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# Antibiotic use among children in low- and middle-income countries

*Studies on global trends, and contextual  
determinants of antibiotic prescribing in Eastern  
Uganda*

GBEMISOLA ALLWELL-BROWN



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### Abstract

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This thesis aimed to systematically map trends in reported antibiotic use (RAU) among sick under-five children across low- and middle-income countries (LMICs) in 2005-2017, and to understand the contextual determinants of antibiotic prescribing in Eastern Uganda.

Based on 132 national surveys from 73 LMICs, and using Bayesian linear regression models, trends in RAU among sick under-five children (with symptoms of fever, diarrhoea or cough with fast/difficult breathing) across LMICs in 2005-2017 were mapped by WHO region, World Bank country income group, symptom complaint (**Study-I**), and by the following user characteristics: rural/urban residence, maternal education, household wealth and source of care (**Study-II**). To provide context, **Study-III** investigated patterns and contextual determinants of antibiotic prescribing for febrile under-five outpatients (FUO) attending 37 primary and secondary healthcare facilities across Bugisu, a sub-region in Eastern Uganda, based on a healthcare facility survey, and a two-year retrospective review of outpatient registers from January 2019-December 2020. To further strengthen the understanding of contextual determinants of antibiotic prescribing, in **Study-IV**, 10 focus group discussions and 10 in-depth interviews were conducted with 85 healthcare providers across primary and secondary healthcare facilities in Bugisu, and analysed using thematic analysis.

A modest (17%) relative increase in RAU for sick under-five children across LMICs in 2005-2017 was found, with about 43% of the children reportedly receiving antibiotics for their illness in 2017. Low-income, African, and South-East Asian countries consistently recorded the lowest RAU for sick under-five children. Within LMICs, RAU for sick under-five children increased across all user groups in 2005-2017 but remained lowest among the poorest children, those living in rural areas, and having mothers with the lowest education levels. In Bugisu, 62.2% of FUO in surveyed healthcare facilities received antibiotic prescriptions. Amoxicillin and co-trimoxazole accounted for two-thirds of all antibiotic prescriptions. Cotrimoxazole and ampicillin/cloxacillin were prescribed, despite not being indicated in any of the reported conditions in Study-III. Among other interrelated factors across multiple levels of the health system, availability of antibiotics and diagnostics within healthcare facilities, caregiver demands, and governance at national and sub-national levels were important health worker considerations in antibiotic prescribing for febrile under-five patients.

These studies suggest that inequitable access to antibiotics remains a challenge between and within LMICs. Yet, misuse and wastage of antibiotics persists in the same populations with the greatest lack of access to antibiotics and formal healthcare services. A health systems strengthening approach is required to improve antibiotic stewardship and overall quality of care in LMICs.

**Keywords:** antibiotic, child, low- and middle-income countries, LMICs, fever, under-five, Uganda, primary healthcare, health systems

*Gbemisola Allwell-Brown, Department of Women's and Children's Health, International Child Health and Nutrition, Akademiska sjukhuset, Uppsala University, SE-751 85 UPPSALA, Sweden.*

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# List of Papers

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

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- II. Allwell-Brown G, Hussain-Alkhateeb L, Sewe MO, Kitutu FE, Strömdahl S, Mårtensson A, Johansson EW. (2021) Determinants of trends in reported antibiotic use among sick children under five years of age across low-income and middle-income countries in 2005–17: A systematic analysis of user characteristics based on 132 national surveys from 73 countries. *International Journal of Infectious Diseases*, 108: 473-82.
- III. Allwell-Brown G, Namugambe JS, Ssanyu JN, Johansson EW, Hussain-Alkhateeb L, Strömdahl S, Mårtensson A, Kitutu FE. Patterns and contextual determinants of antibiotic prescribing for febrile under-five outpatients at primary and secondary healthcare facilities in Bugisu, Eastern Uganda. *Submitted*.
- IV. Ssanyu JN, Allwell-Brown G, Namugambe JS, Harrison R, Johansson EW, Strömdahl S, Mårtensson A, Kitutu FE. Healthcare providers' considerations in antibiotic prescribing and administration for febrile under-five patients attending primary and secondary healthcare facilities in eastern Uganda- a qualitative study. *Manuscript*.

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I have contributed in the following ways to the above studies:

**Studies I and II:** conceptualisation, data review and inclusion, data management and compilation, manuscript preparation, peer review and journal correspondence

**Study III:** conceptualisation, data analysis, and manuscript preparation

**Study IV:** conceptualisation, preparation of data collection tools, data coding and analysis, and manuscript preparation.

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# Abbreviations

AMR	Antimicrobial resistance
ATM	Access to medicines
AURTI	Acute upper respiratory tract infection
AWaRe	Access, Watch, Reserve
CBC	Complete blood count
DHS	Demographic and Health Surveys
EA	Enumeration area
FGD	Focus group discussion
GAP	Global Action Plan
GLASS	Global Antimicrobial Resistance and Use Surveillance System
GLASS-AMC	GLASS antimicrobial consumption module
HC	Health Centre
HDPs	Health Development Partners
IDI	In-depth interview
LIC	Low-income country
LMIC	Low- and middle-income country
LMIC-LM	Lower middle-income country
LMIC-UM	Upper middle-income country
MICS	Multiple Indicator Cluster Surveys
mRDT	Malaria rapid diagnostic test
NAP	National Action Plan
NMS	National Medical Stores
PFP	Private-for-profit
PNFP	Private-not-for-profit
RBF	Results-based financing
SAMSU	Strengthening Healthcare professionals' capability for effective Antimicrobial Stewardship, Consumption and Use in Uganda
UNICEF	United Nations International Children's Emergency Fund
USAID	United States Agency for International Development
WHO	World Health Organization





# Glossary

**Antibiotic:** a chemical compound that kills or inhibits the growth of bacteria and is used to treat bacterial infections.

**Antimicrobial:** a chemical agent that acts against microorganisms, namely bacteria, fungi, viruses and protozoa.

**Antimicrobial resistance (AMR):** the development by a disease-causing microorganism [bacteria, fungi, viruses or protozoa], through mutation or gene transfer, of the ability to survive exposure to an antimicrobial agent that was previously an effective treatment. (“Antibiotic resistance” or “bacterial AMR” is a subset of AMR, referring specifically to bacteria becoming resistant to antibiotics.)

**Antimicrobial/ antibiotic stewardship:** A coherent set of actions which promote the responsible use of antimicrobials/ antibiotics.

**Antimicrobial/ antibiotic consumption data:** This term is used in this report to refer to estimates of aggregated data, mainly derived from import, sales or reimbursement databases.

**Antimicrobial/ antibiotic use data:** This term is used in this report to refer to estimates derived from patient-level data, which may allow disaggregation of data based on patient characteristics (e.g. gender, age), or indication for which the medicine is being used.

**Low- and middle-income countries:** a collective term for low income-, lower-middle-income- and upper-middle-income countries, based on the World Bank’s grouping of countries according to gross national income (GNI) per capita for a specified year.



