotic(s) and the DDD assigned for each drug by the WHO

Collaborating Centre and the WHO International Working Group on Drug Statistics Methodology (80). DDDs were applied for both adults and children, as DDDs specifically for children do not exist (Appendix 7 - Table 1) (188).

Fixed Dose Combinations (FDCs) are defined as "A combination of two or more actives in a fixed ratio of doses". This term is used generically to mean a particular combination of actives irrespective of the formulation or brand. It may be administered as single entity products given concurrently or as a finished pharmaceutical product" (189). Irrational FDCs is a complex topic, for the purposes of this thesis, irrational FDCs refers to formulations with a lack of proven efficacy that are not approved by regulatory agencies such as the US FDA, the European Medicines Agency, or UK medicines and Healthcare products Regulatory Agency (190–192).

3.9 Personnel conducting study activities

Routine clinical care was provided by the resident physicians of the study hospital. Laboratory technologists or technicians were part of the staff from the on-site research laboratory. Dedicated study staff including clinicians, nurses, phlebotomists, research assistants and data entry officers were employed specifically for the study-specific activities of this thesis and are referred to as "study staff". Study staff had backgrounds in clinical, laboratory and/or social science training. All permanent and study staff were trained in the protocol and relevant study procedures and pilot studies were conducted prior to the start of the real data collection to ensure adequate data collection techniques so that the study goals would be met. Members of the expert clinical panel were from Ujjain but not involved in the study and had at least five years post graduate experience in pediatrics or medicine.

3.10 Data entry and quality control

The quantitative data from the CRFs and the microbiological and laboratory reports were double entered by a team of trained data entry officers, using EpiInfo software (Centers for Disease Control and Prevention, GA, USA) (Papers I, II, IV). Thereafter the quantitative dataset was exported to STATA (version 16; Stata Corp. TX, USA) where the PhD student performed data cleaning and validation. The data from the unstructured observations logbooks were entered into Microsoft Excel by the PhD student (Paper III). Interview recordings were transcribed verbatim and translated to English using Microsoft Word (Paper III) by trained data entry officers. A research team member from the study setting reviewed CRFs (Papers I, II, IV) for completion and the translation of interview transcripts (Paper III) for accuracy of translation (Paper III).

3.11 Data analysis

For the cross-sectional study, continuous variables were presented as sum, median (with interquartile range (IQR)), mean (with standard deviation), and range were calculated. Categorical variables were presented as frequency and percentage and compared using the Chi-squared and Wilcoxon rank-sum tests. All study analyses were conducted based on age, children included ages 2 months to 17 years and adults 18-65 years. To evaluate CRP's usefulness in predicting the bacterial cause of fever, non-parametric receiver operating characterizes curves, the area under the receiver operating curve (AUC), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) as well as positive and negative likelihood ratios (LR+, LR-) were all calculated (Paper IV). P-values <0.05 were considered statistically significant and 95% confidence intervals (CI) were calculated. The cut-off values chosen to analyze CRP were based on the literature (123,125,128,193) and in line with cut-offs of existing semi-quantitative points of care tests which measure CRP in 10, 20 or 40 mg/L intervals.

For the rapid ethnographic study, the observations and their respective fieldnotes were used to perform a descriptive analysis of the social, cultural and behavioral aspects of the study setting, to structure the interview guides, cross-check findings and provide insight into the latent content of the interview data (183,184,194). Messy, ordered and relation situational maps were used to capture important elements of the setting, stimulate analytical insight, and reflect on what matters (195). For the interview data, an inductive thematic analysis (196) was conducted followed by a discussion of findings through the lens of the COM-B model for understanding behavior (144). The use of a comprehensive behavior change model provided a structure to conduct a behavioral analysis and reflect on the contextual, organizational and interpersonal factors which influence the utilization of diagnostics. In Paper III, the desired behaviors in the utilization of diagnostics were defined as a caregiver assisting a child to have diagnostics done and return to the department for follow-up of results.

Quantitative data were analyzed using STATA (version 16; Stata Corp. TX, USA) while qualitative data were analyzed using Microsoft Word and Excel.

3.12 Ethical considerations

Before starting both studies, all study materials were reviewed and approved by the Institutional Ethics Committee of RD Gardi Medical College, Ujjain, India (IEC Ref. No- 58/2019, Papers I, II, IV), (IEC Re. No- 18/2018, Paper III). The clinical study (Papers I, II, IV) was registered with Clinical Trials Registry – India (REF/2019/05/026081).

Written and oral information about the studies was provided to study participants and/or their caregivers in English or Hindi. Informed consent was obtained from all participants and/or their caregivers by signature or ink fingerprint for illiterate participants. Assent was obtained for patients aged 13-17 years. Patients/caregivers were assured that their choice to participate in the study, or eventual decision to leave the study at any time, would not affect their subsequent care.

The primary ethical considerations in this project relate to the inconvenience or discomfort for participants to partake in the study. Clinical examination (Papers I, II, IV), and interviews (Paper III), were held in the hospital directly after the outpatient visit to limit unnecessary waiting times. Interviews done outside of the hospital were conducted at participants' homes at a time of their choosing. Patients/caregivers were followed up via phone if they were unable to return to the hospital for a follow-up visit.

The taking of blood samples may have caused discomfort to participants. To avoid unnecessary taking of samples, samples were taken from the blood blank at the hospital for adult control cases. As samples of children's blood is not stored in the blood bank, samples were collected from 100 community controls. Permission to collect these samples was received from the Institutional Ethics Committee.

To limit any potential risk of breach of confidentiality, all participants' names and contact information was removed shortly after completing the interviews and/or follow-up. In place of any personal information, all interview tools, patient data, and samples were anonymized with a unique identifying code.

The presumptive treatment of the enrolled patients as part of routine practice was not interfered with and did not interfere with the study activities. However, study-specific laboratory results with potential influence on patient management were provided to the patients/caregivers and the resident physician. All study investigations were offered free of charge.

3.13 Summary of methods

Table 1. Summary of methods

Title of paper	Methods	Study population, sample size, data collection period	Analysis
I. Classification of non-severe acute febrile illness as bacterial or non-bacterial: A prospective observational study of children and adult outpatients presenting at a rural, tertiary-teaching hospital in Ujjain, India.	Prospective, cross-sectional, hospital study. Microbiological and laboratory investigations, expert panel consensus.	504 children (age 2 months - 17 years) and 496 adult (18 - 65 years) outpatients with measured auxiliary temperature ≥37.5°C or reported history of fever in the last 48 hours and no signs of severe illness. June-August 2019.	Descriptive statistics.
II. Antibiotic use before, during and after seeking care for acute febrile illness at a hospital outpatient department: a cross-sectional study from rural India.	Prospective, cross-sectional, hospital study. Antibiotic use before, during and after outpatient visit described by ATC class in DDDs and AWaRe categories in antibiotic encounters.	504 children (age 2 months - 17 years) and 496 adult (18 - 65 years) outpatients with measured auxiliary temperature ≥37.5°C or reported history of fever in the last 48 hours. June-August 2019.	Descriptive statistics, Chi-squared test.
III. Utilization of diagnostics in India: a rapid ethnographic study exploring context and behavior.	Rapid ethnographic study including structured and unstructured observations and semi-structured interviews.	Unstructured observations: caregivers and resident physicians at the pediatric OPD of RD Gardi Medical College. Structured observations: Caregivers of sick children attending the OPD. 43 Semi-structured interviews with caregivers of sick children attending the OPD. October-December 2018.	Inductive thematic analysis.
IV. Performance characteristics of C-reactive protein to differentiate bacterial from non-bacterial causes of acute febrile illness in India.	Prospective, cross-sectional hospital study. Microbiological and laboratory investigations, expert consensus.	483 children (age 2 months - 17 years) and 479 adult (18 - 65 years) outpatients with measured auxiliary temperature ≥37.5°C or reported history of fever in the last 48 hours. June-August 2019.	Receiver operator curves, Sensitivity, Specificity, PPV, NPV, LR+, LR-, chi-squared test, Wilcoxon rank-sum test.

4.0 Key results

4.1 Patients seeking care for acute febrile illness

During the study period in June to September 2019, a total of 7561 patients presented to the pediatric and medicine OPDs. Recruitment to reach the intended sample size finished within the same week for the two departments. The number of pediatric patients presenting to the department was slightly less than half of the number of adults (n= 2042 children, n=5509 adults), signaling that a higher proportion of children present with fever or a history of fever than adults (530/2042 [26.0%] children, 541/5509 [9.8%]) compared to adults. A total of 504 children and 496 adults were recruited to the study. Participant screening, enrollment, laboratory testing and follow-up are summarized in Figure 8.

Fewer children had a recorded temperature ≥37.5°C at the hospital compared to adults (184/504 [36.5%] children, 276/496 [55.6%] adults, $p<0.0001$). Only one child and eight adults had a temperature ≥39.0°C. Caregivers were more likely to seek care for their children after a shorter duration of illness, waiting a median of 3 days (IQR 2-5) compared to 5 days (IQR 2-10) for adults. Median time to resolution of illness was 3 days (IQR 2-3) for children and 5 days (IQR 4-6) for adults.

A greater proportion of children were reported to have taken antipyretics before seeking care compared to adults (220/504 [43.7%] children, 155/496 [31.3%] adults, $p<0.0001$). Very few patients reported taking an antimalarial before study inclusion, however fewer children were reported to do so than adults (7/504 [1.4%] children, 26/496 [5.2%] adults, $p<0.0001$). In addition to fever, the most common presenting symptoms varied between children and adults. For children, cough (59%) and abdominal pain (30%) were the leading complaints while for adults, headache (80%) and joint paint (62%) were the most common. The most common presumptive diagnosis by the resident physician was acute viral illness 60.1% (n=601) followed by urinary tract infection 11.7% (n=117) and upper respiratory tract infection 9.2% (n=92). Demographic and clinical characteristics of patients are displayed in Table 2.

Table 2. Demographic and clinical characteristics of study participants.

Variable	Children n=504		Adults n=496	
Female sex, n (%)	202	(40)	246	(50)
Age in years, mean (SD)	7.1	(4.6)	33.3	(13.3)
Fever duration in days, median (IQR)	3	(2-4)	4	(3-8)
Temperature ≥37.5°C, n (%)	184	(37)	276	(56)
Most common reported clinical symptoms,* n (%)				
Headache	139	(28)	398	(80)
Cough	299	(59)	173	(35)
Abdominal pain	152	(30)	215	(43)
Joint pain	57	(11)	309	(62)
Vomiting	77	(15)	228	(46)
Self-reported prior medicine use during this illness, n (%)				
Antipyretic	284	(56)	341	(69)
Antibiotic	25	(5)	58	(12)
Antimalarial	7	(1)	26	(5)

*Symptoms in addition to fever

4.2 Causes of acute febrile illness

4.2.1 Microbiology findings

Bacterial cultures detected a total of 181 bacterial isolates of possible clinical significance in 176 (17.6%) patients (79/504 [15.7%] children, 97/496 [19.6%] adults). The post-hoc quality check first reviewed all cases with a positive typhoid RDT or culture positive for *Salmonella.* All 1000 patients were tested for typhoid by RDT and blood culture. Of the 899 cases which were IgG and IgM negative by RDT, one case was culture positive for *S.* Paratyphi and eight cases of *S.* Typhi. A total of 99 cases were IgM positive by RDT but culture negative for *Salmonella enterica* (Table 3). It was therefore decided to update the case definition of typhoid to exclude RDT results and only classify typhoid based on culture results. Therefore, none of the cases which were RDT positive but culture negative received a laboratory classification. Subsequently the post-hoc quality check reviewed the remainder of the bacterial isolates and identified 41 isolates across 38 patients in which the bacterial isolate identified was not likely to be the causative agents of fever (Table 4). Cases with these isolates had their laboratory classifications removed.

Table 3. Typhoid RDT and culture results

	IgM+/ IgG+	IgM+/IgG-	IgM-/IgG-	Total
Salmonella Paratyphi	0	1	1	2
Salmonella Typhi	1	0	8	9
Culture negative for Salmonella	28	71	890	989
	29	72	899	1000

Table 4. Bacterial isolates identified as not likely to be the causative pathogen of fever

	Urine	Throat	Stool
Less likely to cause fever			
Klebsiella pneumoniae	-	-	2
Escherichia coli	-	9	12
Commensals			
Pseudomonas aeruginosa	-	9	2
Sphingomonas paucimobilis	-	1	5
Contaminants			
Salmonella enterica ssp. *enterica*	1	-	-

After the post-hoc review was complete, 140 bacterial isolates likely to cause fever were left across 138 (13.8%) patients (58/504 [11.5%] children, 80/496 [16.1%] adults). The bacterial culture isolated species, by clinical specimen are reported in Table 5. Urinary tract was the site where the most bacterial isolates were identified from. Among the 152 patients who had a urine culture, 37/58 (63.8%) children and 57/94 (60.6%) adults had significant bacterial growth in urine cultures. No enterococci or *Staphylococcus saprophyticus* were detected in the urine. Blood followed as the site with the second most common positive cultures. All 1000 patients had a blood culture performed. Of them, 40 (4.0%) had bacteria isolated (17/504 [3.4%] children, 23/496 [4.6%] adults) of whom 14 had *S. aureus*. Of these patients, typhoid was diagnosed in 11 patients (5/504 [1.0%] children, 6/496 [1.2%] adults) with *Salmonella enterica* isolated from blood cultures in which the serovar Typhi was identified in nine patients and Paratyphi A in two patients. Of the 522 patients with respiratory symptoms, one child had a gram-negative organism isolated from a throat sample. No Streptococci were isolated from any throat samples. Of the 34 patients with stool culture conducted, one child had a gram-negative organism isolated from a stool sample. Four patients presented with ear or joint symptoms. Of them, one child had a gram-negative organism isolated from joint aspirate while two children and one adult had a gram-positive organism isolated from the ear.

A total of four patients had two organisms identified. Two patients had dual bacterial infections. One adult had *S. aureus*. isolated in the blood and *E. coli*

isolated in the urine. And one child had *S. aureus*. isolated in the blood and *P. aeruginosa* isolated in the urine. The other two patients had both bacterial and non-bacterial pathogens identified. One child tested positive for malaria and typhoid, another child tested positive for rotavirus and had a positive urine culture for *K. pneumonia* in the urine.

Non-bacterial pathogens accounted for the identification of 17 pathogens. A total of 33 children and 11 adults presented with gastrointestinal symptoms which indicated the collection of stool sample and testing for rotavirus, of them nine children and one adult provided no sample. Rapid diagnostic testing identified 12 cases of rotavirus (six children, six adults). For dengue, a total of 10 children and 16 adults had a platelet count of <100,000/m^3 which indicated a rapid test. Of these, four adult patients tested positive for dengue. All 1000 patients had a blood sample available to test for malaria via RDT and microscopy. Only one child tested positive for malaria, with positive results from both the RDT and microscopy. This one case also was also culture positive for typhoid.

4.2.2 Classification of cause of fever

A laboratory classification was established in 15.3% (n=153) of patients resulting in 13.8% (n=138) bacterial and 1.5% (n=15) non-bacterial infections.

A total of 809 cases were reviewed by the expert clinical panel. In the first round 71.8% (n=558) had a unanimous classification by all three panel members with 23 cases of bacterial and 558 cases of non-bacterial. The remaining cases which were categorized as indeterminate (n=106) or received non-unanimous classifications (n=122) in the first round of review were discussed in a second round by the full panel, until the panel members came to a consensus (83 bacterial and 145 non-bacterial cases). The first and second rounds of the clinical panel review were combined into the aggregate clinical panel and resulted in 106 bacterial and 703 non-bacterial cases.

Combining the laboratory and clinical panel classifications, the final study classification resulted in 24.4% bacterial (92/504 [18.3%] children, 152/496 [30.6%] adults) and 71.8% non-bacterial causes of infection (391/504 [77.6%] children, 327/496 [65.9%] adults). A total of 3.8% (n=38) of patients (21/504 [4.2%] children, 17/496 [3.4%] adults) remained with an undetermined cause of illness. The classification process AFI can be found in Figure 10.

Table 5. Species of bacterial isolates recovered on culture among 1000 patients, by clinical specimen cultured

	Total	Blood	Urine	Throat	Stool	Ear/Joint
Cultures conducted	1712	1000	152	522	34	4
Gram-negative						
Escherichia coli	52	-	52	-	-	-
Pseudomonas aeruginosa	29	5	23	-	-	1
Klebsiella pneumoniae	17	3	13	1	-	-
Salmonella Typhi	9	9	-	-	-	-
Salmonella Paratyphi A	2	2	-	-	-	-
Acinetobacter lwoffii	2	2	-	-	-	-
Escherichia vulneris	2	2	-	-	-	-
Sphingomonas paucimobilis	1	1	-	-	-	-
Brucella melitensis	1	1	-	-	-	-
Enterobacter spp	1	-	1	-	-	-
Enterobacter cloacae	1	-	1	-	-	-
Citrobacter freundii	1	-	1	-	-	-
Acinetobacter baumannii	1	-	1	-	-	-
Pantoea	1	-	1	-	-	-
Proteus mirabilis	1	-	1	-	-	-
Shigella sonnei	1	-	-	-	1	-
Gram-positive						
Staphylococcus aureus	17	14	-	-	-	3
Streptococcus spp	1	1	-	-	-	-
Organisms possibly causing fever	140	40	94	1	1	4

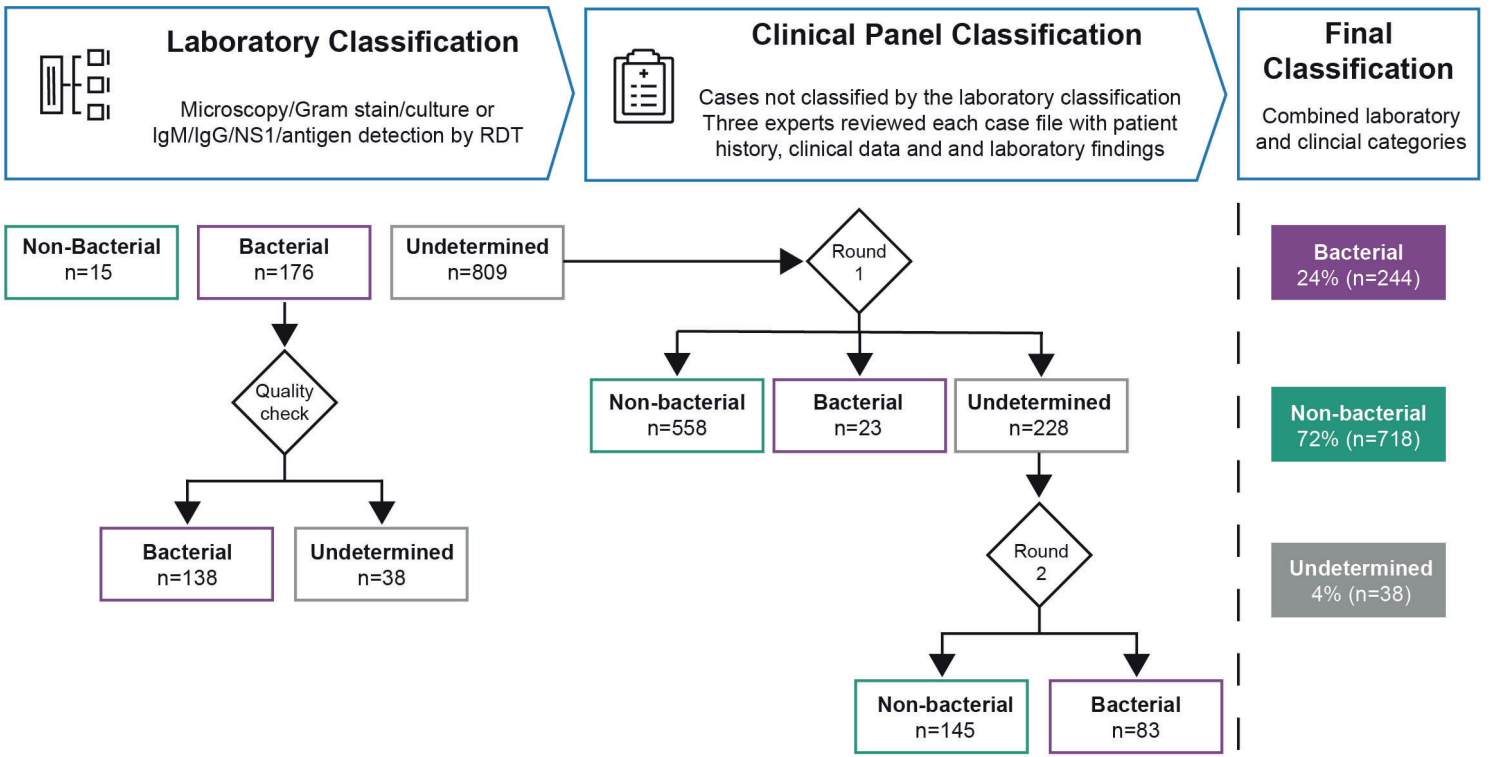

Figure 10. Classification of cause of fever as bacterial or non-bacterial for all 1000 patients.

4.3 Antibiotic use throughout the course of illness

Of all 1000 patients, 41.0% (n=410) received one or more antibiotic courses throughout the course of AFI. A total of 533 antibiotic courses were reported, 31.1% (n=311) received just one antibiotic course, 8.1% (n=81) two, 1.3% (n=13) three, 0.4% (n=4) four, 0.1% (n=1) five, and the remaining 59.0% (n=590) received no antibiotics throughout the episode of illness. Of all patients, 0.5% (5/1000) received antibiotics before the outpatient visit and at follow-up, 3.3% (33/1000) at outpatient visit and follow-up, and 0.2% (2/1000) before, during and after the outpatient visit. Of all courses recorded, 8.1% were parenteral formulations.

A total of 24 different antibiotics were reported; the eight most consumed antibiotic groups accounted for more than 97% of antibiotic use before, during, and after the outpatient visit. The leading contributors of total antibiotic volume in DDDs were macrolides (30.3%), combinations of penicillins, including β-lactamase inhibitors (18.8%), tetracyclines (14.8%), fluoroquinolones (14.6%), and third-generation cephalosporins (13.7%).

4.3.1 Antibiotic use by AWaRe categories

Of all 1000 patients, 8.3% reported the use of antibiotics before, 31.3% received antibiotic prescriptions during the outpatient visit, and 8.9% reported antibiotic treatment modification within the seven-day follow-up period. Watch antibiotics accounted for 72.3%, 52.7%, and 64.0% of all antibiotics before, during, and after the outpatient visit, respectively (Figure 11, Appendix 7 – Table 2a,b,c).