# Introduction

## Antimicrobial resistance – a global challenge with greatest implications for low- and middle-income countries

Antimicrobial resistance (AMR) is a leading global health challenge that threatens our ability to treat common infections or to conduct a wide range of medical procedures often associated with infectious complications. Bacterial AMR, which is the focus of this thesis, is a major contributor to the overall AMR burden. In 2019, 4.97 million deaths were associated with bacterial AMR, with 1.27 million of these deaths being directly attributable to bacterial AMR.<sup>1</sup> The same study found that the highest death rates from bacterial AMR across all ages were seen in Sub-Saharan Africa and South Asia.<sup>1</sup>

The greatest health and economic impacts of AMR are felt in low- and middle-income countries (LMICs), where infectious diseases remain a leading cause of morbidity and mortality, and where weak health systems are inadequately equipped to care for patients with resistant infections.<sup>2</sup> Furthermore, high poverty rates and out-of-pocket health expenditure in LMICs increase the vulnerability of majority of these populations to catastrophic health spending, fuelling a vicious cycle of poverty and infectious diseases. With increasing AMR in LMICs, older, affordable antibiotics lose effectiveness, while newer, more expensive medicines remain inaccessible to the majority.<sup>3</sup>

Bacterial AMR (or antibiotic resistance) is a natural and inevitable phenomenon. The use of antibiotics in humans and animals, and the exposure of bacteria to antibiotics in the environment (such as through antibiotic-containing waste-water) exerts selection pressure on bacteria, such that those susceptible to the antibiotic are killed or inhibited, allowing resistant bacteria to proliferate.<sup>4</sup> To slow the development of resistance, bacterial antibiotic exposure must therefore be kept to a minimum. It is recognised that a “One Health” approach (one that takes into consideration bacterial antibiotic exposure through humans, animals and the environment) must be taken to understand and effectively tackle bacterial AMR.<sup>5</sup> However, this thesis focuses on human antibiotic use, specifically among under-five children in LMICs.

## Antimicrobial resistance on the global agenda

AMR has at least in the past 25 years been acknowledged by the World Health Assembly as a global health threat.<sup>6</sup> By the mid to late 1990s, initiatives to tackle AMR were already being taken at national and regional levels to various degrees, according to the level of priority placed on the problem.<sup>6</sup> In an attempt to harmonise and synergise global efforts in tackling AMR, the World Health Organization (WHO) in 2001 produced a “Global Strategy for Containment of Antimicrobial Resistance”.<sup>7</sup> Yet, because at the time, AMR was still widely perceived as a vague and distant threat, with little evidence to justify immediate political and financial commitment to action, this proposed strategy received little global attention.<sup>5</sup> Over the years, advocacy for action on AMR continued, including the building up of evidence to justify the prioritisation of action on AMR, and improving global awareness and concern about AMR.<sup>8</sup>

In 2013, the World Economic Forum identified bacterial AMR as one of the three most significant global risks requiring mitigating action within the coming decade, and one which was beyond the capacity of any nation or organization to undertake alone.<sup>9</sup> With renewed momentum following this report and as a result of continued advocacy, a request was made at the 2014 World Health Assembly for the WHO to draft a Global Action Plan (GAP) on AMR, building on the 2001 Global Strategy.<sup>10</sup> In May 2015, the WHO GAP on AMR was adopted at the 68<sup>th</sup> World Health Assembly, its overarching goal being to “ensure, for as long as possible, continuity of the ability to treat and prevent infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them”.<sup>5</sup> This goal was to be attained through five key objectives: (i) improving awareness and understanding of AMR, (ii) strengthening the knowledge and evidence base on AMR, (iii) reducing the incidence of infection, (iv) optimising the use of antimicrobials, and (v) developing and economic case for sustainable investment in tackling AMR.<sup>5</sup>

In a commissioned report the following year, an economic cost was attached to AMR.<sup>2</sup> This report projected that by 2050, in the absence of any mitigating actions, the global cost of inaction on AMR would rise to 100 trillion USD, and AMR would lead to the loss of up to ten million lives per year.<sup>2</sup> This report was featured at the United Nations General Assembly in the same year, culminating in a landmark political declaration on AMR.<sup>11</sup> Member states acknowledged AMR as a priority global challenge, and committed to adopting the WHO GAP on AMR as a blueprint for developing their own National Action Plans (NAPs) by 2017.<sup>11</sup> Today (as of October 2021), 148 countries have NAPs in place in line with the GAP, and 38 countries are still in the process of developing NAPs.<sup>12</sup> Implementation of NAPs in many countries however remains stalled, chiefly by lack of sufficient financial backing, and waning political interest.<sup>13, 14</sup>

## Global recommendations to tackle bacterial AMR – innovation, conservation and access

To keep up with resistance development rates, *innovation* in maintaining a flowing “pipeline” of new antibiotics is crucial.<sup>15</sup> Yet, there remains an antibiotic “discovery void”, which has been attributed to a shift of priority in the pharmaceutical industry away from antibiotic development since the late 1980s, as antibiotics are considered to yield low returns on investment, compared for instance to medicines for chronic diseases.<sup>5</sup> Furthermore, the process of bringing a new antibiotic into the market is a highly capital-intensive, technically tedious and long-term endeavour, with relatively low success rates.<sup>16</sup> Though considerable efforts have been made in the last decade to revive the antibiotic pipeline, successful outcomes in the foreseeable future remain uncertain.<sup>13, 17</sup> It is therefore crucial to *conserve* existing antibiotics by limiting their use to situations of absolute necessity. Central to antibiotic conservation are efforts to reduce the incidence of infections through improved hygiene and sanitation and vaccination,<sup>18</sup> as well as investment in research and development of new and affordable point-of-care diagnostic tools to support health workers.<sup>19</sup>

Regulation of antibiotic sales, so that they are available as prescription-only medicines is also a recognised conservation strategy, but one which must be applied with caution, and with careful consideration for context.<sup>20</sup> It has been estimated that lack of *access* to antibiotics is associated with greater mortality in LMICs than bacterial AMR.<sup>21</sup> Thus, strict antibiotic conservation measures in LMICs could lead to inadequate access to antibiotics amongst populations with the greatest need, such as those living in remote rural areas with limited access to formal healthcare services.<sup>20</sup> It is therefore critical that antibiotic conservation efforts, especially in LMICs, are balanced by complementary efforts to ensure sustainable access for all in need.<sup>16</sup>

## Balancing antibiotic conservation and access in LMICs: an ethical dilemma

In many LMICs, the burden of lack of access to antibiotics often co-exists with the opposite problem of antibiotic overuse and misuse, creating unique ethical challenges to stewardship.<sup>22</sup> The fragmented health systems that characterise many LMICs, coupled with the often poorly regulated, yet, pervasive private health sector, creates a situation whereby achieving high level access to an antibiotic in LMIC settings is commonly accompanied by its misuse and overuse.<sup>20</sup> Furthermore, many LMICs are still lacking the infrastructural and regulatory capacity to fully capture, routinely document, and transparently report antibiotic consumption at national level.<sup>23</sup> Unlimited access to the full

“menu” of globally available antibiotics in LMICs [or anywhere] could therefore contribute to the premature loss of their effectiveness and undermine global conservation efforts.<sup>20</sup>