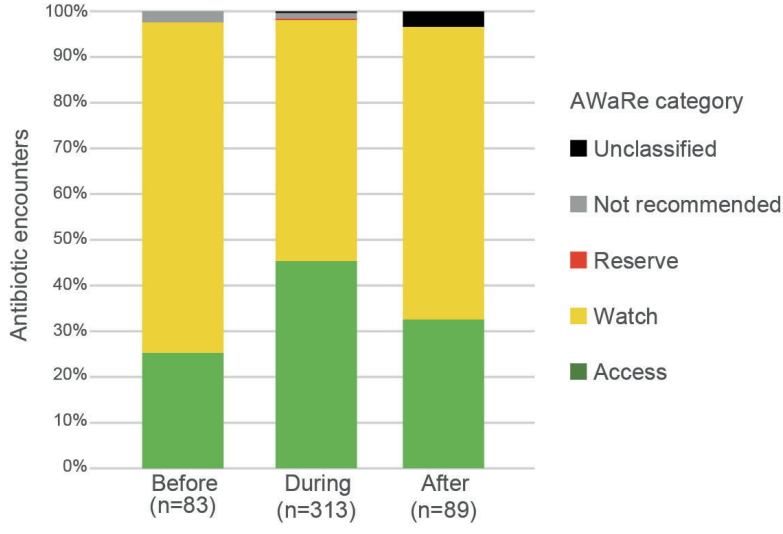

Figure 11. Distribution of antibiotic use before, during, and after outpatient visit patient, according to the WHO AWaRe classification by the percentage of encounters.

4.3.2 Antibiotic use by ATC classes

Fluoroquinolones was the ATC class with the highest volume of DDDs before seeking care, while macrolides had the greatest proportion during and after the outpatient visit (Figure 12, Appendix 7 – Table 3a,b,c). For children of all ages, fluoroquinolones accounted for 17.7% (7.5/42.4) of DDDs before, 5.0% (15.5/309.4) during, and 15.6% (17.2/110.4) after seeking care at the OPD. Irrational FDCs accounted for a total of eight encounters and 1.7% (34/2054) of total DDDs throughout the course of AFI for all patients.

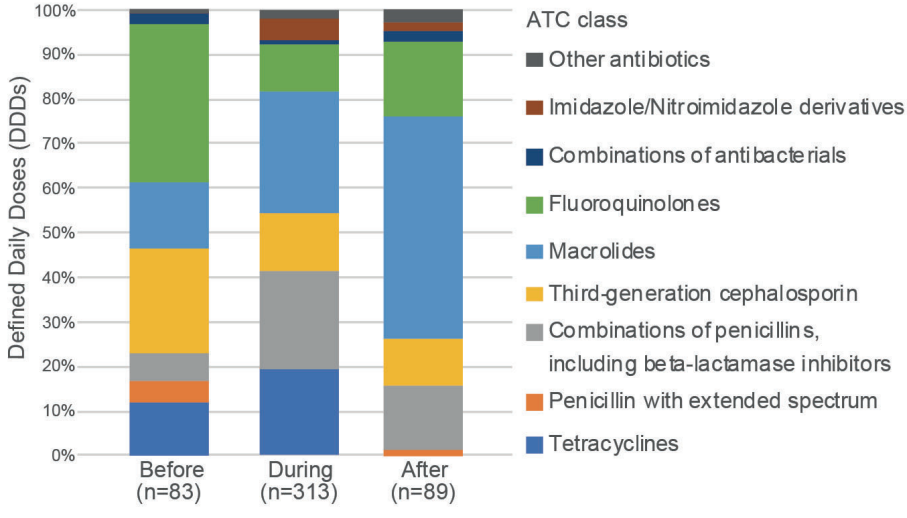

Figure 12. Distribution of antibiotic use before, during, and after outpatient visit patient, according to the WHO ATC classification by the percentage of total Defined Daily Doses

4.3.3 Antibiotic prescription by presumptive diagnosis

Of the 313 patients that were prescribed an antibiotic at outpatient visit, the seven most common presumptive diagnoses were acute viral illness 60.1% (n=601), urinary tract infection 11.7% (n=117), upper respiratory tract infection 9.2% (n=92), lower respiratory tract infection 5.8% (n=58), gastroenteritis 5.8% (n=58), typhoid 4.0% (n=40) and malaria 1.5% (n=15).

The presumptive diagnosis of acute viral illness had the second-highest proportion of 'Watch' antibiotics (79/469, 59.8%) (Figure 13, Appendix 7 – Table 4). Acute viral illness had the lowest proportion of antibiotics prescribed per presumptive diagnosis (132/601, 22.0%) but accounted for half of the total DDDs (642.1/1425.3, 51.6%) (Figure 14, Appendix 7 – Table 5).

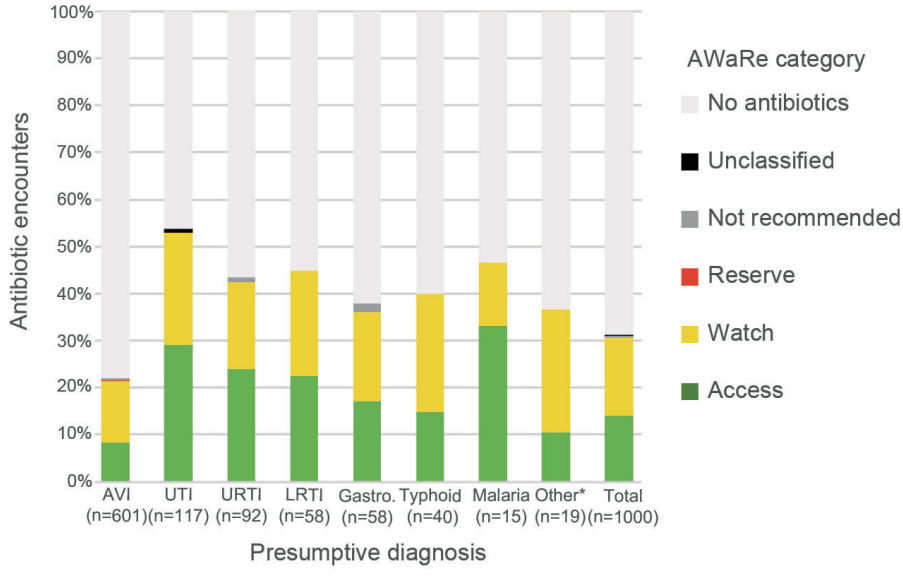

Figure 13. Distribution of antibiotics prescription during the outpatient visit by presumptive diagnosis for all patients in encounters by AWaRe category. AVI-Acute viral illness, UTI - urinary tract infection, URTI - upper respiratory tract infection, LRTI - lower respiratory tract infection, Gastro. - gastroenteritis. *Other includes tuberculosis, appendicitis, severe acute malnutrition, rheumatic heart disease, abscess and septic arthritis

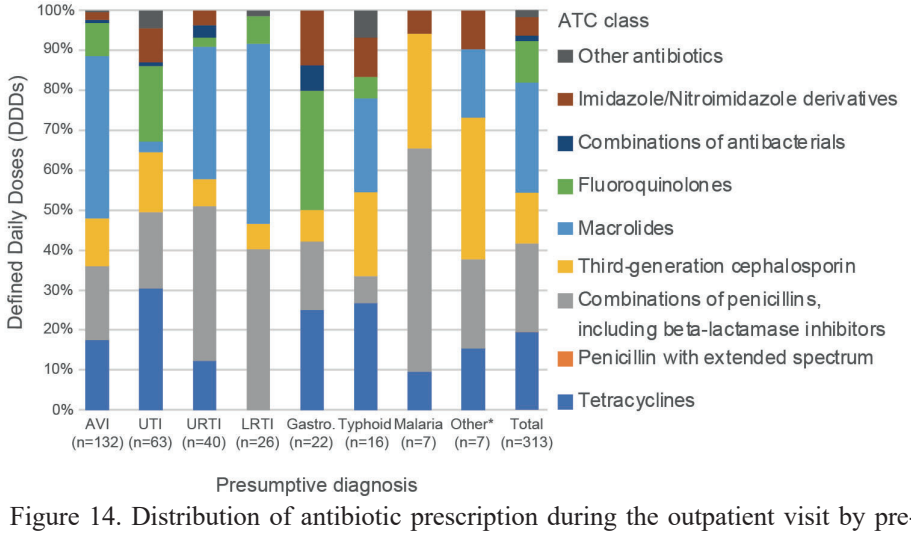

Figure 14. Distribution of antibiotic prescription during the outpatient visit by presumptive diagnosis and WHO ATC classification in the percentage of total Defined Daily Doses (DDD). AVI-Acute viral illness, UTI - urinary tract infection, URTI - upper respiratory tract infection, LRTI - lower respiratory tract infection, Gastro. - gastroenteritis. *Other includes tuberculosis, appendicitis, severe acute malnutrition, rheumatic heart disease, abscess and septic arthritis

4.4 Availability and use of diagnostics

4.4.1 Diagnostic infrastructure

The OPDs are connected to fully equipped microbiology and pathology laboratories with the ability to conduct all routine diagnostic investigations, but currently, no tests are conducted at the point of care. Most of the investigations are available free of charge except for complete blood count and Widal test for typhoid, which cost about 100 INR or 1.36 USD. The testing facilities are spread-out across the hospital. Payment for testing, sample collection, urine analysis, X-ray, ultrasound, electroencephalogram and electrocardiogram are conducted at the OPD. Analyses of blood and other specimens are conducted in the main clinical laboratory which is located at the inpatient department of the hospital, about a five-minute walk from the OPD. When a physician sends a patient for a diagnostic test, patients/caregivers must first go to the respective testing rooms to register for the tests, where they are then informed if there is a charge for the test. If necessary, patients/caregivers then proceed to the payment counter to pay for the test then return to the respective testing rooms to have the sample taken or the test conducted. Patients/caregivers usually must wait in queue at the different testing rooms and payment counter. Time in queue can vary from a few minutes to several hours.

Patients/caregivers are responsible for collecting the test reports from the individual testing rooms and then returning to the OPD for follow-up. If time permits, they can show the reports to the doctor on the same day. Tests which are not picked up at the end of the day are given to the nurse at the pediatric OPD except for x-rays. At the place where x-rays are conducted, there is an entire storage room full of x-ray films which were never picked up by patients/caregivers. Patients/caregivers who do not receive their results on the day of initial visit are advised to return for follow-up on the next day which the physician they met is scheduled to attend the clinic, after approximately three or four days. However, patients/caregivers are free to follow-up with any of the physicians attending the OPD.

4.4.2 Diagnostics ordered for sick children

Over the one-month period, 129 pediatric outpatients were prescribed a total of 245 diagnostics, 57% (n=73) of which were prescribed two or more diagnostics (Table 6). Of the 129 patients who were sent for diagnostics, 73% (n=94) got them done, 39% (n=50) of the caregivers received results and returned for follow-up on the same day, 11% (n=20) returned on another day, and 46% (n=59) never returned for follow-up (Figure 15). The most common tests conducted were complete blood count (55%, n=71) followed by urine routine and microscopy (28%, n=36) then x-ray (24%, n=31) (Paper III).

Table 6. Structured observations on the utilization of diagnostics

	N	%
Patients sent for one or more diagnostic	129	(100)
Test completion and follow-up		
Diagnostic(s) done, and returned for follow-up	69	(53)
Diagnostic(s) done, but did not return for follow-up	25	(19)
Diagnostic(s) not done	35	(27)
Number of diagnostic tests prescribed		
1	56	(43)
2	45	(35)
3	20	(16)
4	4	(3)
5 or more	4	(3)
Time from ordering of test to follow-up		
< 2 hours	15	(12)
2-4 hours	28	(22)
4-7 hours	7	(5)
The next day	12	(9)
2 days later	8	(2)
No follow-up	59	(46)

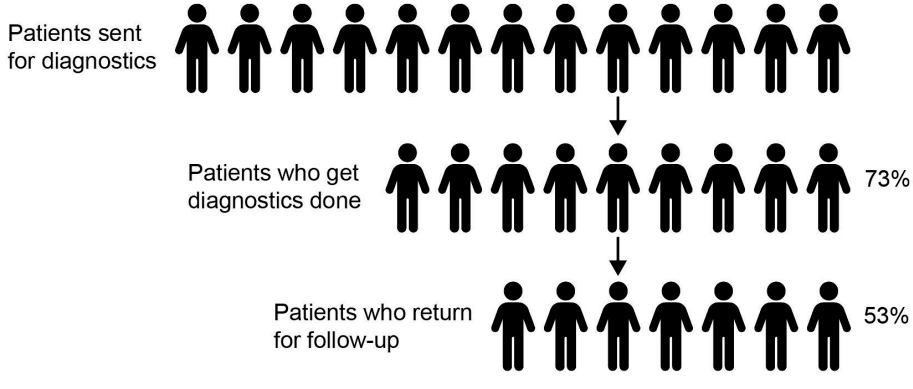

Figure 15. The proportion of patients who are sent for diagnostics, get the diagnostics done and return for follow-up.

4.4.3 Provider perspectives

The unstructured observations in the pediatric OPD which included conversations with resident physicians provided insights on how physicians manage and treat patients from initial to follow-up visit. During patient consultation, physicians take patient history and perform a clinical examination. If patients/caregivers have sought care previously for the same episode of illness they bring with them any relevant documentation. Likewise, patients/caregivers usually bring with them any medications they are taking and show them or their packages to the physician. Physicians reported that cough, cold and fever were the most common complaints by patients/caregivers. They estimated that they order some kind of diagnostic test for about half of their patients. In cases of suspected infection, a complete blood count is routinely performed. In addition, depending on the symptoms, routine urine and microscopy, chest X-ray, ultrasound, routine stool and microscopy, Widal test for typhoid or malaria microscopy may be performed. While waiting for test results to become available, physicians frequently prescribe medication for symptom alleviation and wait for test results to prescribe medication for treatment. Physicians reported that patients/caregivers sent for diagnostics often do not return for follow-up.

4.4.4 Caregiver perspectives

The analysis of the semi-structured interview data found that diagnostic utilization in the study setting is limited by structural factors that determine accessibility and affordability. Interview participant characteristics are presented in Table 7. Three key themes were identified which summarize factors influencing caregivers' utilization of diagnostic tests (Table 8). An example of the thematic analysis process is available in Appendix 8.

Table 7. Interview participant characteristics

	N	(%)
Gender		
Men	28	(39)
Women	44	(61)
Relationship to child		
Parent	49	(68)
Grandparent	8	(11)
Aunt/Uncle	12	(17)
Other relative	3	(4)
Residence		
Rural	57	(79)
Urban	15	(21)

Table 8. The three key themes and underlying categories derived from the analysis

Themes	Categories
Diagnostic acceptability waivers on caregiver preference and assessment of need	Understand the purpose and importance of the tests Trust in care and treatment Severity of illness Preference for medicines instead of tests
Organization of services inadequately meets caregiver needs	Navigating the way around the hospital Long lines, waiting times, and the need to return Limited transportation options Reports shown to other hospital staff other than the physician from initial visit Competing priorities and obligations
Direct and indirect costs of diagnostics impact affordability for caregivers	Cost of diagnostic tests Travel expenses Lost wages Combining providers to maximize care for limited resources

Caregivers viewed diagnostic tests as a valuable tool to determine the cause of illness. However, accepting that getting the tests done and returning to the doctor for follow-up was necessary for their child to get well was influenced by the caregivers' assessment of the child's illness and their preferences for care.

> "After tests, we come to know what the problem is. The doctor can understand the disease with the help of tests. […] He will give treatment according to diagnosis." -Father age 35, interview 11

Some caregivers assessed their child to be "not so sick", and in those cases, caregivers often chose to skip the tests but planned to return to have them done if the child's condition deteriorated. In some cases, they did the tests but the child got better before they received the results and therefore they skipped picking up reports and/or returning for follow-up. In a few cases, children had accompanied their caregivers to the hospital for treatment of a relative and while at the hospital they decided to stop by for a convenient free check-up on the child. One family was staying at the hospital for the entire week to accompany another family member and when their child felt slightly ill, they went to the OPD, and had an x-ray taken. However, they never ended picked up the film or went for follow-up because they decided the child was "not so sick". This was done despite the fact they were still at the hospital and only a short walk away.

> "The doctor told for a blood test, but I thought my child is looking normal and is having slight cough and cold, so there is no need for the test." -Mother age 28, interview 41

Medicines played a strong role in the care and treatment of children. Caregivers saw tests as an intermediary step to getting treatment and one that could be bypassed particularly for children who were "not so sick". For families with limited money, it could mean having to choose between getting the tests done or buying medicines. By skipping the tests and treating directly with medicines, especially those for symptom alleviation, caregivers felt they would save time, money, and their children would be feeling better sooner. Some respondents chose to try the medicines first and, if needed they planned to return for the test but, in many cases the child became well.

> "I did not get the tests done. I thought that the prescribed bottle of medicine would give him relief, so I avoided the tests." -Mother age 34, interview 34

Caregivers described the journey from the moment the diagnostic was ordered until follow-up as arduous and time-consuming. Caregivers hoped for a swift process so that their child could start treatment and begin the road to recovery. Some waiting was expected but caregivers described crowds and queues that caused some families to wait hours and others to skip the tests entirely. After the test was conducted, caregivers had to wait again for the reports to become available.

> "Sometimes there is a waiting of 25-50 patients. So poor people have to keep waiting for hours there hungry and thirsty, sometimes they go home before their turn comes. […] If we can collect reports on the same day then it will be good. Its ok to wait 1-2 hours, but the same day is important." -Mother age 37, interview 42

Participants talked about the time and distance it took them to reach the hospital. While some had their own motorbike, most had to take public transportation, and only a few lived close enough to walk. Most participants traveled to and from the hospital with public transportation. Their mobility was determined by the hours of operation of the buses and this restricted how late they could stay at the hospital. Caregivers expressed their concern for having to travel long distances with their sick children.

> "I came from 100km away to get tests done for my child, and I need to go back and travel the same distance, if they will give the test report on time then the patients can reach their home in a timely manner." -Father age 35, interview 2

Those who arrived early in the day could sometimes collect their reports and visit the doctor for follow-up on the same day, however usually this was not possible and caregivers would have to return for results, follow-up, and eventual treatment on another day. Time spent at the hospital or traveling to and from the hospital was time taken away from work, farming, household activities, and school for the children. Caregivers missed work, re-arranged

their schedules or received help to cover their obligations to bring their child to the hospital for the initial visit. If they had to come back for a return visit, they were often forced to choose between continuing the care for their child and their other competing priorities.

> "We do not have time to come again and again to the hospital if we keep on doing this who will do our work?" -Mother age 30, interview 32

The price of diagnostic testing at RD Gardi was minimal compared to other private facilities but still out of reach for the poor. Caregivers who did not bring enough money with them or could not afford the tests had no choice but to return home without having the tests done. These caregivers hoped to return when they managed to save or borrow money from someone.

> "For one trip we need to burn up petrol of 150 rupees and if we need to return two to three times then it will cause great loss." -Mother age 36 interview 14

Caregivers faced additional costs of travel along with reduction of wages for lost time from work. The most common type of paid employment in rural Ujjain is done based on daily wages. This means there is no insurance or security for time off, and if a worker does not show up for work, they do not receive any pay. As a consequence, caregivers who had to miss work to take their child to the hospital lost their daily wages. Expenses were multiplied when caregivers had to make repeated visits to the hospital.

> "I am a daily wage laborer. We lost our daily wages coming here. If we will not work how will we earn?" -Father age 38, interview 15

Caregivers frequently used a combination of healthcare providers while seeking care for one episode of illness. In some cases, caregivers explained that they would get tests done at RD Gardi, pick up the reports then present for follow-up at another private provider. Similarly, some caregivers had already seen a private provider who prescribed tests, then presented again at RD Gardi hoping to be sent for the same tests at a lower fee. As there is no consultation fee at RD Gardi this was a creative way to have the tests done at a fraction of the cost of a private laboratory. The money saved was then used for follow-up with a private provider.

> "Patients get the tests done at RD Gardi Medical College and then show them to other doctors at private clinics. Tests we can have from anywhere we want." -Mother age 37, interview 42

4.5 Performance of CRP to identify bacterial fever

The median CRP value for all patients was 2.8mg/L, which was below the minimum measuring range of the assay. The median CRP of patients with a final classification of bacterial was higher compared to patients classified as non-bacterial (3.6 [IQR 2.2 - 23.2] mg/L *vs.* 2.7 [IQR 2.0 – 5.7] mg/L, $p<0.0001$, respectively) (Figure 16).

4.5.1 Area under the receiver operating curve

The AUC of CRP to differentiate cases with a final classification of bacterial was low at 0.60 (95% CI 0.56 – 0.65) (Figure 17). No significant difference in the AUC was seen between children and adults, or patients who took antibiotics prior to seeking care and those who didn't. The Youden index suggested an optimal CRP cut-off of 21.0 mg/L for final classification.

4.5.2 Performance characteristics

The sensitivity of CRP for the final classification varied between 18% (95% CI 29-41%) and 34% (95% CI 13-23%) within the thresholds of 10-40 mg/L. The specificity of CRP ranged from 96% (95% CI 94-97%) to 99% (CI 98-100%) using the upper thresholds of 40-80 mg/L. In comparison, the sensitivity of current prescribing practices by the resident physicians as part of routine care for identifying the bacterial cause of infection was 41.8% (95% CI 35.5-48.3%) and specificity was 73.0 (95% CI 69.6-76.2%). The performance characteristics are summarized in Table 9.

4.5.3 Bacterial cases with low CRP

Overall, 78.6% (757/962) of patients had a CRP value of less than 10 mg/L. Of these, 3.4% (26/757) had a positive blood culture, none of which presented with any severity signs, five reported having taken antibiotics before study enrollment and in all but two cases, the fever had been present for at least two days. Of them, 80.8% (21/26) had a CRP less than 5 mg/L. Had a cut-off of 10 mg/L been applied, 65.5% (160/244) of all bacterial cases and 65.0% (26/40) of all blood culture-positive cases would have been missed to treat.

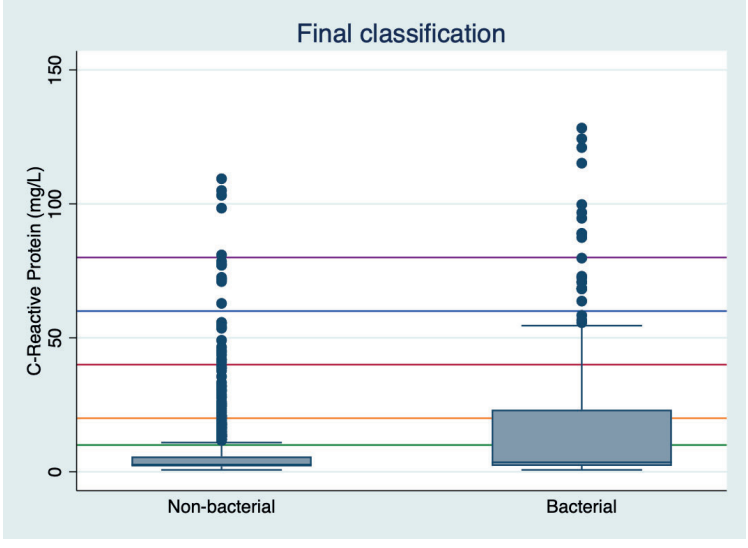

Figure 16. C-reactive protein (CRP) concentration (mg/L) for bacterial and non-bacterial cause of fever by final classification in Ujjain, central India in 2019. Box boundaries show 25th and 75th percentiles of CRP concentrations and lines within the boxes show the medians. The whiskers indicate the 10th and 90th percentile of CRP concentrations. The green, orange, red, blue and purple reference lines indicate the cut-offs of 10, 20, 40, 60 and 80 mg/L respectively.