In an effort to address some of these ethical challenges in balancing antibiotic access and conservation globally, the WHO AWaRe (*Access, Watch and Reserve*) classification system for antibiotics was developed in 2017.<sup>24</sup> *Access* antibiotics have the lowest resistance potential of the three groups, and are the preferred first- or second-line empirical treatment for a broad range of infectious syndromes.<sup>25</sup> They should be widely available, at an appropriate quality, dose, formulation and price.<sup>26</sup> *Watch* antibiotics are recommended as first- or second-line empirical treatment for a limited number of infectious syndromes due to their greater resistance potential, and monitoring their use should be prioritised in antimicrobial stewardship activities.<sup>25</sup> *Reserve* antibiotics are considered as last-resort options, and should be used only for confirmed or suspected infections due to multi-drug resistant organisms.<sup>25, 26</sup> Based on this classification, the WHO recommends that *Access* antibiotics should constitute at least 60% of countries’ national antibiotic consumption by 2023.<sup>27</sup>

## Importance of monitoring of antibiotic consumption patterns

Antibiotic use is recognised as a modifiable and important driver of resistance, both at population and individual levels.<sup>4, 28</sup> Hence, monitoring global trends in antibiotic consumption or use over time is essential to track progress in efforts made to reduce antibiotic overuse.<sup>29</sup>

Antimicrobial “consumption” refers to the quantity of antimicrobials used by a population in a specified setting, over a specified period of time.<sup>23</sup> Typical sources of antimicrobial consumption data include import, wholesale, procurement, reimbursement, and hospital dispensing databases.<sup>23, 30</sup> Antibiotic “use”, on the other hand, could be considered as a subset of antibiotic consumption, with data obtained at patient-level, which allows for more direct measures of usage, including disaggregation by user characteristics (such as age and sex), and clinical indications for use.<sup>30</sup> Antibiotic consumption data, though aggregated and lacking information on user characteristics, are commonly used as a proxy measure of antibiotic use.<sup>23</sup>

Antibiotic consumption trends over time, combined with data on resistance patterns could improve the understanding of bacterial AMR, and strengthen the evidence linking antibiotic consumption to resistance.<sup>31</sup> Furthermore, data on antibiotic consumption and use at national and regional levels could contribute to understanding trends and inequalities in access to antibiotics within

and between countries and world regions. More so, further disaggregating antibiotic use data by user characteristics could provide critical input for targeted antibiotic stewardship.

## Current global antibiotic consumption surveillance initiatives

Harmonizing antimicrobial consumption data collected across countries is considered a priority activity to support the second objective of the WHO GAP on AMR (strengthening the knowledge and evidence base on AMR). To this end, the Global Antimicrobial Resistance and Use Surveillance System (GLASS) which was launched in 2015 [originally as Global Antimicrobial Resistance Surveillance System] included a module for systematic collection of data on antimicrobial consumption at national level (GLASS-AMC) in 2019.<sup>32</sup> In the GLASS-AMC module, reporting on consumption of antibiotics is prioritised for all countries, while reporting for other antimicrobial types (antimalarials, antifungals, antivirals, and antimycobacterials) is considered optional.<sup>33</sup>

The GLASS-AMC promises to be especially useful for data collection from LMICs, but this is still a long-term endeavour. As of the latest GLASS report (2021), only 18 countries had enrolled in the GLASS-AMC.<sup>23</sup> Of these, 15 provided information on the level of implementation of their surveillance systems (which was still in the early stages for the majority), but none of these countries produced actual antimicrobial consumption data. This report also featured data on antimicrobial use among hospitalised patients, obtained via point prevalence surveys across 34 countries.<sup>23</sup> Point prevalence surveys could be a technically and financially feasible means of obtaining “snapshot” measures of antimicrobial consumption across countries.<sup>34</sup> However, many LMICs are still in the early phases of adoption and implementation of this methodology. And, in countries where they have been implemented, surveys so far have only been conducted in selected centres across countries (often by convenience sampling), thus results have not been nationally representative.<sup>23, 35</sup> Furthermore, point prevalence surveys so far have had a focus on hospitalised patients, and methods are not yet sufficiently expanded to accommodate outpatient settings where most antibiotics are prescribed.<sup>35</sup>

## Global trends in antibiotic consumption – the need for evidence from LMICs

Prior to the studies in this thesis, few studies had been conducted since 2000, investigating global trends in antibiotic consumption. These studies were, however, based on pharmaceutical sales data chiefly from high-income coun-

tries and upper-middle income countries (LMICs-UM), with lower-middle income countries (LMICs-LM) and low-income countries (LICs) being underrepresented.<sup>31, 36, 37</sup> This underrepresentation owes, largely, to the fact that many LMICs-LM and LICs lack systems for routine and harmonised national data collection on pharmaceutical sales, that could be drawn upon for such analyses.<sup>23</sup> Furthermore, it is difficult to fully appreciate or accurately quantify the true extent of antibiotic consumption in these settings, where unregulated sales and non-prescription use of antibiotics are highly prevalent.<sup>38, 39</sup> Indeed, it has been acknowledged that methods capable of accounting for non-prescribed antibiotic use (particularly community-based surveys) should be promoted for antibiotic use surveillance in low-income settings.<sup>39</sup>

Nonetheless, when taken together, these assessments of global antibiotic consumption patterns suggest that antibiotic consumption increased globally between 2000 and 2015, and much of this increase was driven by rising consumption in LMICs.<sup>31, 36, 37</sup> Yet, on average, antibiotic consumption rates in high-income countries remained higher than in LMICs, despite the greater infectious disease burden in the latter.<sup>31, 36, 37</sup>

## Under-five children in LMICs – priority need for antibiotic stewardship

Under-five children are an important group of antibiotic users, given the higher prevalence of infectious diseases and associated mortality risk in this age group, compared to older children and adults.<sup>40</sup> Even more so, under-five children living in malaria-endemic LMICs constitute a population with priority need for antibiotic stewardship. The most prevalent medical conditions in under-five children in these settings (respiratory tract infections, malaria and diarrhoea) tend to present with overlapping symptoms, fever being a common feature.<sup>41, 42</sup> With rapid malaria tests now widely available and accessible across LMICs, and in the absence of similar affordable diagnostic tools for non-malarial fevers, healthcare providers in these settings often have to rely on clinical judgement in deciding whether or not to prescribe antibiotics.<sup>43, 44</sup> More often than not, because the decision regarding antibiotic prescribing could be a matter of life and death, they choose to err on the side of caution by prescribing antibiotics.<sup>43, 44</sup>

## Antibiotic consumption and use in under-five children from LMICs: evidence gap and research agenda

Prior to this doctoral work, few studies had attempted to study patterns in antibiotic consumption among under-five children across multiple LMICs. The only available study on global paediatric antibiotic consumption trends over time reported a “slight increase” in global consumption of child-appropriate



antibiotic formulations in 2011-2015.<sup>40</sup> Similar to findings from other global antibiotic consumption trend analyses, the study also found that total antibiotic consumption was higher in LMICs, but consumption per person was higher in high-income countries.<sup>40</sup> However, like the others, this study was also based on national pharmaceutical sales data, hence, also reflected an underrepresentation of LICs and LMICs-LM.

Among studies conducted solely in LMICs, findings point to over-exposure to antibiotics in this age group, with about two-thirds of the children receiving antibiotic prescriptions on outpatient basis.<sup>45,46</sup> One of these studies also found that on average, the children received 24.5 antibiotic prescriptions by the age of five years.<sup>45</sup> These studies<sup>45, 46</sup> were however based on data from a few countries, and did not investigate trends in antibiotic exposure over time. Furthermore, the studies provided evidence for antibiotic prescribing [as proxy for antibiotic exposure] and not use, and did not explore antibiotic exposure in children who did not visit healthcare facilities.<sup>45, 46</sup>

## Rationale for thesis

It is recognised that while many high income countries need to reduce excessive antibiotic consumption, a considerable proportion of people living in LMICs still lack access to life-saving antibiotics.<sup>3, 47</sup> Yet this *access-excess* divide in antibiotic consumption is more complicated than simply between rich and poor countries.<sup>48</sup> Within LMICs, where social gaps are typically wide, there may be important socio-demographic variables that further create their own *access-excess* divide.<sup>20</sup>

LMICs (particularly LMICs-LM and LICs) have been largely underrepresented in previous global analyses on antibiotic consumption trends since 2000.<sup>31, 36, 37, 40</sup> Moreover, these studies have been based on pharmaceutical sales data, which do not directly measure individual-level antibiotic usage or its variations across user groups, such as by socio-economic status. Disaggregating antibiotic consumption trends by user characteristics could contribute to elucidating patterns of inequities in antibiotic use over time, especially among populations with poor access to medicines and formal health services.

Yet, beyond the mapping of global antibiotic consumption trends, there is an equally important need for a contextual understanding of the underlying drivers of the observed trends, to aid in the design and implementation of antibiotic stewardship interventions that would be acceptable, feasible and sustainable in LMICs.

# Aim

This project aimed to systematically map trends in reported antibiotic use among sick under-five children across LMICs in 2005-2017, and, to understand the contextual determinants of antibiotic prescribing in Eastern Uganda

## Objectives

**Studies I and II** address the first part of the aim, that is, the systematic mapping of trends in reported antibiotic use for sick children across LMICs in 2005-2017, using nationally representative community-based surveys. The second part of the aim – understanding the contextual determinants of antibiotic prescribing in Eastern Uganda – is addressed by **Studies III and IV**.

**Study I:** to analyse trends in the proportion of reported antibiotic use among children under five years of age with fever, diarrhoea or cough with fast or difficult breathing across LMICs between 2005-2017 by WHO region, World Bank income classification, and symptom complaint.

**Study II:** to examine trends and differentials in reported antibiotic usage among children under five years of age with fever, diarrhoea or cough with fast or difficult breathing across LMICs during 2005-2017 by the following user characteristics: rural/urban residence, maternal education, household wealth, and healthcare source visited.

**Study III:** to describe patterns and contextual determinants of antibiotic prescribing for febrile under-five outpatients at primary and secondary healthcare facilities across Bugisu, Eastern Uganda.

**Study IV:** to qualitatively explore healthcare providers' considerations in antibiotic prescribing for febrile under-five patients attending primary and secondary healthcare facilities in Bugisu, Eastern Uganda.

## Conceptual framework

The conceptual framework for this thesis is based on an adaptation of the “access to medicines from a health systems perspective” framework by Bigdeli et al (2013).<sup>49</sup> The purpose of the original framework was to help situate access to medicines (ATM) within the larger health systems strengthening discussion.<sup>49</sup> The authors argued that ATM should be seen as a dynamic part of the health system, (one that influences and is influenced by the entire system) and not merely a system input to improve service delivery, which addressing supply issues alone was sufficient to sustain).<sup>49</sup> In 2014, Tomson and Vlad proposed using this same health systems perspective in understanding and addressing the bacterial AMR problem, noting that when adapting this framework to the bacterial AMR context, a key paradigm shift would be to weigh the current benefits of antibiotic use against the potential associated resistance.<sup>50</sup> More recently, lessons learnt from the COVID-19 pandemic on the importance of resilient health systems have inspired a renewed call to reframe bacterial AMR advocacy using a health systems approach.<sup>51</sup>

### Key adaptations and applications of the framework in current thesis

The original framework highlighted five levels at which barriers to ATM could occur, which also provide opportunities for interventions to improve ATM, including (i) individuals, households and communities, (ii) service delivery, (iii) health sector, (iv) national context, and (v) international context.<sup>49</sup> For the purposes of this thesis, these levels are adapted to reflect levels at which contextual determinants of antibiotic prescribing could be analysed. These levels in the adapted framework also serve as a guide to situate the component studies in this thesis. (Figure 1).

At the centre of all the studies in this thesis are the individuals, households (specifically under-five children and their caregivers), and the communities in which they live (Level-I). **Studies I and II** estimate global and regional trends in reported antibiotic use for sick under-five children, and are thus also placed at the international context (Level-V) since the trends are described at this level. **Studies III and IV** are primarily situated at the service delivery level (Level-II), being healthcare facility-based studies. In addition, **Study IV**, being an exploratory qualitative study, touches upon influences on antibiotic prescribing practices at multiple levels of the framework. (Figure 1).

Like the original framework,<sup>49</sup> and in order to help understand contextual determinants of antibiotic prescribing, this framework also highlights the dynamic interactions between the Medicines (antibiotics) and Technologies component of the health system with other health system resources, and how these together influence [and are influenced by] service delivery. As with the original framework,<sup>49</sup> the multi-level role of governance at each of the five

levels is also acknowledged in this thesis, though with a stronger focus on the national and sub-national context (Level-IV). Finally, the underlying message that runs through all aspects of this thesis is that of equity.

Within the next chapters this thesis, this framework (Figure 1) will be used specifically in analysing and presenting the results of **Study IV**, and will guide the discussion of overall thesis findings.