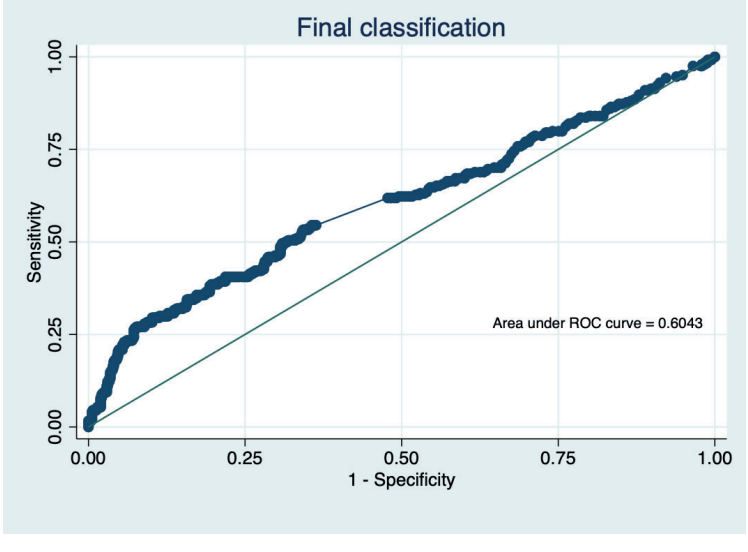

Figure 17. Receiver operating curve for CRP in discriminating between the bacterial and non-bacterial cause of fever for final classification in Ujjain, central India in 2019. On the horizontal axis is the sensitivity of the biomarkers and on the vertical axis is the false positive rate (1-specificity).

Table 9. Performance characteristics of CRP to identify bacterial infection at the thresholds of 10, 20, 40, 60 and 80 mg/L for final classification.

	No. > cut-off		Sensitivity	Specificity	LR+	LR-	PPV	NPV
Cut-off	Bacterial	Non-bacterial	% (95% CI)	% (95% CI)	n (95% CI)	n (95% CI)	% (95% CI)	% (95% CI)
10	84	121	34.4 (28.5-40.8)	83.1 (80.2-85.8)	2.04 (1.61-2.89)	0.79 (0.72-0.87)	41.0 (34.2-48.0)	78.9 (75.8-81.7)
20	66	60	27.0 (21.6-33.1)	91.6 (89.4-93.6)	3.24 (2.36-4.45)	0.80 (0.74-0.86)	52.4 (43.3-61.0)	78.7 (75.8-81.4)
40	43	29	17.6 (13.1-23.0)	86.0 (94.3-97.3)	4.36 (2.79-6.83)	0.86 (0.81-0.91)	59.7 (47.5-71.1)	77.4 (74.5-80.1)
60	19	15	7.8 (4.8-11.9)	97.9 (96.6-98.8)	3.73 (1.92-7.22)	0.94 (0.91-0.98)	55.9 (37.9-72.8)	75.8 (72.9-78.5)
80	10	5	4.1 (2.0-7.4)	99.3 (98.4-99.8)	5.89 (2.03-17.05)	0.97 (0.94-0.99)	66.7 (38.4-88.2)	75.3 (72.4-78.0)

LR+, positive likelihood ratio, LR-, negative likelihood ratio, PPV, positive predictive value, NPV, negative predictive value.

5. Discussion

This thesis highlights five major issues found while studying the management and treatment of outpatients with fever in a resource-limited setting: i) the majority of patients presented with mild illness and all recovered without any sequelae; ii) establishing the underlying cause of fever is challenging even in a research setting; iii) there is over prescribing, under prescribing and inappropriate prescribing of antibiotics for fever; iv) structural barriers prevent patients/caregivers from getting diagnostics done and returning for follow-up, and 5) CRP is of limited value to differentiate between bacterial and non-bacterial cause of AFI in outpatients in India.

5.1 Patients present with relatively mild illness

This thesis found that the outpatients seeking care at RD Gardi Medical College presented with relatively mild illness. In the prospective, cross-sectional study, patients with signs of severe illness were excluded from participation in the study, so a "less sick" population was expected, however the patients had even more mild illness than anticipated. This was also observed in the rapid ethnographic study which did not specifically exclude severe illness.

5.1.1 Relatively mild fever and duration of illness

Children were generally less sick than adults in terms of length of illness and presence of measurable fever ≥37.5°C. children were sick for a total of about 6 days while adults were sick for about 10 days. Only one-third of children, and about half of adults had a documented fever at presentation, and less than 1% of all patients had a temperature ≥39.0°C compared to 22% in a study of outpatient children in Tanzania (102). No deaths were recorded, no patients were admitted, and all patients reported that their symptoms had resolved during the follow-up period. This includes all patients with a positive blood culture of which, less than half received an antibiotic, suggesting that some infections may have self-cleared or that some blood isolates identified may have been contaminants.

5.1.2 Caregivers assessed their children to "not be so sick"

The thematic analysis of the semi-structured interviews (Paper III), identified severity of illness as one of the underlying categories. Several caregivers assessed their child to be "not so sick" and this had an influence on their decisions for testing and treatment. Some families were already at the hospital with another sick relative and when the child started to feel slightly unwell they went for a convenient visit to the OPD.

5.1.3 Inclusion of patients with history of fever

One of the reasons which might explain why the patients included were not so sick could be the inclusion of history of fever during the last 48 hours as criteria for enrollment in the study instead of requiring all patients to have a measured axillary temperature ≥37.5°C. History of fever was included for two reasons. First, several fever-causing infections present with intermittent fever (197). Second, it was expected that a significant share of patients suffering from fever would take antipyretics to alleviate symptoms before seeking care, and as a result may not present with a measurable temperature. Almost two-thirds (63%) of patients/caregivers reported antipyretic use prior to seeking care. This was within the range of reported antipyretic use of 55% by patients in Zanzibar (105) and 77% in India (198). Slightly more than half (54%) of the patients in the study had a measured temperature of <37.5°C at enrollment but reported a history of fever in the previous 48 hours. Similar proportions of patients with history of fever were included in studies from Zanzibar (55%) (105), Thailand and Myanmar (57%) (199), while an even greater proportion (70%) of patients without a documented fever at the time of study inclusion were seen in another study from India (198).

Including patients without a measurable fever but with a history of fever, and not as sick could be seen as a limitation but also a strength as excluding those with a history of fever could decrease the sensitivity to diagnose some infections. It is important to consider the prevalence of fever causing agents with intermittent fever as well as local practices of self-medication to determine the need to include history of fever and prior antipyretic use in any fever epidemiology studies and in the development of treatment algorithms.

5.1.4 Effect of taking antibiotics prior to seeking care

A total of 8.3% (83/1000) of patients reported taking an antibiotic for the current episode of illness prior to enrollment in the study. Antibiotic use in these patients may have inhibited the growth of bacteria, and started patients on the road to recovery, it also have reduced the performance of the RDTs and blood culture (200). While this makes the interpretation of results challenging, it reflects the reality of a patient population who frequently visit and receive

treatment, including antibiotics, from informal healthcare providers prior to visiting a formal healthcare facility (176,201).

5.1.5 Generally low CRP values

Of the 962 patients available for the CRP analyses (Paper IV), CRP levels were found to be relatively low across all patient and control groups with a median CRP value of 2.8 mg/L, which was below the minimum measuring range of the assay. The median CRP value of 3.6 mg/L for bacterial infections was far lower than generally reported in outpatients with non-severe fever, including reports from Tanzania of 16mg/L for children (202) and 46 mg/L for children and adults (203) as well as 18 mg/L for children and adults in Thailand and Myanmar (199). The reason for this is unknown, but may suggest a reduced response to infection or have been influenced by differences in patients' care seeking behavior, including the time from onset of illness to outpatient visit, or due to fact that the included patients were not so sick when they sought care.

5.2 Determining the causes of acute febrile illness

This thesis contributes to the understanding of AFI in children and adult outpatients Ujjain, Madhya Pradesh, India. The extensive culturing of blood, urine, throat, stool, and ear/joint aspirate samples identified 140 bacterial pathogens across 1712 cultures (8.2%), in 13.8% of patients. The most common detected bacterial pathogens were the bacteria *E. coli, P. aeruginosa, K. pneumoniae., S. aureus, and S. Typhi.* The non-bacterial pathogens included 12 cases of rotavirus (5 children, 6 adults), 4 of dengue virus (adults). A handful of the identified bacterial isolates have limited reports of causing disease and warrant further investigation.

Reviews of fever studies have highlighted challenges in comparing results due to variation in study design, patient sampling and case definitions and have called for comprehensive, harmonized, multicenter research and reporting to understand the etiology of AFI (87,96,98,204,205). While the methodology used in the present study was different, our findings are similar to D'Acremont et. al who found 22% of children under five suffering from a bacterial cause of disease despite their more stringent inclusion criteria requiring a documented temperature ≥38°C (102). Our findings are also aligned with reviews of the existing evidence on fever etiology which highlight that the most common causes of AFI are viral in South and Southeast Asia (98), sub-Saharan Africa (206), and Latin America (204).

5.2.1 Blood cultures

Bacteremia, i.e. the growth of a bacteria in blood, was identified in 3% of patients which is in-line with other studies of patients with AFI from India and Southeast Asia with bacteremia prevalence 0%–6% (104,207,208). It is crucial to identify patients with bacteremia since if left untreated it could develop into severe illness. Especially in LMIC outpatient settings, patients may not have the ability to return to seek further care if their condition worsens. In the study setting, *S. aureus* accounted for half of the bacteremia cases. While it is part of the natural skin flora and, therefore, a potential blood culture contaminant, it is also one of the most common causes of blood stream infections worldwide (209). However, blood cultures are frequently contaminated by skin flora as it may be complicated to assure a clean sample and contamination can be difficult to judge when single-sampling is used instead of the collection of two to three blood cultures (210–212). In our study all patients with bacteremia had recovered at follow-up despite that less than half received an antibiotic, suggesting that some blood isolates may have been contaminants. Alternatively, transient or occult bacteremia, i.e. positive blood culture in patients with AFI has been described, and may also partly explain our findings (213).

5.2.2 Urine cultures

The urinary tract was the most common culture positive site of infection identified in 9% of all patients, with a 62% culture positivity rate for cases with leukocyte or nitrate positive urine dipstick. Febrile urinary tract infection can go clinically undetected, especially in young children. The screening of all patients for leukocyte esterase and/or nitrates may have helped to identify cases that otherwise would have been overlooked. However, to avoid overdiagnosing urinary tract infection, especially in adult fever patients, a diagnosis may need to be supported by elevated inflammatory biomarkers (214).

5.2.3 Typhoid

Our culture findings of 0.9% *S.* Typhi and 0.2% *S.* Paratyphi fit within the range of typhoid identified in a retrospective surveillance study of enteric fever in India, Bangladesh, Nepal, and Pakistan where found *S.* Typhi was found to be present in 0.43-2% of all blood cultures, and *S.* Paratyphi in 0.1- 0.67% (215).

Prior to patient enrollment, the established case definition for typhoid was positive culture for *Salmonella* (Table 1) together with positive typhoid RDT using the Onsite Typhoid IgG/IgM Rapid Test. During the post-hoc quality check, it was observed that following the original case definition, nine culture positive cases would have to be excluded, due to the divergent culture and RDT results. The limited previous reports of the performance of this RDT is

mixed with 100% sensitivity, 94.35% specificity reported in Zimbabwe (216) however a much lower, 60.5% sensitivity and 73.9% specificity in Bangladesh (217). Therefore, it was decided to classify all positive culture results as bacterial cases, to disregard the RDT results and instead to send the culture negative, RDT positive cases for review by the expert clinical panel.

The biology of *Salmonella* Typhi makes diagnosis by standard laboratory methods challenging (218). The limitations of rapid testing for typhoid and paratyphoid is well debated in the literature (219) with a Cochrane review of the accuracy RDTs concluding moderate sensitivity and specificity of all the commercially available tests (187). The isolation of *S.* Typhi or *S.* Paratyphi A from blood culture remains the gold standard, however this method has a low sensitivity estimated at 61% by a recent systematic review (220). Considering the low sensitivity of blood culture, uncertain reliability of serological tests, and pre-exposure to antibiotics, our findings are likely to be an underestimation of the true incidence of typhoid in our study population. This study highlights the need for improved typhoid diagnostics suitable for use in low-resource environments.

5.2.4 Malaria

Although the burden of malaria has steadily decreased across South and South-East Asia (221), our finding of only one confirmed case of malaria was lower than expected. Ujjain received exceptionally high rainfall for the entire duration of the study period. Malaria cases do not tend to emerge until after the rains have subsided. Had patient recruitment continued in the period after the rains concluded, more malaria cases might have been identified. Malaria incidence has consistently declined across India with the country-wide annual parasite index reducing from 3.48 to 0.32 in the period 1996-2018 (180). Ujjain district has experienced even lower transmission of malaria with an annual parasite index of 0.1 in 2017 (222) and 0.03 in 2018 (181). As malaria incidence can vary from year to year, it will be important to follow its trend in coming seasons. This thesis highlights the importance to identify other non-malarial causes of fever, and is a reminder of the ever-changing epidemiology of fever.

5.2.5 Bacterial isolates less likely to be the cause of fever

Differentiating between bacteria which are pathogens, contaminants and part of the normal flora is a challenge and studies handle this differently (210–212). The interpretation of bacterial findings must often be done in relation to the clinical presentation of the patient. During the quality check, *P. aeruginosa* and *E. coli* in the throat were excluded as the likely cause of fever since they are infrequent causes of infection and their role as illness-causing pathogens could not be determined. However, another study from India has reported

these isolates as the cause of lower respiratory tract infection (223). *S. paucimobilis* was also excluded during the quality check as isolation from a clinical specimen is rare while recovery from diverse sources in the hospital environment including laboratory equipment has been seen. Likewise, we contemplated whether the *E. coli* found in stool samples should be considered the cause of fever or if it was simply part of the commensal intestinal flora. Diarrhoeagenic *E. coli* strains are commonly found in LMICs and have been reported to account for as much as 30-40% of all diarrhea cases in children (224). However, the fact that we did not type our isolates in combination with the lack of broad viral testing of stools we could not be certain if they were in fact the cause of fever or not. *Klebsiella* spp. in the stool was also judged to be a less likely cause of fever since it is also part of the normal gastrointestinal flora while another study has reported it as an etiological agent in acute diarrhea (225). A handful of the remaining identified bacterial isolates have limited reports of causing disease and warrant further investigation.

5.2.6 Pathogens not identified

A risk of testing by only RDT is that less prevalent pathogens are overlooked because a preselection has already been made. Performing bacterial cultures remains the gold standard for diagnosis and may have helped to identify the less abundant pathogens in this study (226). Still, several viral, bacterial, and parasitic pathogens could have been missed. In urine cultures, no enterococci or *S. saprophyticus* were detected. Also, interesting to note was the lack of *Streptococci* in the throat cultures in combination with the high proportion of *P. aeruginosa* may indicate a high community antibiotic pressure (227) and/or use of antibiotics in the current illness, disrupting the normal flora in the study population. Patient reported antibiotic use for the current episode of illness could have inhibited the growth of bacteria rendering culture not the most appropriate method to detect bacterial infection (200,228). The lack of PCR-based methodologies in our study might have caused us to miss identifying some bacterial causes of fever, however PCR also risks to over-diagnose many pathogens.

5.2.7 Challenges in determining the causes of fever

Paper I highlights the challenges of identifying the cause of AFI in LMICs. Even with the combined use of cultures, and RDTs, conducted at a tertiary teaching hospital with a fully equipped research laboratory and trained staff the diversity of etiologies could not be fully described by laboratory methods alone. Other outpatient fever studies have had broader diagnostic panels, covering the wide spectrum of pathogens which have been repeatedly found to cause AFI such as chikungunya, scrub typhus, leptospirosis, zika, Japanese encephalitis, adenovirus, or influenza amongst others. However, despite their

extensive testing, the cause of fever was only determined in 28.2-85.5% of outpatients (101,199,208,229,230).

Diagnostic testing has both strengths and limitations. In this thesis, serological tests were considered but it was not logistically feasible to collect convalescent samples from our patients and tests for follow-up in recovered patients are not usually collected in the study setting. Advanced technology such as multiplexed PCR panels are not presently part of routine practice at the study hospital. Furthermore, with both serological tests and PCR, just like some culture findings, the identification of an organism does not necessarily represent the cause of the present fever episode, instead the results could be a result of cross-reactivity, a contaminant or commensal, or possibly the identification of an earlier infection. Demonstrating this was the substantial difference between diseases diagnosed on the basis of predefined clinical and laboratory criteria and all pathogens identified but not necessarily considered the underlying cause of fever in children in Tanzania (102). Likewise, Elfving et al. (2016) identified a potential pathogen in 98% of patients and 95% of healthy controls (105). To address this problem, D'Acremont et al. (2014) suggests the combining laboratory findings with clinical information to differentiate between simply colonization and infectious disease (102).

This highlights the limitations of establishing diagnosis using only microbiological and laboratory methods and opens for the potential of an expert clinical panel to assist in the classification of cause of illness (55). Paper I was the first study in India on AFI that both applied a comprehensive laboratory panel as well as a review of cases by an expert clinical panel. The tests used in the study where chosen based on those which would be relevant for the local infectious disease pattern, and could be easily used in the setting.

After the application of predefined study-specific diagnostic criteria, the laboratory classification of cause of fever of 13.8% (n=138) bacterial, 1.5% (n=15) non-bacterial. The use of the two-step classification process allowed for the classification of fever by clinical panel review in an additional 80.9% (n=809) of patients where a pathogen could not be determined using bacterial culture and RDTs. The expert panel review increased the cases classified to a total of 24.4% bacterial, 71.8% non-bacterial. The remaining 3.8% cases which stayed as undetermined should have also been reviewed by the clinical panel but at that time point, the panel members were busy responding the COVID-19 pandemic and the rapid spread of the Delta variant through India so they were unable to assist further in classifying cases. In a research setting, the use of the two-step process combining laboratory methods together with clinical review may be a feasible way to establish the cause of illness. However, this would not be possible in routine clinical practice, especially in LMICs. The challenge to identify the diverse potential causes of fever calls for the development of improved diagnostic tools for classification of AFI.

5.3 Over, under and inappropriate prescribing for fever

It has long been documented that most patients in India seeking care for fever receive antibiotics (112). This was confirmed in Paper II in which 41% of all patients received an antibiotic at some point throughout the episode of illness. Similar prescribing was also recently reported by a multicentric prospective fever surveillance study finding 35.8% of childhood febrile episodes received antibiotics in the period 2017-2019 in India (231). Paper II highlights three interesting points observed about antibiotic use.

5.3.1 Concerning lack of 'Access' antibiotics

Antibiotic use for AFI is not limited to the hospital outpatient setting. Of all patients, 8% reported using antibiotics before seeking care, while 31% of patients received an antibiotic prescription during the outpatient visit and 9% of patients reported antibiotic treatment modification after the outpatient visit. Antibiotics can be obtained from a healthcare provider, either formal or informal, or purchased from pharmacies or drug shops (201,232). This shows that estimates from hospital based studies are likely to underestimate the true quantity of antibiotic use (70). Regardless of the time period observed, the 25-45% of 'Access' antibiotics used in was concerningly low. Antibiotic use at the OPD of 45% was the closest to the WHO country-level target indicator that at least 60% of antibiotic consumption should come from the 'Access' group (28) signaling that still much work needs to be done within and outside of the hospital to meet this goal. A majority of non-'Access' antibiotics came from the 'Watch' category accounting for 72.3%, 52.7%, and 32.6% of encounters before, during and after the outpatient visit. This is aligned with estimates of antibiotic wholesale data, which identified India among the countries with the lowest proportion of use of antibiotics in the 'Access' category (35%), highest from the 'Watch' category (47%), and considerable use of unclassified antibiotics (17%) (233). The widespread use of 'Watch' antibiotics by all types of providers within the follow-up period may be a result of the burden of increasing ABR and providers choosing second-line treatment options for patients who experienced a continuation or worsening of their symptoms.

While only a limited number of antibiotics in the 'Reserve', 'Not recommended' or 'Unclassified' categories were identified, it is concerning as four irrational FDCs were identified despite India's drive to remove irrational FDCs from circulation. In 2018, the Indian Ministry of Health and Family Welfare banned 344 irrational FDCs, prohibiting their manufacture for sale, sale and distribution (234). A recent study of antibiotic consumption data across 75 countries from 2015, i.e., before the ban took place, found India to have the highest total volume and percentage of antibiotic irrational FDCs (235). However, the proportion of FDCs identified was much lower than estimates of 12% (236) and 49% (237) in other studies from India and may be a result of FDCs slowly being removed from circulation. Surprisingly, three of

the four irrational FDCs identified in this thesis were included in the list of the 344 banned substances (234), despite their classification as 'Not recommended' or 'Unclassified' by the AWaRe list (82). The use of these drugs may fly under the radar, as the lack of ATC codes, DDDs, and AWaRe classifications for some FDCs, poses a challenge to drug utilization monitoring and research. It is essential that all drug use, rational as well as irrational can be appropriately quantified and included using standardized methods (78).

5.3.2 Excess prescribing occurs alongside a lack of access

Reducing overuse of antibiotics is equally important as ensuring access to those in need. The access vs. excess dilemma of reducing overuse of antibiotics while simultaneously ensuring access to those in need is often discussed from a global policy perspective (10). This thesis shows that the problem can also exist within a single OPD. A surprising proportion of patients diagnosed with urinary tract infections and lower respiratory tract infections had no antibiotics prescribed. Meanwhile, a presumptive diagnosis of acute viral illness was given to 60.1% of patients during initial consultation, and while this diagnosis had the lowest proportion of antibiotics prescribed, it still accounted for over half of the total volume of antibiotics prescribed despite being a condition that cannot be treated by antibiotics. Similar problems with antibiotic prescribing was seen in a study from eight LMICs which estimated 49-81% of antibiotic prescriptions were unnecessary (238). This prescribing of antibiotics might reflect uncertainty of diagnosis and "just in case" prescribing.

A definitive presumptive diagnosis for AFI can be difficult to establish with only a brief patient consultation, in the absence of diagnostic tests, as the non-specific clinical presentation could be caused by many etiologies (98). In analysis of appropriateness of prescribing compared with a provisional diagnosis by the treating physician for AFI, Karthikeyan and colleagues (2021) estimated that 65.4% of antibiotic use over the two year study period was unwarranted (231). For the purposes of this thesis, the residents were asked to provide a single presumptive diagnosis to the best of their ability. While there is likely a high level of uncertainty in the presumptive diagnosis, it reflects a real-life situation where physicians are forced to make treatment decisions in the period of a short outpatient visit.

A systematic review of factors associated with antibiotic prescribing identified diagnosis and physical exam as the principal drivers of antibiotic prescription (239). In the absence of POCTs, healthcare providers tend to be cautious and initiate antibiotic treatment (239,240). In a setting like Ujjain where typhoid and malaria are endemic, an improved POCT for typhoid as part of a treatment algorithm in conjunction with diagnostics for malaria and other causes of AFI could have a meaningful impact on the overuse of antibiotics (218). Until there are tools, which cover the wide spectrum of pathogens causing fever, to assist healthcare providers to differentiate between bacterial

infections requiring antibiotics and self-limiting infections, and those tools are affordable and adapted to resource limited settings, the presumptive treatment with antibiotics will continue (102).

5.3.3 Mismatch of prescribing patterns with guidelines

In addition to the quantity of antibiotics prescribed, the choice of antibiotics is concerning. The WHO recently released new guidelines for the treatment of 26 infectious syndromes commonly found in primary care and inpatient settings (28). The guidelines are intended to support countries in the development or refinement of their own national standard treatment guidelines. The guidelines aim to support improved antibiotic prescribing to help curb the spread of ABR, and preserve the efficacy of currently available antibiotics (241).

In India, treatment guidelines for antimicrobial use in common syndromes have been developed at the national level (242). The 2019 guidelines state that they are based on antimicrobial susceptibility data from selected tertiary hospitals across the country and treatment of individuals may vary depending upon local conditions and experience and suggest that each healthcare institute should customize their respective guideline accordingly (242). The extensive deviation from recommended initial treatment options in this thesis, could partially be a signal that prescribers were familiar with resistance patterns in their community and adjusted their prescribing accordingly. Up-to-date local epidemiological data and antibiograms or rapid diagnostic testing that pairs the identification of an organism with the related antibiotic susceptibility profile could support targeted prescribing in the hospital setting (243).

The extensive use of broad-spectrum antibiotics like azithromycin and amoxicillin in this thesis is in line with the WHO report on surveillance of antibiotic consumption which lifted these two drugs as the most commonly used and antibiotics in most regions (244). Broad-spectrum antibiotics continue to be the preferred choice in many resource-limited settings due to their low cost, ease of administration and availability (231). Widespread use of azithromycin has been demonstrated to select for macrolide-resistant strains of *S. pneumoniae* (245), and *S.* Typhi in Pakistan and India (246,247) and increase macrolide resistance gene expression in gut microbiota (248).

The overuse and inappropriate use of antibiotics when not indicated poses a significant risk as it may unnecessarily select for resistance rendering important antibiotics no longer as viable treatment options. Evidence-based, context appropriate implementation strategies that complement cost-effective diagnostic tests could improve timely and appropriate management and treatment of AFI.

5.4 Utilization of diagnostics by caregivers of sick children

Basic diagnostic tools are available at the pediatric OPD to support physicians in the management and treatment of patients but the utilization of these tests by caregivers of sick children is compromised by structural factors which limit accessibility and affordability. As part of a tertiary teaching hospital, the OPDs had access to the on-site fully equipped microbiological and clinical laboratory, and all tests were done within the confines of the hospital. In many LMIC outpatient settings, there is a lack of microbiology laboratory facilities and skilled personnel to conduct diagnostic testing (99).

The path from initial visit to testing and follow-up often involved visiting several testing and administrative locations and patients/caregivers were responsible for navigating their way. In cases of suspected infectious illness, complete blood count and chest x-ray were two of the most used diagnostic tools. These tests can help to evaluate the health status of a patient and detect a wide range of disorders but are pathogen-nonspecific. Pathogen-specific tests such as antigen or antibody detection assays, molecular techniques of nucleic acid detection, covering the wide spectrum of pathogens that can cause fever were less common part of routine practice in the study setting (249). In high-income countries, highly accurate diagnostic tests are available for most infectious diseases of public health importance but these tests are generally neither affordable nor accessible to patients in LMICs (116).

5.4.1 Caregiver utilization of diagnostics is low

The desired behaviors in the utilization of diagnostics were defined as a caregiver assisting a child to have diagnostics done and return to the department for follow-up of results. Both the structured and unstructured observations revealed that only about half of the patients/caregivers who are sent for diagnostic testing, got the tests done and returned for follow-up. The structured observations showed that 39% of patients/caregivers who were sent for diagnostic tests managed to receive their results and reach follow-up on the same day as initial visit but almost half, 46%, never returned for follow-up. It would have been interesting to know the reasons why this particular group of patients/caregivers did not return however, the quantitative data from the structured observations were not designed for this purpose.

5.4.2 Approaches to understanding behavior

There have been several calls to promote the use of social and behavioral sciences in the response to ABR in order to understand behavior and develop context appropriate effective interventions (138,141,250–254). Combining behavioral science approaches with qualitative methods has been suggested to

provide an exploratory approach to understand influences on behaviors and how to support behavior change (255). Some researchers caution viewing ABR as a problem of individual behavior, and suggest instead looking towards the systematic and structural issues promoting ABR (256,257). We challenge this perspective, suggesting the use of a comprehensive behavior change framework can allow us to examine the wide-ranging contextual, organizational, and interpersonal factors which influence why people act in the way that they do, and identify appropriate interventions which do not target the individuals themselves, rather aim to support individuals to perform a desired behavior.

The COM-B model for understanding behavior is grounded in behavioral science and was developed with input from the social sciences including psychology, sociology, anthropology, economics, and political science (142). The model is a tool for exploration of the multifaceted influences on why people act in the way they do. Semi-structured interviews were used to delve into the reasons behind caregiver behavior and identified several factors which may explain why only about half of the caregivers got the tests done and returned for follow-up. These phenomena are examined through the lens of the COM-B model.

5.4.3 Reflections on findings through the lens of COM-B

Capability (C) relates to an individual's physical and psychological capacity to perform a desired behavior (144). A handful of caregivers expressed concerns about the arduous journey to get the diagnostics done and return for follow-up, which was described as especially difficult for the uneducated or illiterate. On the other hand, almost all caregivers exhibited psychological capacity in understanding that physicians use diagnostics to help them determine the cause of illness and treat their children appropriately.

Opportunity (O) refers to all the physical and social factors which prompt a behavior or make it possible to enact (144). Opportunity had the strongest influence on caregiver behavior in the current study. Caregivers expressed that it was important to do the tests and reach follow-up on the day as the first visit. Long queues to get the tests one and time to wait for results discouraged caregivers. The amount of time they could wait for results was dependent on the schedules for the busses they needed to take back home. Caregivers also had other responsibilities such as work, or taking care of the home and other family members. Needing to come back on a separate occasion, placed an additional burden on the family as they would have to juggle competing priorities, and their travel expenses and lost wages multiplied. Structural barriers including delays in testing, receiving results and follow-up, further complicated by travel time, distance and competing priorities, reduced access to the available diagnostics. Similar struggles of access to healthcare were reported in a study from South India (109) and have been a long-standing issue in LMICs

(258,259). Anand and colleagues (2019) suggested that to expand access to health services, patients need consultations which combine diagnoses with dispensing of medicines (176). Even though the fees for diagnostic tests were minimal compared to other healthcare facilities, they were still out of reach for the poorest. Similar struggles were also identified by caregivers of febrile children in Uganda where patients withdrew from initiated care due to a lack of money for blood tests (260). In the study setting, the combined costs for the tests plus travel expenses together with lost wages for missing work to get the tests done, prevented caregivers from fully utilizing the diagnostic tests. In an effort to minimize costs and maximize care and treatment for their children, caregivers creatively pieced together patient consultation and testing services from multiple providers. This resulted in some patients/caregivers apearing to be lost to follow-up at RD Gardi OPD when in reality they followed-up with another provider. Combining providers to meet patient needs has also been described by other studies from India (109,261). Finally, the practice of purchasing antibiotics for quick relief and to avoid spending extra time and money on consulting physicians or diagnostics was also identified by Chandy and Engel in sites across southern India (109,261). Until the problem of direct and indirect costs to the patient/caregiver is addressed, people will continue adapting their behavior to fit their available financial resources (262).

In the COM-B model, Motivation (M) – can be understood as the emotions, habits and conscious decision making that strengthen and direct a behavior (144). Motivation may be increased or decreased by the capabilities and opportunities which surround a behavior. In the study setting, the caregivers had trusted in the physician's ability to care for their children and the utility of diagnostics to direct their management and treatment of illness. Caregivers based their healthcare decisions on trust, reputation, and affordability, echoing findings from another study in Ujjain (176). However, their motivation to get diagnostics done and return for follow-up was deterred by the additional time, fees, travel expenses and lost wages which would be incurred to do so. The caregivers wished for their children to become healthy as quickly as possible and they were frustrated by prolonged and laborious hospital visits. In deciding whether or not to follow through with testing, caregivers considered the severity of their child's illness and in some cases decided to short-cut the route to care with the convenience of medicines.

5.4.4 Supporting adoption of the desired behavior

The COM-B analysis of the qualitative interviews from this study can be used to inform the development of tailored implementation strategies and interventions to support caregivers to enact the desired behaviors of getting the diagnostics done and returning for follow-up of (144). The most commonly used approaches to try to create behavior change related to ABR are education and interventions to increase knowledge (162,263). However, it is well

demonstrated that education alone is insufficient to support behavior and has not result in a sustained impact (264,265). This is likely due to the fact that behavior is influenced by much more than just knowledge (144). The findings from this study showed that caregivers possessed the knowledge and had the capability to understand that physicians use diagnostics to help determine the cause of illness. Educational interventions aimed to increase diagnostic utilization would be futile. Looking further, the COM-B model elucidates addressing the structural issues of the existing diagnostic services may increase caregiver motivation to utilize the diagnostics. Within the current diagnostic infrastructure of the study setting, expanded opening hours, or follow-up by phone could eliminate the need for some caregivers to make return visits.

Alternatively, a move from the traditional laboratory based diagnostics, to POCTs has potential to reduce diagnostic and treatment delays and improve the quality of care (33,266). POCTs could help improve the appropriateness of antibiotic prescriptions and reduce patient/caregiver desire or pressure for antibiotics (267). However, the use of POCTs can be costly, time consuming and resource intensive (268). As costs were already identified as a barrier for patients, an economic evaluation would be necessary to understand if POCTs could be economically feasible for patients/caregivers and the hospital. Lastly, for POCTs to be useful to healthcare providers and beneficial for patients in the defined site of use (54), their utility in the defined population and site of use must be established (106).

5.5 CRP is of limited value to identify bacterial fever

This thesis confirmed the consistent finding from several studies that median CRP values are generally higher in bacterial infections than non-bacterial infections (101,125,199,202,203,269). However, the AUC of CRP had a low diagnostic value of 0.60 as evaluated by the reference standard final classification. None of the cut-offs tested, exhibited a PPV sufficient to use it as a stand-alone test. This signals that CRP is too weak as a single indicator of bacterial infection and does not on its own provide sufficient accuracy to guide treatment decisions for febrile outpatients in India.

5.5.1 Performance of CRP

Four studies reporting the AUC for CRP to differentiate between patients with and without a bacterial cause of fever in outpatients in LMICs were identified. The two of these studies which excluded severe illness, had similar AUC to this thesis. In Tanzanian children under five, Hildenwall et al. (2017) reported an AUC 0.620 for all cases of suspected bacterial infections (positive blood culture, urine culture and pneumonia defined by the Integrated Management of Childhood Illness algorithm) (202). In children and adult outpatients from

Thailand and Myanmar, Althaus et al. (2020) reported an AUC of 0.65 for CRP to distinguish bacterial from viral target organisms using a reference standard based on results of molecular and serological assays classifying all organisms identified in blood, and target organisms identified in nasopharyngeal samples (199). The remaining two studies, which did not specifically exclude severe illness, i.e., patients presenting with deranged vital signs or Integrated Management of Childhood illness danger signs, had relatively higher AUCs. In children and adults from Southeast Asia, Lubell and colleagues (2015) reported an AUC of approximately 0.79 for the ability of CRP to discriminate between bacterial and viral causes of fever using a reference standard built on microbiological results; including culture, antigen detection, PCR, and ELISA (125). While Mahende and colleagues (2017), who like Hildenwall also studied children under five in Tanzania, reported an AUC of 0.83 using bloodstream bacterial culture as the reference standard (269). Mahende et al. excluded children who reported having taken antibiotics in the last seven days (269). Compared to the latter two studies, the lower AUCs reported in this thesis, and by Hildenwall (202) and Althaus (199), signals that the utility of CRP is likely less in non-severe fever compared to severe fever.

5.5.2 CRP in cases with positive blood cultures

Bacteremia cases are important to identify because even cases which present without any severity signs could potentially develop into severe illness and death. CRP has been identified as a strong indicator of serious bacterial infectious (CRP 10 mg/L, sensitivity 82% , specificity 90%) (270), (CRP 20 mg/L, sensitivity 79% , specificity 84%) (271) and a valuable laboratory test in the evaluation of febrile children at risk for occult bacteremia and severe bloodstream infection (AUC 0.91) (272). In a study of admitted febrile infants aged 29-90 days with fever without source for less than seven days, 5 mg/L CRP was determined a good cut-off concentration to rule out bacteremia (273). Likewise, a study from Tanzania found only 3% of patients with a bacterial blood stream infection to have a CRP under 10 mg/L (203). On the contrary, in this thesis, of patients with positive blood cultures, half (21/40, 53%) had a CRP <5 mg/L and two-thirds (26/40, 65%) had a CRP <10 mg/L. The difference in findings could be due to the generally low CRP values reported in our study. However, low CRP in cases with positive blood cultures was also reported by Hildenwall (2017). Two of six patients with positive blood culture, had a CRP <5 mg/L, and like our findings, these patients had no severity signs and fever reportedly present for at least two days. This highlights the risk that using CRP as a single indicator of bacterial infection might increase the missed diagnosis rate for patients with bacteremia.

5.5.3 Generally low CRP values identified

The reason for the low levels of CRP concentration found throughout the patient population and in healthy controls is unknown and warrants further investigation. Generally, low levels of CRP are associated with healthy individuals and a sign that patients do not have any disease which is associated with an inflammatory response (274,275). Our study reported a median CRP slightly below the measuring range of the CRP assay and the median CRP of patients with a bacterial cause of infection was slightly above the measuring threshold.

A few recent studies which have investigated very low CRP concentrations with the use of a wide range CRP assay have highlighted the possibility of very low CRP concentrations in admitted hospital patients. Feigin and colleagues (2021) showed that patients can present to the hospital with severe medical conditions and very low CRP concentrations (≤0.03 mg/L) at initial measurement (274) while Wasserman et al. (2019) reported that septic patients who presented to the emergency room had an initial CRP concentration within the same range as healthy community controls (276). Reasons proposed for the low CRP values in patients sick enough to be warranted hospital admission were the short duration from initiation of the inflammatory response, antibiotic exposure and the presence of immune paresis (274,275). A study of very low CRP in healthy individuals suggested that low CRP levels could be due to individual physiology (277). These studies highlight possible reasons for a reduced CRP response in a subgroup of patients but none of the studies reported low CRP levels across the entire study population. A recent study from Israel of patients presenting to the emergency department with acute viral and bacterial infections who all had a relatively low CRP concentrations at admission (defined as ≤31.9 mg/L, 99.7% of CRP measured in healthy controls), took a second CRP measurement within 24 hours and investigated the velocity at which CRP rose between measurements (in milligram per liter, per hour) (278). The study concluded that in patients with a low CRP upon admission, a second CRP measurement and the CRP velocity were useful biomarkers to discriminate between acute bacterial and acute viral infection. While these results are promising, it is unknown if such findings would apply to an outpatient population and regardless, measuring repeat CRP values would not be feasible in outpatients in the study setting (278). Further research on the use of repeat CRP measurements and CRP velocity may be warranted for LMIC inpatient settings as a marker of severe bacterial infections.

5.5.4 Point of care tests

The true value of CRP testing in LIMC settings would be in the use of a POCT that can provide results and feedback within the course of a single outpatient visit. Several different CRP point of care test systems are commercially

available including quantitative assays as well as semi-quantitative strip methods. The beneficial effect of CRP testing is dependent on the analytical performance and user friendliness of the test used (279,280).

A systematic evaluation of CRP immunoassay POCTs reported a good correlation between POCT and reference testing with a coefficient of variation lower than 20% in all studies reviewed (281). In comparison of two semi-quantitative strip methods and six quantitative methods, against an automated routine method, all quantitative methods performed better than the strip tests which had an insufficient correlation with the reference method but there was over and under estimations across both types of tests (279). In addition, the interpretation of the semi-quantitative strip test results proved more difficult than suggested by the manufacturer's instructions (279). Authors highlighted considerable variation between and within POCT methods which can be a result of lot-to-lot variation, i.e. variation between different manufacturing lots of calibrators and reagents, that few POCT methods are calibrated before measurement, or due to incorrect pre-analytical handling of the samples (279). Another evaluation of CRP POCTs showed that only four of five devices tested displayed adequate analytical performance and considerable variation was seen in the performance, agreement, and user-friendliness of the tests (280). None of the aforementioned studies tested the Turbodyne CRP UV by Tulip Diagnostics which was used in this thesis, nor could any evaluations of the test be found in a search in PubMed, making it difficult to assess the if the choice the POCT test had any impact on the CRP values measured in this thesis. The results from these studies highlight that CRP POCTs may not be as user-friendly and full-proof as desired and the test used should be taken into consideration in evaluations of CRP in LMICs.

In light of the limited performance of CRP in the study setting, other POCTs based on the measurement of host biomarkers which perform well in LMICs are needed. Together with CRP, Procalcitonin and white blood cell count are three of the best known, most accessible and frequent used biomarkers (119). Procalcitonin, similar to that of CRP, is one of the most validated biomarkers in the literature which has also been used in high-income settings as a fever triage assay (122) but has generally also been found to be of limited use to discriminate between bacterial and non-bacterial infections in LMIC settings (54,106). White blood cell count is commonly used to differentiate between bacterial and non-bacterial cause of illness and measurements can be done by POCT. Despite its frequent use, the evidence of its ability to identity patients with bacterial infections is lacking (202). In a recent review of studies published from 2015-2019 of biomarkers to differentiate causes of fever, the most promising biomarkers identified which are

potentially fit for LMICs were[7]: the CRP, IP-10, and TRAIL signature; the IL-6 and IL-10 signature, the MxA and CRP signature, and human neutrophil lipocalin (HNL) (119). One of them, HNL, has shown to be uniquely increased in serum of patients with a bacterial infection, with sensitivities and specificities >90%. To overcome challenges related to working with serum samples, the development of a POCT assay for whole blood measurement of HNL in under 10 minutes is currently underway (282). Further high-quality studies are needed to support the development of POCTs suitable for LMICs.

[7] IL-6, interleukin 6; IP-10, interferon-gamma-inducible protein 10; TRAIL, tumour necrosis factor-related apoptosis-inducing ligand

6. Methodological considerations

6.1 Main strengths

The greatest strength of this thesis was that for the quantitative study (Papers I, II, IV), we followed the two-step BFF-Dx methodology (95) with support and guidance from FIND throughout the study. This thesis employed a more limited testing strategy however, the data collection tools and hence clinical data collected, as well as the process for classification of disease by expert clinical panel was the same. This is the first study to repeat the BFF-Dx methodology contributing to the forthcoming data from Malawi, Gabon and Brazil with results from another geographic region (283). Following a standardized approach paves the way for better comparison of results. Harmonized, multicenter research and reporting will facilitate the understanding of the causes of AFI (87,96–99,205).

Furthermore, this study provides important primary data on community, low-severity presentations of fever in a wide range of ages, from an area with relatively few public domain data on the causes of fever to inform management. This data will contribute towards important efforts of improving diagnosis and targeted treatments in high infection-burden settings. The systematic data collection of clinical features and diagnostic testing in an outpatient setting is rare, with most similar data coming from inpatient and/or syndrome-specific cohorts.

6.2 Attempts to minimize systematic errors

All data collection tools, including CRFs, patient logbooks (Papers I, II, III, IV) and interview guides (Paper III), were pre-tested and revised before use. This thesis adapted the CRFs which had been previously tested in the original BFF-Dx study. A pilot study was conducted before the quantitative and qualitative studies started to streamline study procedures and train the study staff. A member of the research team reviewed all CRFs to ensure completeness before data entry. Quantitative data validation (Papers I, II, IV) was done in two phases. First, the team in Ujjain looked for outliers, revisited and corrected data on e.g., height after being in contact with caregivers. Second, a check was conducted on 3% of CRFs selected at random to ensure the electronic database matched the paper forms. The interview material was

translated into English, suggesting the possibility to risk losing important information. We tried to avoid this by reading the translated transcripts and checking to ensure proper translation. By using a combination of Indian and non-Indian researchers, we suggest the credibility of the studies was increased.

A total of 1712 cultures were conducted. Blood cultures were conducted for all patients while urine, respiratory, stool, and or ear/joint cultures were conducted based on a patient's symptoms. This was a strength of the Paper I as few outpatient fever studies include cultures from specimens other than blood. Traditionally LMICs face many challenges implementing cultures including staff training, insufficient infrastructure, delayed incubation due to transport to centralized laboratories, and ambient temperatures that exceed recommended incubation temperatures of pathology services (210). Our cultures were done at the onsite research lab which had the capacity and equipment, including an automated blood culture system, to conduct cultures and likely minimized potential problems due to sample storage and transportation (284). To reduce the potential for contamination, an aseptic technique and standard precautions were used with specimen collection and handling. Trained microbiologists performed all the procedures in the laboratory and standard operating protocols were devised particularly for this study (Paper I and IV).

The analysis of the qualitative data was led by the PhD student, with review, discussion and adjustment at each step of the process together with the research group until consensus was reached. Two members of the research group were from the study setting helping to ensure appropriate interpretation of the contextual data, while the other members outside eyes provided new perspectives and insight into the data. The combination of the team allowed for reflexivity and strengthened the analysis (285,286).

6.3 Attempts to minimize systematic biases

To establish the trustworthiness of the studies, the first author visited India several times over the duration of the project. Several months were spent in the study setting for Paper III, and multiple visits were made before, during and after data collection took place for Papers I, II and IV to deepen the understanding of the study setting, and increase credibility.

Information bias may have affected the validity and reliability of study findings. Data on medication use before and after the outpatient visit were based on patient reports (Paper I and II). Recall bias may have affected the type of drugs, dose and duration reported (287–290). The effect of this is estimated to be minimal in this thesis due to the data collection methods used. Patients attending the hospital OPDs in this study often bring with them any medicines they are currently using to show the physician during the patient consultation. At follow-up, patients/caregivers contacted by phone were asked

to send pictures of their medicines via text message. While this may have helped to ensure the correct drug information and increase the robustness of the data, it is not possible to know if all antibiotics reported were actually consumed, or that no antibiotics were overlooked. Furthermore, social desirability bias may have been introduced if caregivers over-reported desirable responses to interview questions regarding their views on diagnostics (Paper III). Likewise, underreporting may have occurred if patients/caregivers may have been afraid to reveal information regarding their antibiotic use or treatment modification by informal healthcare providers due to the illegal status of their practice (Paper II) (291).