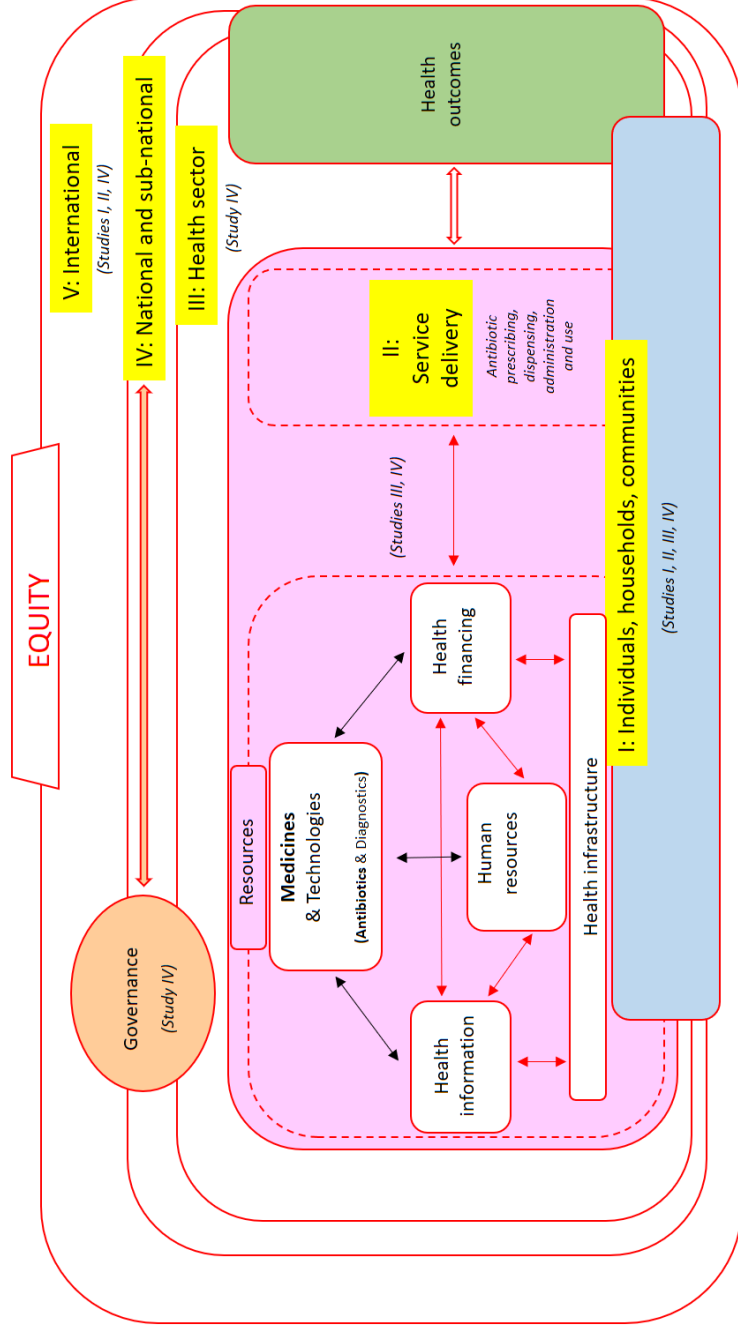


Figure 1: Conceptual framework for thesis. Adapted from Bigdeli et al (2013)

# Methods

## Overview of study methods

In **Studies I** and **II** global trends in reported antibiotic use among sick under-five children across LMICs including by user characteristics were systematically mapped, based on 132 national cross-sectional surveys conducted across 73 LMICs from 2005 to 2017. **Studies III** and **IV** were conducted in primary and secondary healthcare facilities in Bugisu, Eastern Uganda. **Study III** was a cross-sectional healthcare facility survey with a retrospective analysis of outpatient register data for antibiotic treatment prescribed by type, to febrile under-five outpatients, while **Study IV** used qualitative methods to explore healthcare providers' considerations in antibiotic prescribing and administration for febrile under-five patients. Table 1 provides an overview of **Studies I-IV**.

Table 1: Overview of component studies (\*DHS: Demographic and Health Surveys; MICS: Multiple Indicator Cluster Surveys)

Study	Study setting	Study design & data sources	Analysis	Output
I	Global; LMICs	Systematic mapping of global trends in reported antibiotic use for sick children across 73 LMICs, based on 132 national cross-sectional surveys (DHS, MICS)* conducted in 2005-2017	Bayesian linear regression	<p>Trends by:</p> <ul style="list-style-type: none"> <li>• WHO region</li> <li>• World Bank country income classification</li> <li>• Symptom complaint</li> </ul>
II				<p>Trends by the following user characteristics:</p> <ul style="list-style-type: none"> <li>• Rural/urban residence</li> <li>• Maternal education</li> <li>• Household wealth</li> <li>• Healthcare source visited</li> </ul>
III	Public and private-not-for-profit primary and secondary healthcare facilities in Bugisu, Eastern Uganda	<p>Cross-sectional study-Healthcare facility survey with two-year retrospective review of outpatient registers</p> <p>Data from 37 healthcare facilities and 3,598 children's records in Jan 2019-Dec 2020</p>	Descriptive statistics + mixed-effects logistic regression	<p>Antimicrobial prescribing patterns (with a focus on antibiotics by type)</p> <p>Determinants of antibiotic prescribing at patient- and healthcare facility levels</p>
IV		Qualitative study-Focus group discussions (FGDs) and in-depth interviews with 85 healthcare workers from 16 healthcare facilities	Thematic analysis	Themes on healthcare providers' considerations in antibiotic prescribing and administration for febrile under-five patients

## Studies I and II

### Data sources

Two data sources were employed in these studies: Demographic and Health Surveys (DHS), and Multiple Indicator Cluster Surveys (MICS). The DHS and MICS are cross-sectional cluster surveys that have been routinely implemented across LMICs since the mid-eighties (1995 for MICS), based on nationally representative samples of households. The DHS and MICS are funded by the USAID and UNICEF, respectively, and use similar methods and tools. Surveys are routinely conducted (typically every 3-5 years) via the national statistical offices of individual countries by local staff, but with technical guidance and oversight from The DHS Program (DHS) and UNICEF (MICS). Both surveys collect information on a wide range of important socio-demographic and health issues relevant to LMICs, including data on recent illness symptoms experienced by children in surveyed households, how they were managed, and what medications (including antibiotics) were administered. To obtain this information, all women aged 15-49 years in surveyed households are identified and interviewed about their children under five years of age.

The surveys are designed to be representative at national and regional levels, and by rural/urban residence.<sup>52</sup> They aim to cover 100% of the target population, which is all women aged 15-49 years and under-five children living in residential households.<sup>53</sup> Samples are based on a stratified two-stage cluster design. A nationally recognised sampling frame (usually national census files) containing all enumeration areas (EAs) in the country is used. An EA in a country is considered as the smallest geographical statistical unit containing a number of households, created for the purposes of national census-taking.<sup>54</sup> The number of households in EAs vary, but an EA could generally be considered as an area small enough for a single enumerator to cover during a national census (e.g., a city block, a village or part of a village, or group of villages).<sup>54</sup> At the *first stage*, EAs are drawn from the national census files with probability proportional to size. In the *second stage*, a complete listing of households in sampled EAs is made, and a sample of households from each cluster drawn.

Three main considerations are made in sample size determination for the surveys: (i) the number of survey domains in the country, i.e., sub-national units such as regions, (ii) the level of precision required for priority indicators (typically fertility and childhood mortality estimates), and (iii) the budget.<sup>55</sup> For example, a total sample size of about 10,000 women would be considered ideal for a country with 10 domains, with 800-1000 women sampled from each domain (800 in domains with high total fertility rates, and 1000 in areas with low total fertility rates).<sup>55</sup>

Data collection tools are pre-tested over a period of one to two weeks, and fieldwork teams are trained on the use of data collection tools over four to six weeks. Thereafter, data collection is implemented over a period of about four



months.<sup>56</sup> Fieldwork teams are comprised of individuals with at least secondary level education, and include supervisors, drivers, field data editors, and interviewers including persons with healthcare backgrounds (such as nurses, laboratory technicians). Further detail on survey methods and tools are available on the DHS and MICS websites.<sup>57, 58</sup>

## Systematic selection of surveys

For **Studies I** and **II**, all national DHS and MICS conducted from 2000 to 2017 were screened for inclusion. Surveys were excluded if they (i) did not have datasets publicly available as of August 15, 2018, (ii) the questionnaire was not publicly available, (iii) the treatment question did not contain an antibiotic response category for one or more of the illness symptoms, or (iv) the skip pattern of survey questions on reported antibiotic use was not consistent with the primary outcome as defined below. (Flowchart of survey screening and inclusion is available in Figure 1 of attached Paper I).