A strength of the qualitative study (Paper III) was the application of multiple methods of investigation (unstructured and structured observations and semi-structured interviews) allowed for triangulation and cross-validation of our findings. Notably, findings from the structured observations were aligned with those from unstructured observations where physicians reported that only about half of the patients they send for diagnostics, return for follow-up of results.

6.4 Limitations

There are several methodological issues to consider while interpreting results from this thesis. The mild illness of the patients in this thesis likely has implications on the findings of all four studies. Hence, findings may have been different if analyses had been restricted to a subset of patients who were sicker. Discussions were held on developing a severity score based on a combination of clinical signs and symptoms to differentiate more from less sick patients. However, given that patients with signs of severe illness were excluded from the study, it was decided this was not feasible, nor the aim of the thesis. Even if the patients included in this thesis were not that sick, they still represent the target population of all non-severe outpatients seeking care for AFI. This group was the population identified by the target product profile, one of the guiding documents for this work (54).

Both the quantitative and qualitative studies were done over a short period and do not account for seasonal variations in disease. The effects of this on Paper III is likely limited as the purpose was to gain an understanding of the setting, not to provide a representative sample. However, the effect may be more significant for the work on disease prevalence (Paper I) and antibiotic use (Paper II). Some pathogens causing fever that are present at other times of the year may have been missed, and others may have been overrepresented. Antibiotic use has been shown to vary throughout the year following local illness patterns (13).

The qualitative study was focused on the caregivers' perspectives on diagnostics, additional qualitative interviews with physicians, laboratory

technicians, and hospital management would broaden understanding on this topic. The observations (Paper III) were done by one person, observations are subjective in nature and may have been influenced by the Hawthorne effect.

The WHO methodology used for presenting the prescribing data by ATC class in DDDs (Paper II) does not allow for dose adaptation for children and it likely underestimates the total antibiotic use.

The absence of a control group meant there was no baseline data on the carriage of pathogens in the healthy population. The diagnostic tests used are less than 100% sensitive and specific and we did not test for every known pathogen. For dengue and rotavirus, we did not compare RDT results to reference tests as in other studies (292). As a result, we probably underestimated the prevalence of some infections while misclassifying others that were falsely positive. Finally, it is important to note that the data collection for this study took place before the outbreak of COVID-19. It is an important reminder that the etiology of fever is changing over time, and results must be taken into context of current global trends.

Traditionally, culture has been the gold standard for pathogen detection but cultures are far from capturing all pathogens as it is challenging to investigate the entire spectrum of pathogens responsible for causing fever (293). Patients may have non-bacterial illness (294) and some organisms are not easily detectable by conventional culture methods (295). A limitation of the study is that Japanese encephalitis virus, melioidosis, leptospirosis, scrub typhus, Indian spotted fever, murine typhus, etc. were not included in the laboratory analysis. For blood culture, the yield is greatest when bacteremia is at its peak, and bacteria may be present at in the blood at very low densities (294). The quantity of blood sample taken, and use of just one blood sample instead of multiple samples may have affected the culture yields (210). Lastly, prior antibiotic use may have also reduced the possibility of bacterial growth. These factors may have led to an underestimation of the number of bacteremia cases identified. Likewise, over-estimation of bacterial pathogens may have been caused by contamination introduced during blood sampling or processing of the blood sample. Despite progress in aseptic techniques, rates of blood culture contamination are still commonly reported from 2-6% (296).The distinction between pathogen and contamination is usually determined by clinical assessment or number of blood cultures that show growth for particular pathogens (210). In this thesis, the post-hoc review of bacterial isolates was used to help distinguish between which isolates were pathogens, commensals or contamination.

No perfect method exists for classifying AFI cases as bacterial or non-bacterial etiology to use as a gold reference standard for evaluating the performance diagnostic tests. A limited percentage of confirmed etiology has been obtained in even the most comprehensive fever studies (102,104). In the absence of a gold reference standard, each study aiming to establish the cause of fever and evaluate the performance of CRP, must establish a reference

standard that best fits the purposes of the study. This is important to consider in comparison of results. To capture the cause of fever in this thesis, across the intended-use population for which CRP-guided prescribing was expected to be used (non-severe AFI in outpatients) (54), laboratory analysis was complemented with an expert clinical panel review as was previously suggested (55) and done in the BFF-Dx study (95). In Paper IV, the performance characteristics of CRP was evaluated across several reference standards. Nine standards were used to classify the cause of fever as bacterial or non-bacterial. On one end of the spectrum the cause of fever was more confirmed, i.e., positive blood cultures, while on the other end was less confirmed, i.e., the final classification which included both microbiological results and expert clinical panel review. Stratifying the reference standard allowed for a more nuanced view of the findings and facilitates comparison of results with other studies. Little variation was seen across the spectrum.

7. Conclusions

This thesis reflects on both clinical and socio-behavioral aspects of diagnostics as a tool to improve antibiotic use and contain the spread of ABR and hopes to shine light on how the studies included, fall within the overall research and policy landscape of the global response to ABR.

This thesis highlights the challenges in determining the cause of AFI and shows that the classification of bacterial versus non-bacterial infections can be supported by combining laboratory methods with expert clinical review in a research environment. This study classified the majority of infections to be of non-bacterial similar to findings in febrile children and adults in other studies. The diversity of potential causes of fever which cannot be diagnosed on clinical grounds alone, calls for the development of point-of-care tests.

Overuse and misuse of antibiotics within and outside the OPDs are of major concern. Support to assist providers in improving their prescribing practices in line with the WHO AWaRe recommendations is needed. Monitoring of drug utilization by ATC class helps to scrutinize prescribing at a granular level in relation to treatment guidelines, while the WHO AWaRe classification system makes complex prescribing data easier to understand in relation to ABR and therefore can be a useful tool for policy makers. Both metrics play an important role in understanding and improving antibiotic use. While it is easy to say "don't use antibiotics when they are not needed", this thesis highlights the difficulties of knowing when they are, and when they are not, needed.

Tools to support the management and treatment of AFI and address ABR are greatly needed. As novel diagnostic platforms are being developed and legacy technologies tested in LMICs, it is essential to ensure the needs of their end-users are taken into consideration and that solutions are contextually appropriate. Furthermore, if we aim to support the adoption of diagnostics into sustainable clinical practice, especially in LMICs, guidance is needed to develop tailored implementation strategies.

To the best of our knowledge, this study is the first to address the diagnostic performance of CRP in outpatients presenting with AFI in India. We believe CRP is too weak as a single indicator of bacterial infection and does not on its own provide sufficient accuracy to assign a definite diagnosis and guide treatment decisions for febrile outpatients in India. We hope the data provided will facilitate discussion amongst researchers and global health professionals in the ongoing debate about CRP's utility to aid in differentiating bacterial from non-bacterial causes of infection and target antibiotic use in LMICs.

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10. Appendices

Appendix 1. Case report forms

Appendix 2. Interview topic guides

Appendix 3. Test specifications

Appendix 4. Case definitions

Appendix 5. Example summary case file

Appendix 6. Patient classification process and guidelines

Appendix 7. Supplementary antibiotic use data

Appendix 8. Example of the thematic analysis process

Appendix 9. Supplementary CRP analyses at additional reference standards

Appendix 1. Case report forms

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Case report form - Enrollment

Patient details	
OPD Number:	Interview Date__ __/__ __/__ __ __
Name:	Sex Male☐ Female☐
Age _____ years _____ months	Date of Birth. __ __/__ __/__ __ __ DK ☐
Address:	Contact Number:
Unique Identifier:	Pediatrics ☐ Medicine ☐

Vital signs

All patients

Pulse	SP02	Temp	RR	Wt
____/ min	___ %	____°C	____/min	___.__ kg

Children

Ht	MUAC
_____cm	___cm

Adults

Systolic BP	Diastolic BP	Ht
_____mmHg	_____mm Hg	__cm

Vaccination history

Has the subject been vaccinated according to EPI?	1.**Y**	0.**N**
If yes is the subject 1= Completed vaccination 2 = Partially vaccinated 98= Don't Know		

Presenting history

Symptoms	**If Yes duration (days)**		
Duration of illness			.....duration days
Fever	1.**Y**	2.**N**	.....duration days
Cough	1.**Y**	2.**N**	.....duration days
Chest pain	1.**Y**	0.**N**	.....duration days
Difficulty breathing	1.**Y**	0.**N**	.....duration days
Sneezing and rhinorrhoea	1.**Y**	0.**N**	.....duration days
Post nasal drip	1.**Y**	0.**N**	.....duration days
Sore throat	1.**Y**	0.**N**	.....duration days
Pain while swallowing	1.**Y**	0.**N**	.....duration days
Abdominal pains	1.**Y**	0.**N**	.....duration days
Vomiting	1.**Y**	0.**N**	.....duration days

Diarrhoea	1.**Y**	0.**N**	.....duration days
Blood in stool	1.**Y**	0.**N**	.....duration days
Convulsions	1.**Y**	0.**N**	.....duration days
Headache	1.**Y**	0.**N**	.....duration days
Neck stiffness	1.**Y**	0.**N**	.....duration days
Photophobia	1.**Y**	0.**N**	.....duration days
Joint pain or swelling	1.**Y**	0.**N**	.....duration days
Rash	1.**Y**	0.**N**	.....duration days
Redness of eyes	1.**Y**	0.**N**	.....duration days
Eye discharge	1.**Y**	0.**N**	.....duration days
Ear discharge	1.**Y**	0.**N**	.....duration days
Swelling behind ear	1.**Y**	0.**N**	.....duration days
Dysuria	1.**Y**	0.**N**	.....duration days
Urinary frequency or urgency	1.**Y**	0.**N**	.....duration days
Other symptoms	1.**Y**	0.**N**	
Other symptom 2, specify ……..	.....duration days		
Other symptom 1, specify ……..	.....duration days		

Treatment history

Prior antibiotic use during this illness	1.**Y**	0.**N**	98.**DK**

Antibiotic name	Dose in mg	Frequency	Route oral/IM/IV	Duration

Treatment start date	(dd/ mm/ yyyy)	
Treatment end date	(dd/ mm/ yyyy)	
Has the subject taken antimalarial?	1.**Y**	0.**N**
Has the subject taken antipyretic?	1.**Y**	0.**N**
Other treatment	1.**Y**	0.**N**

If other treatment **Yes**, specify
.....

Past medical history

Does the subject have Diabetes Mellitus?	1. **Y**	0. **N**	98 **DK**
Does the subject have TB?	1. **Y**	0. **N**	98 **DK**
Does the subject have chronic disease	1. **Y**	0. **N**	98 **DK**
If other chronic disease **Yes**, specify ……			

Physical examination

General appearance		
1 = Healthy looking (healthy/strong) 3 = Chronically sick-looking (prominent facial bones/emaciation) 2 = Acutely sick-looking (high fever/cardiopulmonary distress/prostrate)		
Peripheral signs of malnutrition		
Are there signs of malnutrition?	1. **Y**	0. **N**
Does the subject have hair colour change?	1. **Y**	0. **N**
Does the subject have oedema?	1. **Y**	0. **N**
Does the subject have skin lesions?	1. **Y**	0. **N**
Pharynx		
Does the subject have pharyngeal erythema	1. **Y**	0. **N**
Does the subject have pharyngeal enlargement	1. **Y**	0. **N**
Eyes		
Does the subject have conjunctival exudate	1. **Y**	0. **N**
Does the subject have conjunctival redness	1. **Y**	0. **N**
Mouth		
Does the subject have pain and swelling around teeth	1. **Y**	0. **N**
Lymphadenopathy		
Does the subject have lymphadenopathy	1. **Y**	0. **N**
Lymphadenopathy site 1 = Neck 2 = Submental 3 = Axilla 4 = Groin		
If Lymphadenopathy **Yes,** indicate size (in millimetres)		**……..mm**
Lungs		
Fast breathing	1. **Y**	0. **N**
Retractions	1. **Y**	0. **N**
Chest in drawing	1. **Y**	0. **N**

Wheeze	1.**Y**	0.**N**
Finger clubbing	1.**Y**	0.**N**
Dullness at percussion	1.**Y**	0.**N**
Crepitation	1.**Y**	0.**N**
Decreased air entry	1.**Y**	0.**N**
Other lung findings	1.**Y**	0.**N**
If **yes** specify ……		
Heart		
Pallor	1.**Y**	0.**N**
Jaundice	1.**Y**	0.**N**
Tachycardia	1.**Y**	0.**N**
Ejection murmur	1.**Y**	0.**N**
Other findings	1.**Y**	0.**N**
If other findings **yes,** specify ……		
Abdomen		
Tenderness	1.**Y**	0.**N**
Hepatomegaly	1.**Y**	0.**N**
Splenomegaly	1.**Y**	0.**N**
Fluid collection	1.**Y**	0.**N**
Other abdominal findings	1.**Y**	0.**N**
If **yes** specify ……		
Genitourinary		
Costovertebral angle tenderness	1.**Y**	0.**N**
Other genitourinary findings	1.**Y**	0.**N**
If **yes** specify ……		
Nervous system		
Positive meningeal signs	1.**Y**	0.**N**
Focal neurological deficit	1.**Y**	0.**N**
Other nervous system findings	1.**Y**	0.**N**
If **yes** specify ……		
Integumentary		
Impetigo >5mm on the face	1.**Y**	0.**N**

impetigo >10mmelsewhere	1.**Y**	0.**N**
Cellulites >5mm	1.**Y**	0.**N**
Abscess >5mm	1.**Y**	0.**N**
Dermatovesicular rash	1.**Y**	0.**N**
Other integumentary findings	1.**Y**	0.**N**
If **yes** specify ……		
Joint swelling	1.**Y**	0.**N**
If joint swelling **Yes,** specify location		
Any other findings		
Other findings	1.**Y**	0.**N**
If other findings **yes**, specify ……		

Presumed diagnosis

Presumed diagnosis ……		
Bacterial infection	1.**Y**	0.**N**
Viral infection	1.**Y**	0.**N**
Parasitic infection	1.**Y**	0.**N**
Non-infectious illness	1.**Y**	0.**N**
Unknown cause of illness	1.**Y**	0.**N**

Prescribed treatment

Prescribed treatment	1.**Y**	0.**N**
Antibiotics	1.**Y**	0.**N**
Specify antibiotics		

Antibiotic name	Dose in mg	Frequency	Route oral/IM/IV	Duration

Other types of treatment/care	1.**Y**	0.**N**
If other types of treatment/care, specify		

Study Assistant name _____
Study Assistant Signature _____ Date __/ __/ ____

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Case Report Form – Laboratory

PATIENT DETAILS	
OPD Number:	Interview Date__ __/__ __/__ __ __
Name:	Sex ☐ Male ☐ Female
Age _____ years _____ months	Date of Birth. __ __/__ __/__ __ __
Address:	Contact Number:
Unique Identifier:	☐Paediatrics ☐ Medicine

Study Assistant: Tick/fill in the requested information in the grey boxes
Lab Scientist: Tick/note the results at the appropriate place in the white boxes

STANDARD PANEL		
BLOOD		**Tubes collected:**❑Plain Tube❑ EDTA❑Blood Culture **Collection Time: _____Date: _____**
CRP		_____ mg/L
Hematology full blood count		Report attached? ❑YES ❑ NO
Peripheral smear for RBC and WBC morphology		Finding:
Malaria Microscopy		Finding:
Malaria RDT		❑Positive ❑Negative ❑Invalid
Typhidot RDT	IgG	❑Positive ❑Negative ❑Invalid
	IgM	❑Positive ❑Negative ❑Invalid
Dengue (if platelet count<1lac/m^3)	NS1	❑Positive ❑Negative ❑Invalid ❑NA
	IgG	❑Positive ❑Negative ❑Invalid ❑NA
	IgM	❑Positive ❑Negative ❑Invalid ❑NA
Blood culture	Site of draw:	Finding:
URINE		**Collection Time: _____Date: _____**
Urine dipstick		Leukocyte esterase ❑Positive ❑Negative ❑Invalid
		Nitrates ❑Positive ❑Negative ❑Invalid
Urine culture (if positive for leucocyte esterase and/or nitrates then urine culture)		Finding: ❑NA

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SYMPTOM BASED TESTING (Tick if required)			
RESPIRATORY PANEL	☐	Cough, and/or Sore throat, Physical exam findings consistent with pneumonia	
Swab collected: ❑YES ❑NO		**Collection Time: _____ Date: _____**	**Received by:**
Throat Swab		❑Positive ❑ Negative ❑Invalid	
Throat Swab (if Throat Swab positive)		Finding: ❑NA	
DIARRHEAL PANEL	☐	Stool frequency > 3 loose or liquid stools per day on at least one day in the week prior and or blood in stool.	
Stool Collected: ❑ YES ❑NO		**Collection Time: _____ Date: _____**	**Received by:**
Rotavirus RDT		❑Positive ❑ Negative ❑Invalid	
Direct stool microscopy		Finding: RBC: WBC:	
Stool culture		Finding:	
SKIN/JOINT/ASPIRATE	☐	Cutaneous lesion and/or joint effusion consistent with infectious arthritis, mucosal infection or ear discharge	
Type of sample collected:		**Collection Time: _____ Date: _____**	**Received by:**
Gram stain		Finding:	
Culture		Finding:	

COMMENTS

Study Assistant: _____ *Date completion:* __ __/__ __/__ __ __ __

Laboratory scientist: _____ Date completion: __ __/__ __/__ __ __ __

Review and diagnosis: _____ Date completion: __ __/__ __/__ __ __ __

First data entry: _____ Date completion: __ __/__ __/__ __ __ __

Second data entry: _____ Date completion: __ __/__ __/__ ____ __

UPPSALA UNIVERSITET

FIND
Because diagnosis matters

Case Report Form – Follow up

PATIENT DETAILS	
Unique Identifier:	Interview Date__ __/__ __/__ __ __
Name:	Age _____ years _____ months

PATIENT STATUS		
Follow up questions	Result	
Patient found	❑ Alive ❑ Dead	Note:
Time to resolution of illness:	_____ days	
Has the patient taken the prescribed treatment?	❑YES❑NO	Note:
Have any of the symptoms worsened?	❑YES ❑NO	Note:
Has the treatment been modified?	❑YES ❑NO	Note:
If YES, where have they sought care from?	❑ Self-medication ❑ Formal healthcare provider ❑ Informal healthcare provider	Note:
If YES, which medicine? • Ask if they have a prescription • If they do not, ask them to send a photo of the modified drugs		

Specify medicines

Medicine name	Dose in mg	Frequency	Route oral/IM/IV	Duration

Study Assistant: _____ Date completion: __ __/__ __/__ __ __ __

First data entry: _____ Date completion: __ __/__ __/__ __ __ __

Second data entry: _____ Date completion: __ __/__ __/__ __ __ __

FINAL REVIEW: _____ Date completion: __ __/__ __/__ __ __ __

Appendix 2. Interview topic guides

Topic Guide I
Interviews conducted at the hospital at the time of initial visit

1. **Why did you bring your child to RD Gardi Pediatric Outpatient Department?**

Potential probes:

- How long has the child been sick?
- How did you treat this child before coming to this hospital and why?
- Before coming to the hospital, have you taken the child for care somewhere else?

2. **What were the reasons for you to come to C. R. Gardi Hospital to get help for your sick child?**

3. **What were your expectations from this visit to this doctor? What would make you satisfied with your visit?**

Potential probes:

- For the doctor to find a cause of the illness?
- To receive advice?
- To be prescribed medicine?
- To have investigations done?

4. **The doctor gave you some advice and recommendations. What do you think and what will you do?**

Potential probes:

- Were you satisfied with your visit?
- Will you seek a second opinion?

5. **What do you think about investigations?**

Potential probes:

- What are your previous experiences with these investigations?
- Have you heard of anyone else doing these investigations?
- Are they helpful in figuring out the cause of illness?
- Are they necessary to make your child healthy?

6. **What would you be doing right now if you were not bringing this child here today?**

Potential probes:

- Have you taken time off work or lost income to bring the child here?
- How did you get here today and how long did it take you to get here today?

7. **What is your general opinion about the services provided at this hospital for children?**

Potential probes:

- General quality of services?
- Quality and efficacy of medicines?
- Knowledge, capacity, skills and experience of the doctors?
- Information sharing about the illness, diagnosis, treatment or referral?

8. **You were sent for investigations. What factors do you consider before getting investigations done?**

Potential probes:

- Cost of investigation?
- Type of investigation? (ex. X-rays/Ultra sound/blood tests?)
- Child's symptoms or illness severity?
- Child's age (infant or older child)?
- Time to get results and return to doctor?

Topic Guide I
Interviews conducted at the hospital at the time of initial visit

9. **In what ways, if any, could your experience at the pediatric outpatient department at this hospital be improved?**

10. **Do you have any other thoughts to share with me today?**

Additional/alternative questions for caregivers who had already done the investigations at the time of the interview:

11. **How was your experience getting the investigations done?**

Potential probes:

- How were you treated by the staff while getting the investigations done?
- Did they explain about the tests being done?
- Did they tell you about the amount of blood or sample to be taken?

12. **Tell me about how long it took from when the doctor sent you to get the investigations until the doctor told you what your child is sick with and what kind of treatment is needed?**

Potential probes:

- How long did you wait in line to get the samples taken?
- When you took the samples, how long did they say it would take for results?
- How long did you actually have to wait for results?
- Were you able to come back to the see the doctor at OPD on the same day or did you have to come back another day?

13. **What was the cost of getting the tests done? How much did you have to pay for the investigations?**

Potential probes:

- Do you think it was worth it?
- Why or why not?

Thank you for your time

Topic Guide II
Interviews conducted at home with caregivers who did not return for follow-up

1. **How is your child feeling today?**

Potential probes:

- How long has the child been sick?
- Is the child feeling better now?

2. **What did you think about your visit to RD Gardi hospital?**

Potential probes:

- What did you think about what the doctor told you?
- Were you satisfied with your visit?

3. **After your visit to RD Gardi Hospital, have you taken the child anywhere else for treatment?**

Potential probes:

- If yes, where?
- What did they do for your child?

4. **After your visit to RD Gardi Hospital, have you given any treatment to your child?**

Potential probes:

- Have you given your child any medicine? If yes, what did you give?
- Have you given your child any other treatment? If yes, what did you give?

5. **If your child is not becoming healthy, or the illness becomes more severe? What will you do?**

Potential probes:

- Will you take your child for treatment? Tell me more?
- Will you get the investigations done?

6. **In the general population, it is often seen that doctors are telling patients to get investigations done, but the patients are not getting them done.**
    - Do you think that is the case?
    - What do you think might be the reason for this?
    - Generally speaking, in your village, what do people think of investigations?

7. **In the general population, it is often seen that doctors are telling patients to get investigations done, and they are getting them done, but the patients are not coming back to OPD.**

Potential probes:

- Do you think that is the case?

8. **Do you have any other thoughts to share with me today?**

Additional/alternative questions for caregivers who had NOT done the investigations done at the time of the interview:

9. **When the doctor told you to get investigations, did they counsel you on the investigations?**

Potential probes:

- Did someone explain the need for the test?
- Did someone explain how the outcome of the test would change the management of the child?
- Did someone explain where the tests would be done?
- Did someone discuss with you what the costs of the test would be and if you could afford the cost?
- Did someone explain how long it would take to get the results back?

Topic Guide II
Interviews conducted at home with caregivers who did not return for follow-up

10. **You were sent for investigations. But we did not find any record of you getting those investigations done. What are the reasons you didn't get those investigations done?**

Potential probes:

- Cost of investigation?
- Type of investigation? (ex. X-rays/Ultra sound/blood tests?)
- Child's symptoms or illness severity?
- Child's age (infant or older child)?

11. **This time, you were not able to get the investigations done. What suggestions do you have so that you can get the investigations done next time?**

Additional/alternative questions for caregivers who had the investigations done but did not return for follow-up:

12. **You were sent for investigations. How was your experience getting the investigations done?**

Potential probes:

- How were you treated by the staff while getting the investigations done?
- Did they explain about the tests being done?
- Did they tell you about the amount of blood or sample to be taken?

13. **What was the cost of getting the tests done? How much did you have to pay for the investigations?**

Potential probes:

- Do you think it was worth it?
- Why or why not?

14. **Tell me about how long it took to get the investigations done?**

Potential probes:

- How long did you wait in line to get the samples taken?
- When you took the samples, how long did they say it would take for results?
- How long did you actually have to wait for results?

15. **And we found records that you had the investigations done and you collected the results but we did not notice you coming back to OPD. What are the reasons that you didn't you return to OPD?**

Potential probes:

- Was it an issue of time?
- Did you get the reports at the end of the day and OPD was closed?
- Would you have to come back another day to the hospital?
- What did you do with the reports of the investigations if you didn't take them to OPD?

16. **After having done the investigations, what do you think about investigations?**

Potential probes:

- Were they helpful in figuring out the cause of illness?
- Were they necessary to make your child healthy?

Thank you for your time

Appendix 3. Test specifications

Test	Company test name	Company Name	Manufacturer reported performance characteristics
CBC	Sysmex XNL 550 (6 Part Analyser)	Transasia Bio-Medicals Ltd, Daman, India	
CRP	Turbodyne CRP UV	Tulip Diagnostics (P) Ltd.	
Malaria RDT	Erbaqik Malaria Ag Pf/Pan Card	Transasia Bio-Medicals Ltd, Daman, India	sensitivity 97%, specificity 100%
ESR	Disposable E.S.R Pipette (With vacuum plug)	Unitek Scientific corporation Thane Bhiwandi oad Palghar Mumbai (Mahrashtra)	
Typhoid IgG, IgM (Rapid Test)	Onsite Rapid Test Typhoid IgG/IgM Rapid Test.	M/s. CTK Biotech, Inc 10110, Mesa Ring Road, San Diego, California USA	IgM: sensitivity 91%, specificity 99% IgG: sensitivity 93%, specificity 99%
Dengue	Dengue Day 1 Test. Rapid Visual test for detection of Dengue NS1 Antigen and differential detection of IgG & IgM Antibodies in Human Serum/Plasma.	J. Mitra & Company Pvt. Ltd. A 180181 Okhla Industrial area phase 1, New Delhi, India	NS1 Ag: sensitivity 96%, specificity 98% IgM /IgG: sensitivity95%, specificity 97%
Rotavirus	Rotavirus Group A Diagnostic Kit (Colloidal Gold Device)	Wantai Bio Pharm Import & Marketed in India by: IMMUNOSHOP INDIA PVT. LTL Jagdish Complex Dwarka New Delhi India	sensitivity 96%, specificity 99%
Urine (Leucocyte and Nitrate)	Multistix	Siemens Healthcare Private Limited Vadodara India	
Blood culture	Blood Culture FA Plus Bottle (For adult patients)	BioMerieux Inc. 100 Rodolphe Street Durham, North Carolina USA	
Blood culture	Blood Culture PF Plus Bottle (For pediatric patients)	BioMerieux Inc. 100 Rodolphe Street Durham, North Carolina USA	
Throat swab (collection tube)	Sterile Cotton swab PW003	HiMedia Laboratoreis Pvt. Ltd. 23 Vadhani Ind Est. LBS marg Mumbai 40086 India	
Urine culture	Sterile Uricol PW016	HiMedia Laboratoreis Pvt. Ltd. 23 Vadhani Ind Est. LBS marg Mumbai 40086 India	
Stool culture		HiMedia Laboratoreis Pvt. Ltd. 23 Vadhani Ind Est. LBS marg Mumbai 40086 India	

Appendix 4. Case definitions

Table 1: Classification of subjects as having "Bacterial" or "Non-bacterial" infections based on symptoms/signs and available confirmatory investigations

Test performed for	Sample	Classification	Diagnosis	Confirmed by the following test
All patients	Blood	Bacterial	Bacteremia	Positive blood culture with a bacterial pathogen. Agents considered as contaminants: Bacillus sp, Bacillus cereus, Corynebacterium sp, Micrococcus sp, Propionibacterium sp, Streptococcus viridans and coagulase-negative Staphylococcus (CNS).
	Blood	Bacterial	Typhoid	Positive culture for Salmonella
	Blood	Non-bacterial	Fungal Sepsis	Positive blood culture with yeast
	Blood	Non-bacterial	Malaria	Positive malaria RDT or peripheral smear for malarial parasite
	Blood	Non-bacterial	Dengue	Positive NS1 or Positive IgM or IgG against dengue
	Urine	Bacterial	Urinary tract infection	Positive leukocytes or nitrites on urine dipstick AND positive urine culture with non-contaminant bacteria other than mixed flora bacteria. Either the pure (single) or predominant growth of a uropathogen (*Enterobacteriaceae* and *Pseudomonadales*) at ≥105 colony-forming units (CFU)/mL.
Respiratory sympotoms	Throat swab	Bacterial	Upper respiratory tract infection	Positive culture from oropharyngeal throat swab
Gastro-intestinal symptoms	Stool	Bacterial	Gastroenteritis	Positive stool culture for: Clostridium difficile, Salmonella serovars, Bacillus cereus, Campylobacter spp, Yersinia enterocolitica, Vibrio spp, Aeromonas spp
	Stool	Non-bacterial	Rotavirus	Positive RDT for rotavirus
	Stool	Non-bacterial	Amoebic or parasitic gastroenteritis	Entamoeba histolytica, Ascari lumbricoids, Trichuris trichuria, Taenia species or Hookworm species on direct stool examination
Skin/ear/joint symptoms	Aspirate	Bacterial	Significant skin/ joint/ ear infection/ neck or dental abscess	Positive Gram stain for: Gram positive OR Gram negative OR rods OR cocci
	Aspirate	Non-bacterial	Significant skin/ joint/ ear infection/ neck or dental abscess	Positive Gram stain for fungus OR parasite

Appendix 5. Example summary case file

Patient Report Unique ID: 1001

Date of initial visit: 2019-06-03

1. Clinical Data

Demographic Information

Sex of patient:	Male	
Age of patient:	1	years

Symptoms

		Duration
Curent illness:	7	days
Fever:	7	days
Cough:	1	days
Vomiting:	2	days

Treatment history during this illness

Prior medicine use

Prior antimalarial use:	No	
Prior antipyretic use:	Yes	
Prior antibiotic use:	Yes	
Prior antibiotic treatment start date:	2019-05-26	
Prior antibiotic treatment end date:	2019-06-02	
Prior antibiotic 1 drug name:	AZITHROMYCIN	
Prior antibiotic 1 route:	Oral	
Prior antibiotic 1 dose:	100	mg
Prior antibiotic 1 frequency:	12	hours
Prior antibiotic 1 duration:	3	days

Past medical History

Vaccination status:	Completed vaccination	
Diabetes Mellitus?	No	
TB?	No	
Chronic disease?	No	

Physical Examination

Vital Signs measurement

Temperature:	37	°C
Respiratory rate:	42	pm
Pulse:	92	pm
SP02:	96	%

Anthropometry

Weight:	7.5	kg

Height:	80	cm
MUAC:	12.5	cm

Clinical Examination

General appearance:	Acutely sick looking
Signs of malnutrition:	Yes
Fast breathing:	Yes
Wheeze:	Yes
Pallor:	Yes

Prescribed Treatment

Prescribed antibiotics?	No

2. Laboratory Data

Standard Panel

Peripheral smear for RBC and WBC morphology:	MICROCYTIC HYPROCHRONIC RBC- MORPHOLOGY, LYMPHOCYTOSIS? REACTIV, THROMBOCYTOSIS? REACTIVE

HGB:	7	g/dL
WBC:	14	10^3/uL
NEUT:	18	%
LYMPH:	78	%
MONO:	4	%
EO:	0.6	%
BASO:	0.4	%
IG:	0.1	%
RBC:	6	10^6/uL
HCT:	28	%
MCV:	50	fL
MCH:	14	pg
MCHC:	27	g/dL
RDW-CV:	23	%
PLATELETS:	733	10^3/uL
ESR:	12	mm
Malaria Microscopy:	Negative	
Malaria RDT:	Negative	
Typhidot RDT IgG:	Negative	
Typhidot RDT IgM:	Negative	
Dengue NS1:	NA	
Dengue IgG:	NA	
Dengue IgM:	NA	
Blood culture growth:	No growth	

Urine Panel

Urine panel:	Yes
Leukocyte esterase:	Negative
Nitrates:	Negative

Respiratory Panel

Respiratory panel:	Yes
Swab collected:	Yes
Throat swab culture:	Negative

Diarrheal Panel

Dirrheal panel:	No

3. Follow-up Data

Time to resolution of illness:	3 days
Was prescribed treatment taken?	Yes
Have symptoms worsened?	No
Has the treatment been modified?	No

Appendix 6. Patient classification process and guidelines

POCT Study

Patient classification process and guidelines

Background

A lack of simple, inexpensive, and rapid diagnostic tests for febrile illnesses other than malaria leads to overtreatment with antibiotics for those who test negative for malaria, and contributes to the global rise in antimicrobial resistance. New tests for the detection of host biomarkers provide promising tools to differentiate bacterial from non-bacterial infections in febrile patients. However, most available biomarker tests are not currently used in resource-limited settings, and very few evaluations have been performed in low- and middle-income country (LMIC) populations with non-severe febrile illness. In order to evaluate the performance of these biomarker tests, the source of the fever needs to be identified as bacterial infection or non-bacterial infection for each febrile patient. Many different laboratory tests are performed in order to inform of the source of infection. However, even after having completed an extensive battery of microbiological tests, a large proportion of fevers will remain undiagnosed. For this reason, the combination of clinical and microbiological data reviewed by an independent panel provides a good compromise between quality and quantity of diagnostic data.

Objective

As a member of the clinical panel, your task is to review patient documentation (clinical and microbiological data) in order to classify each patient into the 3 categories: “bacterial infection”, “non- bacterial infection” or “indeterminate cause of fever”.

Study population

The set of patients includes 1000 patients. That data set has gone through the first round of classification resulting in X patients for round two of which X are pediatric and X are adults. Inclusion criteria were set as a patient between 2 months and 65 years presenting at the outpatient department with a fever of less than 14 days and no signs of severe illness.

Guidelines for second classification by the clinical panel

- You will be provided patient files with clinical and microbiological data.
- You will be provided an Excel file to report the classification group of each patient and if the patient should be recommended an antibiotic prescription or not.
    - Classification is restricted to the 3 following categories:
        - Bacterial infection
        - Non-bacterial infection
        - Indeterminate cause of fever
- Unique ID numbers have already been entered in the Excel file and cannot be modified.
- Any bacterial infections, regardless of co-infection should be classified as “Bacterial Infection”.

Appendix 5. Patient classification process and guidelines.

You can provide more information on the type of infection diagnosed as free text in the comments section available for each patient.

You do not need to follow any specific clinical guidelines to orientate your diagnosis.
If you have any questions or doubts, i.e. on the clinical data or the type of laboratory tests used, do not hesitate to contact Ashish Pathak ashish.pathak@ki.se

Patient classification is a 2-step process leading to the classification of patients.

1. First decision round: Electronical algorithm
Each study subject will be classified by the established cause of fever as either "bacterial," "non-bacterial," or "undefined" by an electronical algorithm based on patient symptoms and microbiological test results accordingly to predefined criteria. See below Table 1.

In brief, all subjects with positive blood, urine or stool culture results with a identified bacteria will be classified as "bacterial" and all subjects with a positive result for a recent arboviral infection and no bacterial infection detected, will be classified as "non-bacterial". Polymicrobial infections that include at least one pathogenic bacterium consistent with the subject's presentation will be classified as "bacterial," as the consequences for treatment and the impact on expression of bacterial markers would be expected to be the same as subjects with a unique microbiologic diagnosis of bacterial infection.

2. Second decision round: Clinical panel
A panel of three experts will review all study subjects classified in the first round as "Undefined". The experts will be provided with all patient history, clinical and microbiological data for each patient to guide their appraisal. Diagnosis provided by clinicians onsite and biomarker test results including CRP values will not be provided to the experts in order to not influence their judgement. Each expert will make an independent (blinded for the decisions of their peers) classification into one of the three categories, "bacterial," "non-bacterial," or "indeterminate".

Once all three independent classifications are established by each expert, all study subjects with a unanimous decision will be classified appropriately.
For all subjects with a non-unanimous decision, subjects will be classified as follows:
If all 3 experts disagree on the classification, these subjects will be considered as "indeterminate"
If 2/3 expert agree on "indeterminate", these subjects will be considered as "indeterminate"
If 2/3 expert agree with a classification of "bacterial," these subjects will be considered "probable bacterial infection"
If 2/3 experts agree with a classification of "non-bacterial", these subjects will be considered "probable non-bacterial"

Table 1. WHO ATC classification, AWaRe category, oral and parenteral Defined Daily Doses (DDDs).

Antibiotic Chemical Subgroup	ATC code	Antibiotic Type	AWaRe Category	DDDs Oral g	DDDs Parenteral g
Intestinal Antibiotics	A07AA11	Rifaximin	Watch	0.6	-
Tetracyclines	J01AA02	Doxycycline	Access	0.1	0.1
Penicillin with extended spectrum	J01CA04	Amoxicillin	Access	1.5	3
Combinations of penicillins*	J01CR02	Amoxicillin and clavulanic acid	Access	1.5	3
Second-generation cephalosporins	J01DC02	Cefuroxime	Watch	0.5	3
Third-generation cephalosporin	J01DD01	Cefotaxime	Watch	-	4
	J01DD02	Ceftazidime	Watch	-	4
	J01DD04	Ceftriaxone	Watch	-	2
	J01DD08	Cefixime	Watch	0.4	-
	J01DD13	Cefpodoxime	Watch	0.4	-
	J01DD64	Cefpodoxime proxetil and clavulanic acid	Not recommended	0.4	-
Monobactams	J01DF01	Aztreonam	Reserve	-	4
Macrolides	J01FA10	Azithromycin	Watch	-	0.5
Aminoglycosides	J01GB03	Gentamicin	Access	-	0.24
Fluoroquinolones	J01MA01	Ofloxacin	Watch	0.4	0.4
	J01MA02	Ciprofloxacin	Watch	1	0.8
	J01MA06	Norfloxacin	Watch	0.8	-
	J01MA12	Levofloxacin	Watch	0.5	0.5
Combinations of antibacterials	J01RA09	Ofloxacin and ornidazole	Not recommended	2 UD=2 tabs	-
	J01RA13	Norfloxacin and tinidazole	Unclassified	2 UD=2 tabs	-
	J01RAXX	Cefixime and azithromycin	Not recommended	2 UD=2 tabs	-
Glycopeptide antibacterials	J01XA01	Vancomycin	Watch	-	2
Imidazole/Nitroimidazole derivatives	J01XD01/P01AB01	Metronidazole	Access	2	1.5
Nitrofuran derivatives	J01XE01	Nitrofurantoin	Access	0.2	-

*including β-lactamase inhibitors

Table 2a. Distribution of patient reported antibiotic use before outpatient visit across age groups in years, according to the WHO AWaRe classification by encounters and percentage.

	<5 (n=17)		5-17 (n=8)		18-34 (n=36)		35-49 (n=13)		50-65 (n=9)		Total (n=83)	
AWaRe Category	n	%	n	%	n	%	n	%	n	%	n	%
Access	5.0	29.4%	4.0	50.0%	7.0	19.4%	3.0	23.1%	2.0	22.2%	21.0	25.3%
Watch	10.0	58.8%	4.0	50.0%	29.0	80.6%	10.0	76.9%	7.0	77.8%	60.0	72.3%
Reserve	-	-	-	-	-	-	-	-	-	-	-	-
Not recommended	2.0	11.8%	-	-	-	-	-	-	-	-	2.0	2.4%
Unclassified	-	-	-	-	-	-	-	-	-	-	-	-
Total	17.0		8.0		36.0		13.0		9.0		83.0	100.0%

Table 2b. Distribution of patient reported antibiotic prescription during outpatient visit across age groups in years, according to the WHO AWaRe classification by encounters and percentage.

	<5 (n=38)		5-17 (n=64)		18-34 (n=134)		35-49 (n=49)		50-65 (n=28)		Total (n=313)	
AWaRe Category	n	%	n	%	n	%	n	%	n	%	n	%
Access	9.0	23.7%	27.0	42.2%	66.0	49.3%	25.0	51.0%	15.0	53.6%	142.0	45.4%
Watch	28.0	73.7%	37.0	57.8%	64.0	47.8%	24.0	49.0%	12.0	42.9%	165.0	52.7%
Reserve	-	-	-	-	1.0	0.7%	-	-	-	-	1.0	0.3%
Not recommended	1.0	2.6%	-	-	2.0	1.5%	-	-	1.0	3.6%	4.0	1.3%
Unclassified	-	-	-	-	1.0	0.7%	-	-	-	-	1.0	0.3%
Total	38.0		64.0		134.0		49.0		28.0		313.0	100.0%

Table 2c. Distribution of patient reported antibiotic treatment modification after outpatient visit across age groups in years, according to the WHO AWaRe classification by encounters and percentage.

	<5 (n=11)		5-17 (n=27)		18-34 (n=36)		35-49 (n=13)		50-65 (n=2)		Total (n=89)	
AWaRe Category	n	(%)	n	%	n	%	n	%	n	%	n	%
Access	2.0	18.2%	13.0	48.1%	10.0	27.8%	4.0	30.8%	-	-	29.0	32.6%
Watch	9.0	81.8%	13.0	48.1%	25.0	69.4%	8.0	61.5%	2.0	100.0%	57.0	64.0%
Reserve	-	-	-	-	-	-	-	-	-	-	-	-
Not recommended	-	-	-	-	-	-	-	-	-	-	-	-
Unclassified	-	-	1.0	3.7%	1.0	2.8%	1.0	7.7%	-	-	3.0	3.4%
Total	11.0		27.0		36.0		13.0		2.0		89.0	100.0%

Table 3a. Distribution of patient reported antibiotic use before outpatient visit by age groups in years and WHO ATC class in Defined Daily Doses (DDD).

		<5 (n=17)		5-17 (n=8)		18-34 (n=36)		35-49 (n=13)		50-65 (n=9)		Total (n=83)	
Antibiotic Chemical Subgroup	Antibiotic Type	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%
Intestinal Antibiotics	Rifaximin	-	-	-	-	-	-	-	-	-	-	-	-
Tetracyclines	Doxycycline	-	-	-	-	18.0	13.6%	8.0	22.1%	2.0	8.2%	28.0	12.0%
Penicillin with extended spectrum	Amoxycillin	1.9	8.5%	-	-	5.0	3.8%	2.5	6.9%	2.0	8.2%	11.4	4.9%
Combinations of penicillins*	Amoxycillin and clavulanic acid	1.7	7.5%	7.2	35.9%	5.1	3.8%	0.8	2.3%	-	-	14.8	6.3%
Second-generation cephalosporins	Cefuroxime	-	-	-	-	1.6	1.2%	-	-	-	-	1.6	0.7%
Third-generation cephalosporin	Cefotaxime	-	-	-	-	-	-	0.5	1.4%	0.5	-	0.5	0.2%
	Ceftazidime	-	-	-	-	-	-	-	-	-	-	-	-
	Ceftriaxone	-	-	5.3	26.4%	-	-	-	-	-	-	5.3	2.2%
	Cefixime	0.5	2.2%	1.0	5.0%	27.0	20.4%	4.0	11.0%	3.0	12.4%	35.5	15.2%
	Cefpodoxime	3.3	14.4%	-	-	8.0	6.1%	-	-	-	-	11.3	4.8%
	Cefpodoxime proxetil and clavulanic acid	2.0	8.9%	-	-	-	-	-	-	-	-	2.0	0.9%
Monobactams	Aztreonam	-	-	-	-	-	-	-	-	-	-	-	-
Macrolides	Azithromycin	4.7	20.7%	2.5	12.6%	22.5	17.0%	3.3	9.2%	2.0	8.2%	35.0	15.0%
Aminoglycosides	Gentamicin	-	-	-	-	-	-	-	-	-	-	-	-
Fluoroquinolones	Ofloxacin	3.5	15.6%	-	-	18.0	13.6%	3.0	8.3%	3.0	12.4%	27.5	11.8%
	Ciprofloxacin	-	-	-	-	26.1	19.7%	14.0	38.7%	2.0	8.2%	42.1	18.0%
	Norfloxacin	-	-	-	-	-	-	-	-	6.0	24.7%	6.0	2.6%
	Levofloxacin	-	-	4.0	20.1%	-	-	-	-	4.0	16.5%	8.0	3.4%
Combinations of antibacterials	Ofloxacin and ornidazole	5.0	22.2%	-	-	-	-	-	-	-	-	5.0	2.1%
	Norfloxacin and tinidazole	-	-	-	-	-	-	-	-	-	-	-	-
	Cefixime and azithromycin	-	-	-	-	-	-	-	-	-	-	-	-
Glycopeptide antibacterials	Vancomycin	-	-	-	-	-	-	-	-	-	-	-	-
Imidazole/Nitroimidazole derivatives	Metronidazole	-	-	-	-	0.4	0.3%	-	-	-	-	0.4	0.2%
Nitrofuran derivatives	Nitrofurantoin	-	-	-	-	-	-	-	-	-	-	-	-
Total		22.5		19.9		131.6		36.2		24.5		234.2	100%

*including β-lactamase inhibitors

Table 3b. Distribution of antibiotic prescription at outpatient visit across age groups in years and WHO ATC class in Defined Daily Doses (DDD).