## Primary outcome

**Studies I** and **II** focused on survey questions related to the management of recent reported illness symptoms of fever, diarrhoea or cough with fast or difficult breathing among under-five children in the two weeks prior to the survey interviews. Caregivers were asked how these symptoms were managed, including if and where they sought care, and what medicines (including antibiotics), if any, were administered. In **Studies I** and **II**, a child was considered to have received an antibiotic if the caregiver reported administering an antibiotic in any form (pill, syrup, injection, or specific antibiotic type).

The *primary outcome* was defined as the proportion of under-five children with reported symptoms of fever, diarrhoea, or cough with fast or difficult breathing in the two weeks prior to the survey interview that were reportedly given antibiotics to treat the condition. This is subsequently referred to in this thesis as “reported antibiotic use for sick children” or “the outcome” for **Studies I** and **II**.

## Data analysis

In **Study I**, global trends in reported antibiotic use for sick under-five children across LMICs were analysed by:

- WHO region: African, Americas, Eastern Mediterranean, European, South-East Asia, or Western Pacific region
- World Bank country income classification: LIC, LMIC-LM, or LMIC-UM

- Symptom complaint: fever, diarrhoea, or cough with fast or difficult breathing

In **Study II**, these trends were analysed by user characteristics associated with access to medicines and treatment outcomes in LMICs: rural/urban residence, maternal education, household wealth, and healthcare source visited.<sup>59-61</sup>

### **User characteristics**

- Rural/urban residence was as defined by individual national statistical offices in the surveys.
- Maternal education was categorised as (i) no formal education or some primary school attendance, (ii) primary school completion or some secondary school attendance; and (iii) secondary school completion or higher education.
- Household wealth was a measure of relative economic status of households within their society at the time of the survey interview, and grouped into quintiles from poorest to richest, based on survey-specific wealth indices.
- Source of care visited was grouped as (i) public medical sector (government hospitals, government health centres, government health posts, mobile clinics, community health workers, or other country-specific public sector); (ii) private medical source (private hospitals or clinics, pharmacies, private doctors, or other country-specific medical private sector); and (iii) private informal source (shops, traditional practitioners, or other informal sources) or no care sought. This was coded such that if a sick child was taken to multiple sources, the public medical source took priority, followed by private medical and private informal source.

### **Statistical analysis**

**Studies I and II** used hierarchical Bayesian linear regression models to estimate trends in reported antibiotic use for sick under-five children across LMICs and to account for uncertainty around estimates.

**Bayesian methodology** is not as well-known in epidemiological studies as the more traditional “frequentist” methods. While the frequentist approach to probability and inference making is based on the number of times an event would occur if an experiment were to be repeated many times, the Bayesian approach expresses the degree of belief in a hypothesis (possibly based on pre-existing evidence), given the data at hand.<sup>62</sup> When applied, Bayesian methods are often favoured because of their intuitiveness and flexibility, and they are especially suitable for making inferences when available data are scarce.

Bayesian methods need not rely on observed data alone, but are capable of incorporating pre-existing knowledge about a given parameter of interest (known as the “prior”) to generate an updated belief about the parameter, referred to as the “posterior”. The “posterior” (i.e., the end-product of the Bayesian analysis) is presented in the form of a probability distribution of the parameter of interest, which, as in our studies, could be described by a mean and a measure of uncertainty about the mean. Uncertainty in Bayesian analysis is expressed within a “Credible Interval” (although in our studies we used the term “Uncertainty Interval” which is in line with earlier epidemiological analyses using the same methodology).<sup>63, 64</sup> The Credible Interval in Bayesian analysis has a direct interpretation. For example, a 95% Credible Interval means that there is a 95% probability that the parameter of interest lies within the stated interval. Where there is no pre-existing evidence about a parameter of interest, or the researcher prefers to begin with no assumptions, a “flat” or “non-informative” prior is used. Bayesian analyses often rely on “Markov Chain Monte Carlo” simulations to generate the posterior distributions of the parameter of interest.

A commonly cited limitation of Bayesian methodology also stems from its flexibility, as results of analyses are influenced not only by observed data, but by the researcher’s prior beliefs which may be subjective or based on faulty pre-existing evidence. Therefore, importantly, in Bayesian analyses, prior beliefs must be explicitly stated and justified, so that readers can draw well-informed conclusions.

In **Studies I and II**, the proportion of sick children that received antibiotics in each survey were logit-transformed to ensure that estimates always fell between 0 and 1 before regression models were run. To generate estimates for missing country-year data points, country-level socioeconomic, disease incidence, and health system covariates were included in the models. These included: (i) Human Development Index value,<sup>65</sup> (ii) national population of under-five children,<sup>66</sup> (iii) national incidence rates of malaria and respiratory and diarrhoeal infections for children aged 0–4 years,<sup>67</sup> and (iv) national public and private health spending per capita (in international dollars).<sup>68</sup> Non-informative priors were used in both studies.

Markov Chain Monte Carlo simulations were used to generate the posterior distributions of model coefficients, and to generate estimates of the outcome for all country-years. A burn-in period of 30,000 samples and three chains each with a sample size of 10,000 were used. Country-level values for the proportion of reported antibiotic use for sick under-five children were then weighted to regional or country income groupings using national population estimates for under-five children. The 2<sup>nd</sup> and 98<sup>th</sup> percentiles (10<sup>th</sup> and 90<sup>th</sup> percentiles for **Study II**) of posterior samples were obtained based on 30,000 posterior draws.

In **Study I**, trends in reported antibiotic use for sick under-five children across LMICs were modelled by WHO region, World Bank income classification, and symptom complaint. In **Study II**, the data were disaggregated by the various user characteristics. **Study II** further compared these trends between the WHO regions of Africa and South-East Asia, with the sample limited to these regions.

## Studies III and IV

### Study setting

Uganda is a low-income country in Eastern Africa with a population of 45.7 million inhabitants,<sup>69</sup> majority (75%) living in rural areas.<sup>70</sup> The population is predominantly young, with an average fertility rate of 4.8 births per woman,<sup>71</sup> and 46% of the population aged fourteen years or below.<sup>72</sup> Between 2000 and 2020, Uganda saw a decline in under-five mortality rate from 146.1 to 43.3 deaths per 1,000 live births.<sup>73</sup> Today, the leading causes of under-five mortality in Uganda are still infectious diseases – pneumonia, malaria, and diarrhoea, implicated in 16%, 13% and 10% of under-five deaths, respectively.<sup>74</sup>

### Healthcare in Uganda

Healthcare services in Uganda can be accessed through the public and private healthcare sectors. The private sector as formally recognised by the government includes private-for-profit (PFP), private-not-for-profit (PNFP), and Traditional and Complimentary Medicine Practitioners.<sup>75</sup>

Public healthcare facilities in Uganda are owned and managed by the government, with services (including medicines and diagnostics) available free-of-cost to the population.<sup>76</sup> PFPs are owned and run by private entities, and are fully dependent on user fees for revenue generation. PNFPs are mostly faith-based organisations with a central mission to reach rural and underserved populations.<sup>77</sup> They are funded by foreign development partners, but also receive financial and material support from the government.<sup>78</sup> In addition, they are expected to charge subsidized user fees to supplement revenues.<sup>78, 79</sup> Overall, out-of-pocket expenditure contributes 41% of total health expenditure in Uganda, with government funding contributing 15%, and external aid up to 42% (as of 2016).<sup>80</sup>