		<5 (n=38)		5-17 (n=64)		18-34 (n=134)		35-49 (n=49)		50-65 (n=28)		Total (n=313)	
Antibiotic Chemical Subgroup	Antibiotic Type	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%
Intestinal Antibiotics	Rifaximin	-	-	-	-	-	-	-	-	-	-	-	-
Tetracyclines	Doxycycline	-	-	-	-	202.0	26.9%	48.0	19.8%	26.0	21.3%	276.0	19.5%
Penicillin with extended spectrum	Amoxycillin	0.5	0.5%	-	-	-		-	-	-	-	0.5	0.0%
Combinations of penicillins*	Amoxycillin and clavulanic acid	7.8	7.7%	45.7	21.9%	157.3	20.9%	68.8	28.4%	35.3	28.9%	314.9	22.3%
Second-generation cephalosporins	Cefuroxime	-	-	-	-	2.4	0.3%	6.0	2.5%	-	-	8.4	0.6%
Third-generation cephalosporin	Cefotaxime	-	-	-	-	2.2	0.3%	1.8	0.7%	2.5	2.0%	6.5	0.5%
	Ceftazidime	-	-	-	-	-		0.4	0.2%	-	-	0.4	-
	Ceftriaxone	0.3	0.3%	-	-	5.0	0.7%	1.0	0.4%	-	-	6.3	0.4%
	Cefixime	20.4	20.2%	54.5	26.2%	57.5	7.7%	5.5	2.3%	7.5	6.1%	145.4	10.3%
	Cefpodoxime	1.3	1.2%	-	-	8.0	1.1%	8.1	3.4%	-	-	17.4	1.2%
	Cefpodoxime proxetil and clavulanic acid	-	-	-	-	7.5	1.0%	-	-	-	-	7.5	0.5%
Monobactams	Aztreonam	-	-	-	-	0.8	0.1%	-	-	-	-	0.8	-
Macrolides	Azithromycin	54.7	54.1%	100.0	48.0%	188.0	25.0%	43.4	17.9%	5.0	4.1%	391.1	27.7%
Aminoglycosides	Gentamicin	-	-	-	-	-		-	-	-	-	0.0	0.0%
Fluoroquinolones	Ofloxacin	5.5	5.4%	7.0	3.4%	6.0	0.8%	2.5	1.0%	-	-	21.0	1.5%
	Ciprofloxacin	-	-	-	-	37.0	4.9%	26.1	10.8%	8.6	7.0%	71.7	5.1%
	Norfloxacin	-	-	-	-	21.0	2.8%	9.0	3.7%	24.5	20.0%	54.5	3.9%
	Levofloxacin	3.0	3.0%	-	-	-		-	-	-	-	3.0	0.2%
Combinations of antibacterials	Ofloxacin and ornidazole	5.0	5.0%	-	-	-		-	-	5.0	4.1%	10.0	0.7%
	Norfloxacin and tinidazole	-	-	-	-	3.0	0.4%	-	-	-	-	3.0	0.2%
	Cefixime and azithromycin	-	-	-	-	5.0	0.7%	-	-	-	-	5.0	-
Glycopeptide antibacterials	Vancomycin	1.1	1.1%	-	-	-		-	-	-	-	1.1	0.1%
Imidazole/Nitroimidazole derivatives	Metronidazole	1.5	1.5%	1.2	0.6%	38.2	5.1%	18.8	7.8%	7.8	6.4%	67.5	4.8%
Nitrofuran derivatives	Nitrofurantoin	-	-	-	-	10.5	1.4%	3.0	1.2%	-	-	13.5	1.0%
Total		101.0		208.4		751.3		242.4		122.2		1425.3	100%

*including β-lactamase inhibitors

Table 3c. Distribution of patient reported antibiotic treatment modification after outpatient visit across age groups in years and WHO ATC class in Defined Daily Doses (DDD).

		<5 (n=11)		5-17 (n=27)		18-34 (n=36)		35-49 (n=13)		50-65 (n=2)		Total (n=89)	
Antibiotic Chemical Subgroup	Antibiotic Type	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%
Intestinal Antibiotics	Rifaximin	-	-	-	-	6.7	3.2%	-	-	-	-	6.7	1.7%
Tetracyclines	Doxycycline	-	-	-	-	-	-	-	-	-	-	-	-
Penicillin with extended spectrum	Amoxycillin	-	-	1.0	1.5%	3.3	1.6%	-	-	-	-	4.3	1.1%
Combinations of penicillins*	Amoxycillin and clavulanic acid	1.5	4.2%	20.0	30.0%	22.5	10.8%	12.5	21.9%	-	-	56.5	14.3%
Second-generation cephalosporins	Cefuroxime	-	-	-	-	-	-	-	-	-	-	-	-
Third-generation cephalosporin	Cefotaxime	3.8	10.6%	-	-	3.8	1.8%	-	-	-	-	7.5	1.9%
	Ceftazidime	-	-	-	-	-	-	-	-	-	-	-	-
	Ceftriaxone	-	-	-	-	-	-	-	-	-	-	-	-
	Cefixime	-	-	17.5	26.2%	6.0	2.9%	6.0	10.5%	3.0	50.0%	32.5	8.2%
	Cefpodoxime	3.1	8.9%	-	-	-	-	-	-	-	-	3.1	0.8%
	Cefpodoxime proxetil and clavulanic acid	-	-	-	-	-	-	-	-	-	-	-	-
Monobactams	Aztreonam	-	-	-	-	-	-	-	-	-	-	-	-
Macrolides	Azithromycin	12.5	35.4%	25.8	38.7%	132.3	63.8%	25.0	43.9%	-	-	195.7	49.6%
Aminoglycosides	Gentamicin	3.4	9.7%	-	-	-	-	-	-	-	-	3.4	0.9%
Fluoroquinolones	Ofloxacin	5.0	14.2%	-	-	7.5	3.6%	-	-	-	-	12.5	3.2%
	Ciprofloxacin	-	-	2.4	3.6%	20.7	10.1%	3.0	5.3%	3.0	50.0%	29.1	7.4%
	Norfloxacin	-	-	-	-	4.5	2.2%	10.5	18.4%	-	-	15.0	3.8%
	Levofloxacin	9.8	17.0%	-	-	-	-	-	-	-	-	9.8	2.5%
Combinations of antibacterials	Ofloxacin and ornidazole	-	-	-	-	-	-	-	-	-	-	-	-
	Norfloxacin and tinidazole	-	-	4.0	-	4.0	-	3.0	-	-	-	11.0	2.8%
	Cefixime and azithromycin	-	-	-	-	-	-	-	-	-	-	-	-
Glycopeptide antibacterials	Vancomycin	-	-	-	-	-	-	-	-	-	-	-	-
Imidazole/Nitroimidazole derivatives	Metronidazole	-	-	0.6	-	3.0	-	3.8	-	-	-	7.4	1.9%
Nitrofuran derivatives	Nitrofurantoin	-	-	-	-	-	-	-	-	-	-	-	-
Total		39.1		71.4		214.3		63.8		6.0		394.5	100%

*including β-lactamase inhibitors

Table 4. Distribution of antibiotic encounters for all 1000 patients by presumptive diagnosis and AWaRe category, in encounters and percentages.

	Presumptive diagnosis																	
	AVI (n=601)		UTI (n=117)		URTI (n=92)		LRTI (n=58)		Gastro. (n=58)		Typhoid (n=40)		Malaria (n=15)		Other* (n=19)		Total (n=1000)	
AWaRe Category	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Access	50.0	8.3%	34.0	29.1%	22.0	23.9%	13.0	22.4%	10.0	17.2%	6.0	15.0%	5.0	33.3%	2.0	10.5%	143.5	14.3%
Watch	79.0	13.1%	28.0	23.9%	17.0	18.5%	13.0	22.4%	11.0	19.0%	10.0	25.0%	2.0	13.3%	5.0	26.3%	166.4	16.6%
Reserve	1.0	0.2%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.0	-
Not recommended	2.0	0.3%	-	-	1.0	1.1%	-	-	1.0	1.7%	-	-	-	-	-	-	4.0	-
Unclassified	-	-	1.0	0.9%	-	-	-	-	-	-	-	-	-	-	-	-	1.0	-
Sub-total AWaRe	132.0	22.0%	63.0	53.8%	40.0	43.5%	26.0	44.8%	22.0	37.9%	16.0	40.0%	7.0	46.7%	7.0	36.8%	313.0	31.3%
No antibiotics	469	78.0%	54.0	46.2%	52.0	56.5%	32.0	55.2%	36.0	62.1%	24.0	41.4%	8.0	53.3%	12.0	63.2%	687.0	68.7%

AVI-Acute viral illness, UTI - urinary tract infection, URTI - Upper respiratory tract infection, LRTI - Lower respiratory tract infection, Gastro. - Gastroenteritis

*Other includes tuberculosis, appendicitis, severe acute malnutrition, rheumatic heart disease, abscess and septic arthritis

Table 5. Distribution of antibiotics for all patients prescribed antibioitcs at outpatient visit by presumptive diagnosis and ATC class in defined daily doses (DDDs).

		AVI (n=132)		UTI (n=63)		URTI (n=40)		LRTI (n=26)		Gastro. (n=22		Typhoid (n=1		Malaria (n=7)		Other (n=7)		Total (n=313)	
Antibiotic Chemical Subgroup	Antibiotic Type	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%
Intestinal Antibiotics	Rifaximin	-		-		-		-	-	-	-	-	-	-	-	-	-	0.0	0.0%
Tetracyclines	Doxycycline	112.0	17.4%	92.0	30.4%	20.0	12.2%	-	-	20.0	25.0%	24.0	26.8%	2.0	9.6%	6.0	15.3%	276.0	19.5%
Penicillin with extended spectrum	Amoxycillin	0.5	0.1%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.5	0.0%
Combinations of penicillins*	Amoxycillin and clavulanic acid	118.5	18.5%	57.8	19.1%	63.7	38.9%	34.8	40.1%	13.7	17.1%	6.1	6.8%	11.7	55.8%	8.8	22.4%	314.9	22.3%
Second-generation cephalosporins	Cefuroxime	2.4	0.4%	-	-	-	-	-	-	-	-	6.0	6.7%	-	-	-	-	8.4	0.6%
Third-generation cephalosporin	Cefotaxime	2.7	0.4%	-	-	3.8	2.3%	-	-	-	-	-	-	-	-	-	-	6.4	0.5%
	Ceftazidime	0.4	0.1%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.4	0.0%
	Ceftriaxone	3.0	0.5%	-	-	-	-	-	-	0.3	0.3%	-	-	-	-	3.0	7.7%	6.3	0.4%
	Cefixime	50.5	7.9%	40.5	13.4%	7.1	4.4%	5.5	6.4%	6.0	7.5%	18.8	20.9%	6.0	28.7%	11.0	28.1%	145.4	10.3%
	Cefpodoxime	12.4	1.9%	5.0	1.6%	-	-	-	-	-	-	-	-	-	-	-	-	17.4	1.2%
	Cefpodoxime proxetil and clavulanic	7.5	1.2%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7.5	0.5%
Monobactams	Aztreonam	0.8	0.1%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.8	0.1%
Macrolides	Azithromycin	261.3	40.7%	8.3	2.7%	54.5	33.3%	39.2	45.2%	-	-	21.0	23.4%	-	-	6.7	17.1%	391.0	27.7%
Aminoglycosides	Gentamicin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.0	0.0%
Fluoroquinolones	Ofloxacin	14.0	2.2%	-	-	2.5	1.5%	-	-	4.5	5.6%	-	-	-	-	-	-	21.0	1.5%
	Ciprofloxacin	40.0	6.2%	3.0	1.0%	1.2	0.7%	3.0	3.5%	19.5	24.4%	5.0	5.6%	-	-	-	-	71.7	5.1%
	Norfloxacin	-	-	54.5	18.0%	-	-	-	-	-	-	-	-	-	-	-	-	54.5	3.9%
	Levofloxacin	-	-	-	-	-	-	3.0	3.5%	-	-	-	-	-	-	-	-	3.0	0.2%
Combinations of antibacterials	Ofloxacin and ornidazole	5.0	0.8%	-	-	-	-	-	-	5.0	6.3%	-	-	-	-	-	-	10.1	0.7%
	Norfloxacin and tinidazole	-	-	3.0	1.0%	-	-	-	-	-	-	-	-	-	-	-	-	3.0	0.2%
	Cefixime and azithromycin	-	-	-	-	5.0	3.1%	-	-	-	-	-	-	-	-	-	-	5.0	0.4%
Glycopeptide antibacterials	Vancomycin	-	-	-	-	-	-	1.1	1.3%	-	-	-	-	-	-	-	-	1.1	0.1%
Imidazole/Nitroimidazole derivatives	Metronidazole	11.2	1.7%	25.5	8.4%	6.0	3.7%	-	-	11.0	13.8%	8.8	9.8%	1.2	5.7%	3.8	9.7%	67.5	4.8%
Nitrofuran derivatives	Nitrofurantoin	-	-	13.5	4.5%	-	-	-	-	-	-	-	-	-	-	-	-	13.5	1.0%
Total		642.1	45.0%	303.1	21.3%	163.7	11.5%	86.6	6.1%	79.9	5.6%	89.7	6.3%	20.9	1.5%	39.2	2.8%	1425.3	100.0%

*including β-lactamase inhibitors

AVI - Acute viral illness, UTI - urinary tract infection, URTI - Upper respiratory tract infection, LRTI - Lower respiratory tract infection.

Other includes tuberculosis, appendicitis, severe acute malnutrition, rheumatic heart disease, abscess and septic arthritis

Appendix 8. Example of the thematic analysis process

Theme 1: Diagnostic acceptability waivers on caregiver preference and assessment of need	
Data extract	Category
"After tests, we come to know what the problem is. The doctor can understand the disease with the help of tests. […] He will give treatment according to diagnosis." - Father age 35, interview 11	Understand the purpose and importance of the tests
"We came here because here there is treatment of every disease. Doctors can detect the problem of the patient properly. When we go somewhere else, they only give the medicine and send us back." -Mother age 40, interview 18	Trust in care and treatment
"The doctor told for a blood test, but I thought my child is looking normal and is having slight cough and cold, so there is no need for test." -Mother age 28, interview 41	Severity of illness
"I thought that the prescribed bottle of medicine would give him relief, so I avoided the tests." -Mother age 34, interview 34	Preference for medicines instead of tests

Theme 2: Organization of diagnostic services inadequately meets caregiver needs	
Data extract	Category
"If they can explain what is written on the doctor's slip, which room we should go to, then the person coming to the hospital will not need to wander here and there in search of the correct place to get their work done." -Mother age 28, interview 37	Navigating the way around the hospital
"Sometimes there is a waiting of 25-50 patients. So poor people have to keep waiting for hours there hungry and thirsty, sometimes they go home before their turn comes. […] If we can collect reports on the same day then it will be good. Its ok to wait 1-2 hours, but same day is important." -Mother age 37, interview 42	Long lines, waiting times, and the need to return
"I came from 100km away to get tests done for my child, and I need to go back and travel the same distance, if they will give the test report on time then the patients can reach their home in a timely manner." -Father age 35, interview 2	Limited transportation options
"Some caregivers show the report to another hospital staff sitting at ground floor and ask 'Is there any problem in test report?'. If she says 'No', the patient will take only medicine and will go home." -Mother age 34, interview 34	Reports shown to hospital staff other than the physician from initial visit
"We do not have time to come again and again to the hospital, if we keep on doing this who will do our work?" -Mother age 30, interview 32	Competing priorities and obligations

Theme 3: Direct and indirect costs of diagnostics impact affordability for caregivers	
Data extract	Category
"Today I did not take my child for the test because I did not have money. If I manage money by tomorrow I will come for the test." -Mother age 40, interview 18	Cost of diagnostic tests
"For one trip we need to burn up petrol of 150 rupees and if we need to return two to three times then it will cause great loss." -Mother age 36 interview 14	Travel expenses
"I am a daily wage labourer. We lost our daily wages coming here. If we will not work how will we earn?" -Father age 38, interview 15	Lost wages
"Patients get the tests done at RD Gardi Medical College and then show them to other doctors at private clinics. Tests we can have from anywhere we want." -Mother age 37, interview 42	Combining providers to maximize care for limited resources

Table 1 Reference standards applied ranging from more confirmed cases, positive blood culture to less confirmed, classified cases (including all positive culture and rapid diagnostic test (RDT) results together with clinical panel review) on the right.

Reference standard	Description	N	Classification	
			Non-bacterial	Bacterial
Blood culture positive	Positive blood culture *vs.* all other cases. See supplementary file S2 Table 2 for details on bacterial isolates.	962	922	40
Urine culture positive	Positive urine culture *vs.* all other cases. See supplementary file S2 Table 2 for details on bacterial isolates.	962	906	94
All culture positive	All positive blood culture *vs.* all other cases. See supplementary file S2 Table 2 for details on bacterial isolates.	962	824	138
Laboratory classification	Microscopy/gram stain/culture or IgM/IgG/NS1 antigen detection by RDT. See supplementary file S2 Table 2 for details on bacterial isolates and Table 3 for combined culture and RDT results.	153	15	138
Unanimous clinical panel classification	Cases without a laboratory classification had their case files reviewed by an expert panel of three clinicians. Cases with a unanimous classification by all three panel members received the appropriate classification accordingly.	581	558	23
Reassessment clinical panel classification	Cases without a laboratory classification or unanimous clinical panel classification had their case files reassessed by the expert panel of three clinicians. Cases which were categorized as indeterminate or received non-unanimous classifications in the first round of review were discussed by the panel as a whole, until the panel members came to a consensus. Cases received the appropriate classification accordingly.	228	145	83
Aggregate clinical panel classification	A combined classification of all cases that did not have a laboratory classification and were classified by the panel. Includes cases classified with a unanimous clinical panel classification and cases classified with a reassessment clinical panel classification.	809	703	106
Laboratory classification and unanimous panel classification	A combined classification of all cases with a laboratory classification and all cases with a unanimous clinical panel classification.	734	573	161
Final classification	A combined classification including all cases i.e., cases with a laboratory classification, plus the aggregate clinical panel classification.	962	718	244

Table 2 Species of bacterial isolates recovered on culture among 962 patients, by clinical specimen cultured.

		Blood		Urine		Nasopharyngeal		Stool		Ear/Joint	
	Total	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults
Cultures conducted	n=1712	n=483	n=479	n=58	n=92	n=305	n=187	n=12	n=9	n=3	n=1
Gram-negative											
Escherichia coli	52	-	-	15	37	-	-	-	-	-	-
Pseudomonas aeruginosa	29	1	4	6	17	-	-	-	-	1	-
Klebsiella pneumoniae	17	3	-	12	1	1	-	-	-	-	-
Salmonella Typhi	9	5	4	-	-	-	-	-	-	-	-
Sphingomonas paucimobilis	6	1	-	-	-	-	5	-	-	-	-
Salmonella Paratyphi A	2	-	2	-	-	-	-	-	-	-	-
Acientobacter lwoffii	2	1	1	-	-	-	-	-	-	-	-
Escherichia vulneris	2	-	2	-	-	-	-	-	-	-	-
Acinetobacter baumannii	1	-	-	1	-	-	-	-	-	-	-
Enterobacter spp	1	-	-	-	1	-	-	-	-	-	-
Enterobacter cloacae	1	-	-	1	-	-	-	-	-	-	-
Citrobacter freundii	1	-	-	-	1	-	-	-	-	-	-
Brucella melitensis	1	-	1	-	-	-	-	-	-	-	-
Pantoea	1	-	-	1	-	-	-	-	-	-	-
Proteus mirabilis	1	-	-	1	-	-	-	-	-	-	-
Shigella sonnei	1	-	-	-	-	-	-	1	-	-	-
Gram-positive											
Staphylococcus aureus	17	5	9	-	-	-	-	-	-	2	1
Streptococcus spp	1	1	-	-	-	-	-	-	-	-	-
Organisms possibly causing fever	140	17	23	37	57	1	0	1	0	3	1

Data are no. of total clinical cultures.

Table 3 Laboratory classification of cause of fever in children and adults as bacterial or non-bacterial by single and co-infections.

Laboratory classification	Children N=63	Adults N=90	Total N=153
Bacterial n=138			
Single infections			
Urine culture positive	35	56	91
Blood culture positive	15	22	37
Ear/joint culture positive	3	1	4
Nasopharyngeal culture positive	1	0	1
Stool culture positive	1	0	1
Co-infections			
Blood and urine culture positive	1	1	2
Blood culture positive and malaria	1	0	1
Urine culture positive and rotavirus	1	0	1
Non-bacterial n=15			
Rotavirus	5	6	11
Dengue	0	4	4

Table 4 Median, interquartile range (in mg/L), and area under the receiver operating curve for CRP at all the reference standards.

Reference standard	n	Median	IQR	*p*-value	AUC	95% CI
Blood culture						
Bacterial	40	4.45	1.93 - 27.47	0.0848	0.58	0.47 - 0.69
Non-bacterial	922	2.79	2.06 - 7.14			
Urine culture						
Bacterial	94	3.72	2.18 - 17.55	0.0077	0.58	0.52 - 0.65
Non-bacterial	868	2.79	2.05 - 6.88			
All positive cultures						
Bacterial	138	3.77	2.11 - 23.45	0.0013	0.59	0.53 - 0.64
Non-bacterial	824	2.76	2.06 - 6.24			
Laboratory classification						
Bacterial	138	3.77	2.11 - 23.45	0.4652	0.58	0.42 - 0.70
Non-bacterial	15	2.79	1.93 - 7.14			
Unanimous clincial panel classification						
Bacterial	23	3.04	2.09 - 20.96	0.0324	0.63	0.50 - 0.77
Non-bacterial	558	2.67	2.02 - 4.48			
Reassessment clinical panel classification						
Bacterial	83	2.89	2.24 - 23.18	0.1981	0.55	0.47 - 0.63
Non-bacterial	145	2.79	2.12 - 13.09			
Aggregate clinical panel classification						
Bacterial	106	2.97	2.24 - 23.14	0.0002	0.61	0.55 - 0.67
Non-bacterial	703	2.71	2.04 - 5.69			
Laboratory and unanimous clinical panel classification						
Bacterial	161	3.72	2.11 - 23.18	0.0000	0.62	0.56 - 0.67
Non-bacterial	573	2.68	2.02 - 4.50			
Final classification						
Bacterial	244	3.56	2.20 - 23.18	0.0000	0.60	0.56 - 0.65
Non-bacterial	718	2.72	2.04 - 5.71			

p-value for comparison of medians between bacterial and non-bacterial infection

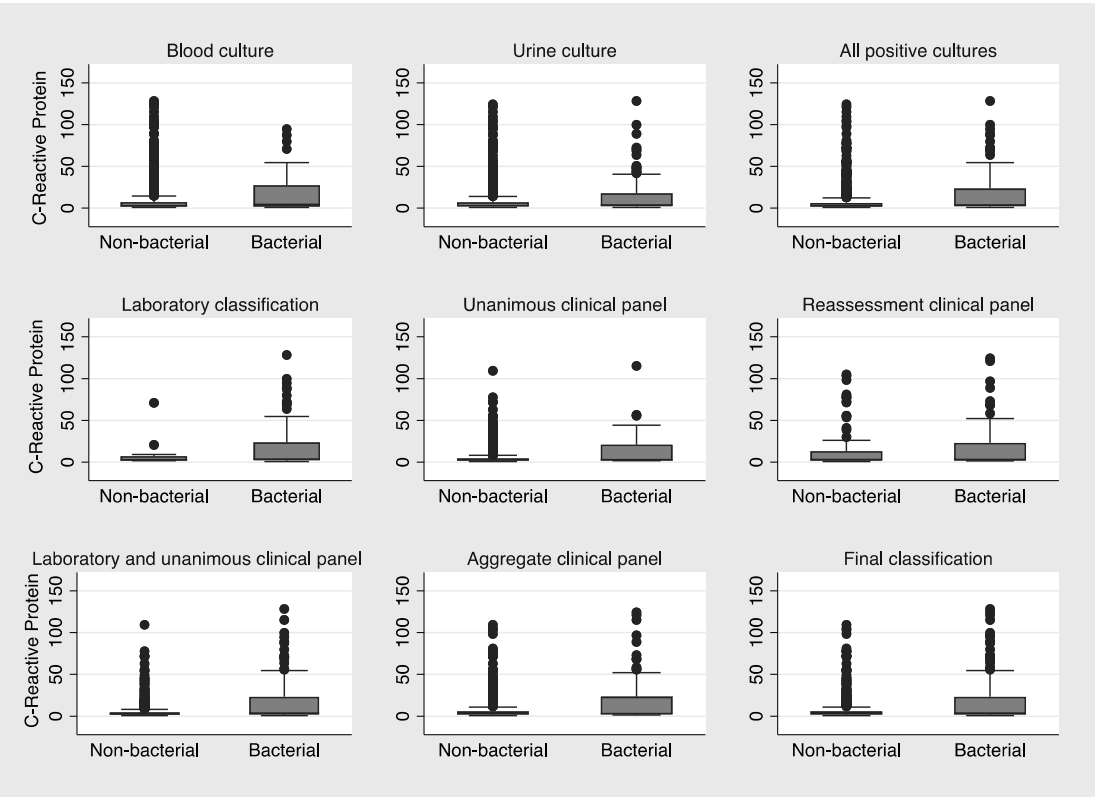

Figure 1 C-reactive protein (CRP) concentration (mg/L) for bacterial and non-bacterial cause of fever for all reference standards in Ujjain, central India in 2019. Box boundaries show 25th and 75th percentiles of CRP concentrations and lines within the boxes show the medians. The whiskers indicate the 10th and 90th percentile of CRP concentrations.