There are 6,937 documented healthcare facilities in Uganda. Of these, 45% are public healthcare facilities, 40% are PFP, and 15% are PNFPs.<sup>81</sup> About 86% of the Ugandan population live within 5km of a healthcare facility providing at least primary healthcare services.<sup>80</sup> And, care-seeking for febrile illness among under-five children in Uganda is mostly from private sources.<sup>82</sup>

There are six recognised levels of formal healthcare services in Uganda, based on the catchment area covered and the range of services provided,<sup>81</sup> as

presented in Table 2. Health Centre level II (HC-II) and HC-III are primary healthcare facilities, HC-IV and General Hospitals provide secondary-level healthcare services, and tertiary healthcare services are offered at Regional and National Referral Hospital levels. (Table 2)

Table 2: Formal healthcare services in Uganda (Adapted from: Uganda Health Sector Strategic and Investment Plan 2010/11-2014-15 <sup>83</sup> ; and Katende et al (2015) <sup>84</sup> )

	Health centre level	Population served	Services provided
Primary healthcare facilities	HC-II	5,000	Preventive, Promotive and Outpatient Curative Health Services, outreach care, and first-line emergency care
	HC-III	20,000	In addition to HC-II services, Maternity and simple laboratory services.
Secondary healthcare facilities	HC-IV	100,000	In addition to HC-III services, Emergency surgery and Blood transfusion and Laboratory services
	General Hospital	500,000	In addition HC-IV services, in-service training, consultation and research to support community-based healthcare programmes
Tertiary healthcare facilities	Regional Referral Hospital	2,000,000	In addition to services offered at General Hospital, RRH offer specialist services such as Ophthalmology and Dentistry.
	National Referral Hospital	10,000,000	These provide comprehensive specialist services. In addition, they are involved in teaching and research.

### Antibiotic use and resistance in Uganda

Following a situational analysis of the nation's AMR landscape in 2015,<sup>85</sup> Uganda adopted a National Action Plan on AMR in 2018, with a goal to “prevent, slow down, and control the spread of resistant organisms”.<sup>86</sup> The situational analysis had indicated that bacterial infections were responsible for 37%

of all hospital admissions and 20% of in-patient deaths across all age groups.<sup>85</sup> Among under-five children, 25% of deaths were attributed to bacterial infections, with pneumonia taking the largest share at 12%.<sup>85</sup> The report also highlighted widespread irrational antibiotic use with associated spread of resistance.<sup>85</sup>

Antibiotics can be obtained free-of-cost at public healthcare facilities in Uganda, but must be paid for by private means at PFPs and PNFPs. Among under-five children, care-seeking from a healthcare facility has been reported as a key determinant of antibiotic use in Uganda.<sup>87, 88</sup> Outside healthcare facilities and licenced pharmacies, antibiotics are widely sold over-the counter by drug shops.<sup>89, 90</sup>

### **Studies III and IV specific setting**

Studies III and IV were conducted in Bugisu, a sub-region in Eastern Uganda, bordering Kenya and lying on the slopes of Mt. Elgon. (Figure 2). Bugisu has a population of 1.8 million inhabitants,<sup>91</sup> and is comprised of six districts (Bulambuli, Sironko, Bududa, Manafwa, Mbale and Namisindwa), with Mbale as its commercial hub. It is a mostly rural population, with under-five mortality and poverty rates higher than the national average.<sup>92, 93</sup> Altogether, Bugisu has 160 primary and secondary healthcare facilities, including public facilities, PFPs and PNFPs: 146 primary healthcare facilities (66 Health Centre level II (HC-II) and 80 HC-III), and 14 secondary healthcare facilities (10 HC-IV and four general hospitals).<sup>81</sup> The focus of Studies III and IV was on primary and secondary healthcare facilities of public and PNFP ownership in Bugisu.

# UGANDA

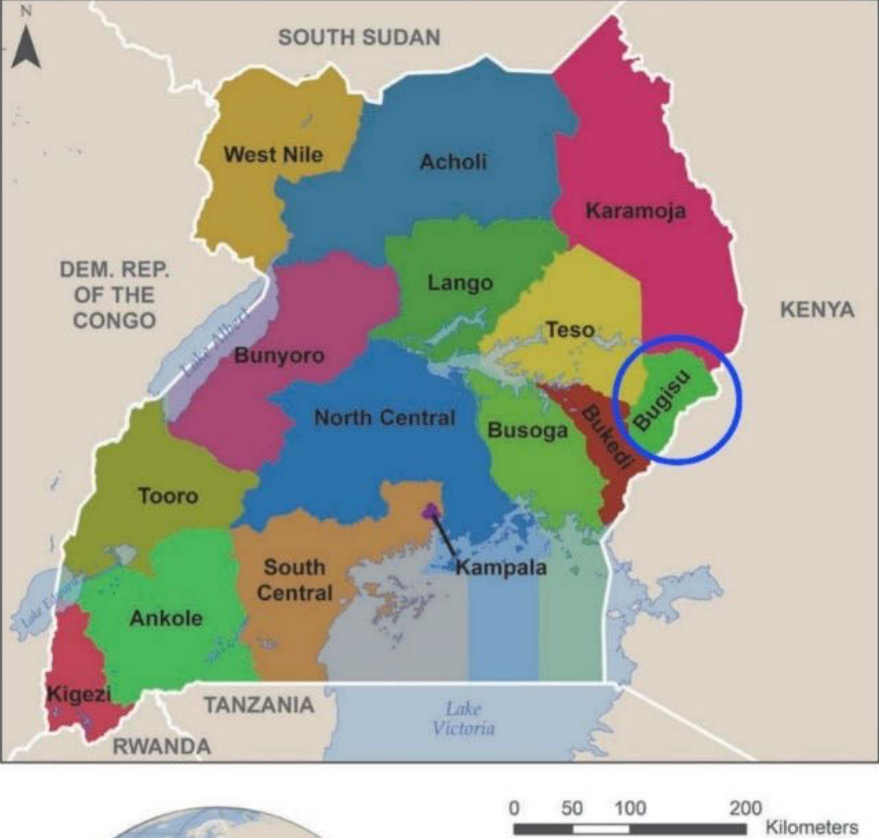


Figure 2: Map of Uganda indicating Bugisu sub-region (Adapted from: Uganda Demographic and Health Surveys (2016) final report)

## Study III data collection and analysis

All public and PNFP General Hospital and HC-IV facilities in Bugisu sub-region were included in the study. For logistic purposes, HC-III and HC-II facilities were purposively selected, taking into consideration the districts, health sub-districts, and ownership (public versus PNFP). Two General Hospitals and 10 HC-IV were initially included in the study. However, one General Hospital was excluded because it provided only specialised services, which did not match the aim of the study. Additionally, one HC-IV facility was excluded due to absence of medical records staff on all occasions when the facility was visited for data collection. Altogether, 37 primary and secondary healthcare facilities in Bugisu sub-region were surveyed (including 11 HC-II, 16 HC-III, nine HC-IV, and one General Hospital). Of the total 37 facilities, 31 were public and six were PNFP facilities. In these facilities, a two-year retrospective review of antimicrobial prescribing patterns for febrile under-five outpatients from 1st January 2019 to 31st December 2020 was conducted based on outpatient registers, with a focus on antibiotics.