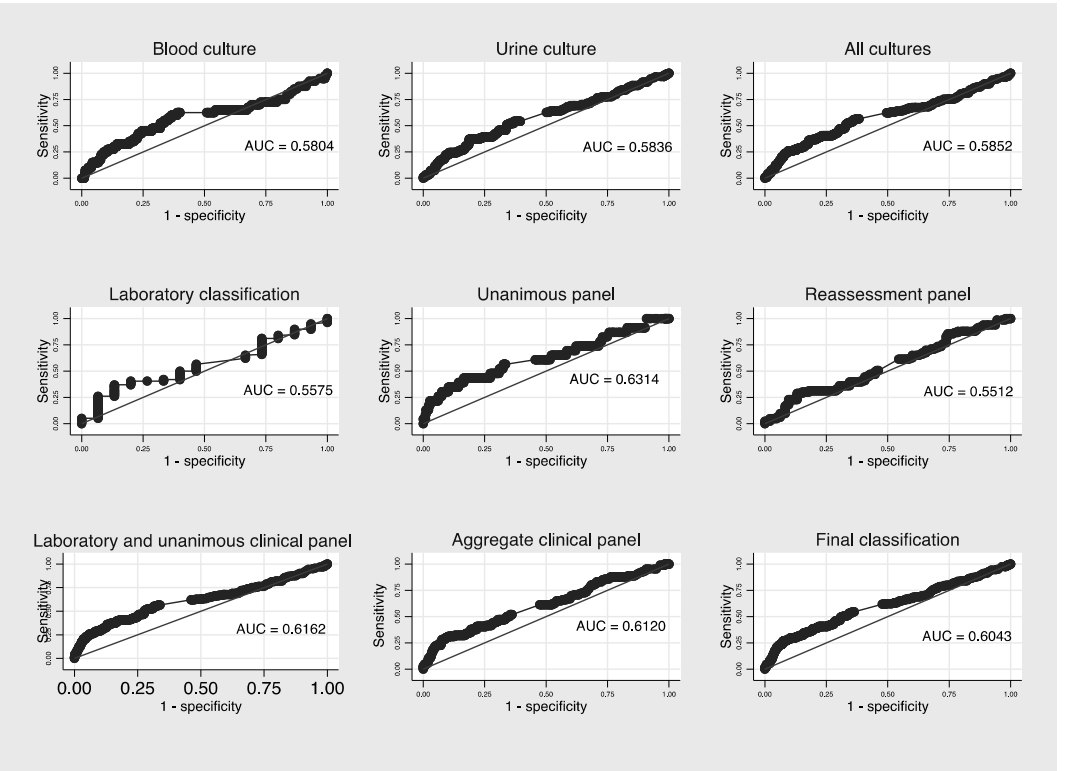

Figure 2 Receiver operating curve for CRP to discriminate between bacterial and non-bacterial cause of fever for all reference standards in Ujjain, central India in 2019. On the horizontal axis is the sensitivity of the biomarkers and on the vertical axis is the false positive rate (1-specificity).

Table 5 Comparison of the area under the receiver operating curve for children vs adults, prior antibiotics or not, and fever duration of greater than one day or not for the reference standards blood culture and final classification.

Reference standard		n	AUC	95% CI			*p*
Blood culture	Children	483.00	0.61	0.44	-	0.78	0.6234
	Adults	479.00	0.55	0.41	-	0.70	
	No antibiotic	883.00	0.57	0.45	-	0.70	0.9348
	Antibiotic	79.00	0.56	0.33	-	0.79	
	Fever >1 day	904.00	0.57	0.46	-	0.69	0.0051
	Fever 1 day	58.00	0.79	0.69	-	0.90	
Urine culture	Children	493.00	0.62	0.51	-	0.73	0.3181
	Adults	479.00	0.55	0.46	-	0.00	
	No antibiotic	883.00	0.58	0.51	-	0.65	0.3874
	Antibiotic	79.00	0.68	0.46	-	0.90	
	Fever >1 day	904.00	0.59	0.52	-	0.65	0.7306
	Fever 1 day	58.00	0.51	0.06	-	0.95	
All positive cultures	Children	483.00	0.63	0.54	-	0.72	0.1471
	Adults	479.00	0.54	0.47	-	0.62	
	No antibiotic	883.00	0.58	0.52	-	0.64	0.9599
	Antibiotic	79.00	0.59	0.41	-	0.76	
	Fever >1 day	904.00	0.59	0.53	-	0.64	0.9619
	Fever 1 day	58.00	0.58	0.23	-	0.93	
Laboratory classification	Children	63.00	0.38	0.16	-	0.59	0.0470
	Adults	90.00	0.65	0.48	-	0.81	
	No antibiotic	135.00	0.55	0.40	-	0.69	N/A
	Antibiotic	18.00	N/A	N/A	-	N/A	
	Fever >1 day	146.00	0.61	0.47	-	0.75	0.3070
	Fever 1 day	7.00	0.33	0.00	-	0.84	
Unanimous clincial panel classification	Children	343.00	0.84	0.69	-	1.00	0.0063
	Adults	238.00	0.53	0.36	-	0.69	
	No antibiotic	541.00	0.64	0.49	-	0.80	0.3504
	Antibiotic	40.00	0.48	0.17	-	0.79	
	Fever >1 day	540.00	0.63	0.49	-	0.76	N/A
	Fever 1 day	41.00	N/A	N/A	-	N/A	

Reference standard		n	AUC	95% CI			*p*
Reassessment clinical panel classification	Children	77.00	0.56	0.42	-	0.70	0.8724
	Adults	151.00	0.55	0.45	-	0.64	
	No antibiotic	207.00	0.56	0.48	-	0.64	0.4805
	Antibiotic	21.00	0.46	0.19	-	0.73	
	Fever >1 day	218.00	0.56	0.48	-	0.64	0.3375
	Fever 1 day	10.00	0.36	0.00	-	0.77	
Aggregate clinical panel classification	Children	420.00	0.66	0.55	-	0.77	0.1492
	Adults	389.00	0.56	0.48	-	0.64	
	No antibiotic	748.00	0.63	0.56	-	0.69	0.0921
	Antibiotic	61.00	0.45	0.25	-	0.65	
	Fever >1 day	758.00	0.62	0.56	-	0.68	0.2216
	Fever 1 day	51.00	0.40	0.06	-	0.75	
Laboratory and unanimous clinical panel classification	Children	406.00	0.67	0.58	-	0.75	0.0738
	Adults	328.00	0.56	0.49	-	0.64	
	No antibiotic	676.00	0.62	0.56	-	0.68	0.5182
	Antibiotic	58.00	0.56	0.39	-	0.73	
	Fever >1 day	686.00	0.62	0.56	-	0.67	0.8515
	Fever 1 day	48.00	0.58	0.22	-	0.94	
Final Classification	Children	483.00	0.65	0.57	-	0.72	0.0666
	Adults	479.00	0.56	0.50	-	0.62	
	No antibiotic	883.00	0.61	0.56	-	0.66	0.2822
	Antibiotic	79.00	0.53	0.39	-	0.67	
	Fever >1 day	904.00	0.61	0.56	-	0.65	0.2597
	Fever 1 day	58.00	0.47	0.22	-	0.71	

Table 6 Performance characteristics of CRP to discriminate between bacterial and non-bacterial cause of fever for all reference standards to identify bacterial cause of fever at the thresholds of 10, 20, 40, 60 and 80 mg/L for all reference standards.

		No. > cut-off		No. < cut-off																				
Reference standard	Cut-off	Non-bacterial	Bacterial	Non-bacterial	Bacterial	Sensitivity	95% CI	Specificity	95% CI	AUROC	95% CI	LR+	95% CI	LR-	95% CI	PPV	95% CI	NPV	95% CI	CC
Blood culture	10	191	14	731	26	35.0%	20.6% - 51.7%	79.3%	76.5% - 81.9%	0.57	0.50 - 0.65	1.69	1.09 - 2.63	0.82	0.65 - 1.03	6.8%	3.8% - 11.2%	96.6%	95.0% - 97.7%	77.4%
positive n=962	20	115	11	807	29	27.5%	14.6% - 43.9%	87.5%	85.2% - 89.6%	0.58	0.50 - 0.65	2.20	1.30 - 3.75	0.83	0.68 - 1.00	8.4%	4.4% - 15.1%	96.5%	95.1% - 97.7%	85.0%
	40	65	7	857	33	17.5%	7.3% - 32.8%	93.0%	91.1% - 94.5%	0.55	0.49 - 0.61	2.48	1.22 - 5.06	0.89	0.77 - 1.02	9.7%	4.0% - 19.0%	96.3%	94.8% - 97.4%	89.8%
	60	30	4	892	36	10.0%	2.8% - 23.7%	96.7%	95.4% - 97.8%	0.53	0.49 - 0.58	3.07	1.14 - 8.30	0.93	0.84 - 1.03	11.8%	3.3% - 27.5%	96.1%	94.7% - 97.3%	93.1%
	80	13	2	909	38	5.0%	0.6% - 16.9%	98.6%	97.6% - 99.2%	0.52	0.48 - 0.55	3.55	0.83 - 15.19	0.96	0.90 - 1.04	13.3%	1.7% - 40.5%	96.0%	94.5% - 97.1%	94.7%
Urine culture	10	170	35	698	59	37.2%	27.5% - 47.8%	80.4%	77.6% - 83.0%	0.59	0.54 - 0.64	1.90	1.42 - 2.55	0.78	0.67 - 0.92	17.1%	12.2% - 22.9%	92.2%	90.1% - 94.0%	76.2%
positive n=962	20	103	23	765	71	24.5%	16.2% - 34.4%	88.1%	85.8% - 90.2%	0.56	0.52 - 0.61	2.06	1.38 - 3.07	0.86	0.76 - 0.96	18.3%	11.9% - 26.1%	91.5%	89.4% - 93.3%	81.9%
	40	57	15	811	79	16.0%	9.2% - 25.0%	93.4%	91.6% - 95.0%	0.55	0.51 - 0.59	2.43	1.43 - 4.12	0.90	0.82 - 0.98	20.8%	12.8% - 32.0%	91.1%	89.1% - 92.9%	85.9%
	60	27	7	841	87	7.4%	3.0% - 14.7%	96.9%	95.5% - 97.9%	0.52	0.49 - 0.55	2.39	1.07 - 5.35	0.96	0.90 - 1.01	20.6%	8.7% - 37.9%	90.6%	88.6% - 92.4%	88.1%
	80	12	3	856	91	3.2%	0.7% - 9.0%	98.6%	97.6% - 99.3%	0.51	0.49 - 0.53	2.31	0.66 - 8.03	0.98	0.98 - 1.02	20.0%	4.3% - 48.1%	90.4%	88.3% - 92.2%	89.3%
All culture positive n=	10	155	50	669	88	36.2%	28.2% - 44.8%	81.2%	78.4% - 83.8%	0.59	0.54 - 0.63	1.93	1.48 - 2.51	0.79	0.69 - 0.89	24.4%	18.7% - 30.9%	88.4%	85.9% - 90.6%	74.7%
	20	90	36	734	102	26.1%	19.0% - 34.2%	89.1%	86.7% - 91.1%	0.58	0.54 - 0.61	2.39	1.70 - 3.36	0.83	0.75 - 0.92	28.6%	20.9% - 37.3%	87.8%	85.4% - 89.9%	80.0%
	40	49	23	775	115	16.7%	10.9% - 24.0%	94.1%	92.2% - 95.6%	0.55	0.52 - 0.56	2.80	1.77 - 4.45	0.89	0.82 - 0.96	31.9%	21.4% - 44.0%	87.1%	84.7% - 89.2%	83.0%
	60	23	11	801	127	8.0%	4.0% - 13.8%	97.2%	95.8% - 98.2%	0.53	0.50 - 0.55	2.86	1.42 - 5.72	0.95	0.90 - 1.00	32.4%	17.4% - 50.5%	86.3%	83.9% - 88.5%	84.4%
	80	10	5	814	133	3.6%	12.0% - 83.0%	98.8%	97.8% - 99.4%	0.51	0.50 - 0.53	2.99	1.04 - 8.60	0.98	0.94 - 1.01	33.3%	11.8% - 61.6%	86.0%	83.6% - 88.1%	85.1%
Laboratory	10	2	50	1	88	36.2%	28.2% - 44.8%	86.7%	59.5% - 98.3%	0.61	0.52 - 0.71	2.72	0.73 - 10.06	0.74	0.58 - 0.96	96.2%	86.8% - 99.5%	12.9%	7.0% - 21.0%	41.2%
classification n=153	20	2	36	13	102	26.1%	19.0% - 34.2%	86.7%	59.5% - 98.3%	0.56	0.47 - 0.66	1.96	0.52 - 7.33	0.85	0.68 - 1.06	94.7%	82.3% - 99.4%	11.3%	6.2% - 18.6%	32.0%
	40	1	23	14	115	16.7%	10.9% - 24.0%	93.3%	68.1% - 99.8%	0.55	0.48 - 0.62	2.50	0.36 - 17.22	0.89	0.77 - 1.04	95.8%	78.9% - 99.9%	10.9%	6.1% - 17.5%	24.2%
	60	1	11	14	127	8.0%	4.0% - 13.8%	83.3%	38.1% - 99.8%	0.51	0.44 - 0.58	1.20	0.17 - 8.63	0.99	0.85 - 1.14	91.7%	61.5% - 99.8%	9.9%	5.5% - 16.1%	16.3%
	80	0	5	15	133	3.6%	1.2% - 8.3%	100.0%	78.2% - 100.0%	0.52	0.50 - 0.53	-	- - -	-		0.96	0.93 - 1.00	100.0%	47.8% - 100.0%	10.1%	5.8% - 16.2%	13.1%
Unanimous clinical	10	77	8	481	15	34.8%	16.4% - 57.3%	86.2%	83.1% - 89.0%	0.60	0.50 - 0.71	2.52	1.39 - 4.58	0.76	0.56 - 1.02	9.4%	4.2% - 17.7%	97.0%	95.1% - 98.3%	84.2%
panel classification	20	37	6	521	17	26.1%	10.2% - 48.4%	93.4%	91.0% - 95.3%	0.60	0.50 - 0.69	3.93	1.85 - 8.37	0.79	0.62 - 1.01	14.0%	5.3% - 27.9%	96.8%	95.0% - 98.1%	90.7%
n=581	40	15	5	543	18	21.7%	7.5% - 73.7%	97.3%	95.6% - 98.5%	0.60	0.51 - 0.68	8.09	3.22 - 20.34	0.80	0.65 - 1.00	25.0%	8.7% - 49.1%	96.8%	95.0% - 98.1%	94.3%
	60	5	1	553	22	4.3%	0.1% - 21.9%	99.1%	97.9% - 99.7%	0.52	0.47 - 0.56	4.85	0.59 - 39.87	0.97	0.88 - 1.05	16.7%	0.4% - 64.1%	96.2%	94.3% - 97.6%	95.4%
	80	1	1	557	22	4.3%	0.1% - 21.9%	99.8%	99.0% - 100.0%	0.52	0.48 - 0.56	24.26	1.57 - 375.82	0.96	0.88 - 1.05	50.0%	1.3% - 98.7%	96.2%	94.3% - 97.6%	96.0%
Reassessment	10	42	26	103	57	31.3%	21.6% - 42.4%	71.0%	62.9% - 42.4%	0.51	0.45 - 0.57	1.08	0.72 - 1.63	0.97	0.81 - 1.16	38.2%	26.7% - 50.8%	64.4%	56.4% - 71.8%	56.6%
clinical panel	20	21	24	124	59	28.9%	19.5% - 39.9%	70.9%	63.5% - 77.5%	0.50	0.44 - 0.56	0.99	0.66 - 1.49	1.00	0.85 - 1.19	32.0%	21.7% - 43.8%	67.8%	60.5% - 74.5%	64.9%
classification n=228	40	13	15	132	68	18.1%	10.5% - 28.0%	91.0%	85.2% - 95.1%	0.55	0.50 - 0.59	2.02	1.01 - 4.03	0.90	0.80 - 1.01	53.6%	33.9% - 72.5%	66.0%	59.0% - 72.5%	64.5%
	60	9	7	136	76	8.1%	3.3% - 16.1%	93.8%	88.5% - 97.1%	0.51	0.47 - 0.54	1.31	0.51 - 3.39	0.98	0.91 - 1.06	43.8%	19.8% - 70.1%	63.3%	56.4% - 69.7%	62.7%
	80	4	4	141	79	4.8%	1.3% - 11.9%	97.2%	93.1% - 99.2%	0.51	0.48 - 0.54	1.75	0.45 - 6.80	0.98	0.93 - 1.03	50.0%	15.7% - 84.3%	64.1%	57.4% - 70.4%	63.6%
Aggregate clinical	10	119	34	584	72	32.1%	23.3% - 41.8%	83.1%	80.1% - 85.8%	0.58	0.53 - 0.62	1.89	1.37 - 2.61	0.82	0.71 - 0.94	22.2%	15.9% - 29.6%	89.0%	86.4% - 91.3%	76.4%
panel classification	20	58	30	645	76	28.3%	20.0% - 37.9%	91.7%	89.5% - 93.7%	0.60	0.56 - 0.64	3.43	2.32 - 5.07	0.78	0.69 - 0.88	34.1%	24.3% - 45.0%	89.5%	87.0% - 91.6%	83.4%
n=809	40	28	20	675	86	18.9%	11.9% - 27.6%	96.0%	94.3% - 97.3%	0.57	0.51 - 0.61	4.74	2.77 - 8.10	0.84	0.77 - 0.93	41.7%	27.6% - 56.8%	88.7%	86.6% - 90.9%	85.9%
	60	14	8	689	98	7.5%	3.3% - 14.3%	98.0%	96.7% - 98.9%	0.53	0.50 - 0.55	3.78	1.63 - 8.82	0.94	0.89 - 1.00	36.4%	17.2% - 59.3%	87.5%	85.0% - 89.8%	86.2%
	80	5	5	698	101	4.7%	1.5% - 10.7%	99.3%	98.3% - 99.8%	0.52	0.50 - 0.54	6.63	1.95 - 22.52	0.96	0.92 - 1.00	50.0%	18.7% - 81.3%	87.4%	84.9% - 89.6%	86.9%
Laboratory	10	79	58	494	103	36.0%	28.6% - 44.0%	86.2%	83.1% - 88.9%	0.61	0.57 - 0.65	2.61	1.98 - 3.49	0.74	0.66 - 0.84	42.3%	33.9% - 51.1%	82.7%	79.5% - 85.7%	75.2%
classification and	20	39	42	534	119	81.8%	78.6% - 84.7%	51.9%	40.5% - 63.1%	0.67	0.61 - 0.72	1.70	1.35 - 2.14	0.35	0.27 - 0.46	93.2%	90.8% - 95.1%	26.1%	19.5% - 33.6%	78.5%
unanimous clinical	40	16	28	557	133	17.4%	11.9% - 24.1%	97.2%	95.5% - 98.4%	0.57	0.54 - 0.60	6.23	3.46 - 11.22	0.85	0.79 - 0.91	63.6%	47.8% - 77.6%	80.7%	77.6% - 83.6%	79.7%
panel classification	60	6	12	567	149	7.5%	3.9% - 12.7%	99.0%	97.7% - 99.6%	0.53	0.51 - 0.55	7.12	2.71 - 18.67	0.94	0.89 - 0.98	66.7%	41.0% - 86.7%	79.2%	76.0% - 82.1%	79.8%
n=734	80	1	6	572	155	3.7%	1.4% - 7.9%	99.8%	99.0% - 100.0%	0.52	0.50 - 0.53	21.35	2.59 - 176.09	0.96	0.94 - 0.99	85.7%	42.1% - 99.6%	78.7%	75.5% - 81.6%	78.7%
Final classification	10	121	84	597	160	34.4%	28.5% - 40.8%	83.1%	80.2% - 85.8%	0.59	0.56 - 0.62	2.04	1.61 - 2.89	0.79	0.72 - 0.87	41.0%	34.2% - 48.0%	78.9%	75.8% - 81.7%	70.8%
n=962	20	60	66	658	178	27.0%	21.6% - 33.1%	91.6%	89.4% - 93.6%	0.59	0.56 - 0.62	3.24	2.36 - 4.45	0.80	0.74 - 0.86	52.4%	43.3% - 61.0%	78.7%	75.8% - 81.4%	75.3%
	40	29	43	689	201	17.6%	13.1% - 23.0%	96.0%	94.3% - 97.3%	0.57	0.54 - 0.59	4.36	2.79 - 6.83	0.86	0.81 - 0.91	59.7%	47.5% - 71.1%	77.4%	74.5% - 80.1%	76.1%
	60	15	19	703	225	7.8%	4.8% - 11.9%	97.9%	96.6% - 98.8%	0.53	0.51 - 0.55	3.73	1.92 - 7.22	0.94	0.91 - 0.98	55.9%	37.9% - 72.8%	75.8%	72.9% - 78.5%	75.1%
	80	5	10	713	234	4.1%	2.0% - 7.4%	99.3%	98.4% - 99.8%	0.52	0.50 - 0.53	5.89	2.03 - 17.05	0.97	0.94 - 0.99	66.7%	38.4% - 88.2%	75.3%	72.4% - 78.0%	75.2%

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