Data about healthcare facility characteristics were collected by means of questionnaires administered to facility persons-in-charge, and a checklist-guided inspection of the healthcare facilities. These data included health centre level and ownership, services provided, diagnostics availability, patient attendance at outpatient clinics, staffing, and physical availability of Uganda Clinical Guidelines. Outpatient registers collected information including the patient's name, age, sex, weight, height, residence, body temperature, diagnostic tests performed, diagnosis, medicines prescribed (including dosage), attendance classification (new- or re-attendance), and referral details.

Records for febrile under-five outpatients were selected systematically at the healthcare facilities. Sampling intervals at each facility were determined by dividing the total number of under-five children attending the outpatient clinic during the study period, by the required sample size for the healthcare facility. All records of under-five children attending the study healthcare facilities in the study period were eligible for inclusion. Records were excluded if: (i) fever was not documented as a presenting clinical sign or symptom, or (ii) records had incomplete or illegible entries about the diagnoses and prescriptions.

The study sample size was estimated using the Kish Leslie formula for sample size determination for cross-sectional studies,<sup>94</sup> using a 5% level of precision and a 95% confidence interval. The proportion of under-five children prescribed an antibiotic was taken as 84.9% from a cross-sectional study conducted in Tanzania assessing antibiotic prescribing patterns in the management of diarrhoea and cough among children under five years old attending hospitals in the region.<sup>95</sup> This yielded a sample size of 196. Because the study



was to be conducted at four levels of service delivery (HC-II, -III, -IV and General Hospital), the sample size was adjusted to cater for clustering. Assuming the clusters were of equal weights, the average number of responses expected per cluster,  $b$ , was  $(196/4) = 49$ .

The Design Effect (DE), was then calculated using the formula,  $DE = 1 + (b-1) \rho$  where  $\rho$  was the expected inter-cluster variability estimated at 0.20.

$$DE = 1 + (49-1)0.2 = 10.6$$

This gave a sample size,  $N = 196 * 10.6 = 2,078$ . After an adjustment of 10% for missing data and incomplete records, this came to a final sample size of 2,309.

Descriptive statistics on antimicrobial prescribing patterns were summarized using a bar graph, pie chart and cross-tabulations. Specifically, antibiotics were defined as medications belonging to the Anatomical Therapeutic Chemical (ATC) J01 (Antibacterials for systemic use), and P01AB (Nitroimidazole derivatives) classes, and were further categorised by WHO Access, Watch and Reserve (AWaRe) group.

### **Multilevel analysis**

Multilevel analysis is an approach to statistical inference making when observations are clustered (that is, the outcome variable is measured at a level of analysis contained within larger grouping units). Specifically, we applied multilevel logistic regression to identify determinants of antibiotic prescribing at patient- (Level-1) and healthcare facility levels (Level-2), taking the 37 healthcare facilities as clusters. The outcome variable, Level-1 variables, and Level-2 variables are presented in Table 3.

The outcome of interest (whether or not a child received an antibiotic prescription) could be explained by a combination of factors intrinsic to the individual patient (Level-1 variables), and external to the patient (Level-2 variables). Multilevel analysis enables us to quantify the effects on the outcome that are attributable to individual-level characteristics, as separate from the contextual (healthcare facility) effects.

Observations within a cluster tend to be correlated. That is, in our study, antibiotic prescribing patterns for children attending the same healthcare facility may be more similar, than if compared to that for a patient attending another healthcare facility. The application of multilevel analysis is therefore to account for the cluster nature of such data, thereby avoiding the attribution of group effects to individuals or vice versa, as can be the case when different levels of analysis are mixed.

Table 3: Study III variables and variable descriptions (\*AURTI: Acute upper respiratory tract infection; \*\* Includes the diagnoses “bacteraemia”, “septicaemia”, “sepsis”, and “bacterial infection”)

	<b>Variable</b>	<b>Categories or description</b>
Outcome variable	Antibiotic prescribed	Yes/ No
Level-1 variables	Child’s age	<6 months/ 6-24 months/ >24 months
	Child’s sex	Male/ Female
	Date of presentation	Categorical variable obtained by dividing the two-year study period into six successive three-month periods, to account for seasonality
	Child’s malaria test result	Positive/ Negative
	Pneumonia diagnosis	Yes/ No
	AURTI* diagnosis	Yes/ No
	Acute watery diarrhoea diagnosis	Yes/ No
	Skin infection diagnosis	Yes/ No
	Non-specific bacterial infection** diagnosis	Yes/ No
	Helminthiasis diagnosis	Yes/ No
Level-2 variables	Health centre level	HC-II/ HC-III/ HC-IV/ General hospital
	Healthcare facility ownership	Public/ PNFP
	Uganda Clinical Guidelines available	Yes/ No
	Patient/prescriber ratio	Continuous variable obtained by dividing the average outpatient attendance over the five working days preceding the survey, by the total number of prescribers available at the healthcare facility. (At HC-II and HC-III, nurses and Clinical Officers were considered as prescribers, and at HC-IV and General Hospital, Clinical Officers and Medical Doctors were considered as prescribers).

In our analyses, three models were run: Model 1, the null-model containing only the outcome variable and the healthcare facility identifier (cluster) variable; Model 2, which included Level-1 variables with the facility identifier; and Model 3, which included Level-1 and Level-2 variables with the facility identifier. The level of statistical significance was set at 0.05. Variance inflation factor (VIF) was used to assess covariates for multicollinearity. The mean VIF was 1.14. (Multicollinearity was defined as a VIF value of 10 or greater). Data were analysed using Stata 15.1 (Stata Corp., College Station, TX).

## Study IV data collection and analysis

Ten focus group discussions (FGDs) and 10 in-depth interviews were conducted with 85 purposively selected healthcare workers involved in the prescribing, dispensing or administration of medicines to under-five children at primary and secondary, public and PNFP facilities in Bugisu. Cadres of healthcare workers interviewed included medical officers, clinical officers, nurses, midwives, laboratory staff, and medicine dispensers. FGDs and in-depth interviews sought to understand healthcare providers' considerations when prescribing antibiotics to febrile under-five patients attending their healthcare facilities, with particular interest in contextual influences beyond the patients' clinical presentation, physical examination findings and guideline recommendations.

Data were collected by two female Ugandan researchers with experience and training in qualitative research methods: JNS, a pharmacist with a Master's degree in Public Health, and another researcher (OLP) with a Bachelor's degree in Social Sciences. Interviews were conducted in English, audio-recorded, and transcribed verbatim. Data were analysed by **thematic analysis**, which is a method for qualitative data analysis that entails searching the data to identify and report patterns (or themes) in the data. In this study, we used the methodology for thematic analysis proposed by Braun and Clarke:<sup>96</sup> the transcripts were repeatedly read for familiarization with the data and identification of general patterns and meanings, all data were coded, and the codes were sorted into overarching themes and sub-themes which were revised and modified based on rounds of discussion among authors. An *inductive* approach to thematic analysis was taken in the main study (manuscript), that is, themes were data-driven, and did not rely on any pre-existing framework. However, for the purposes of this thesis, I have taken a *deductive* approach to re-analyse the data, using the framework guiding this thesis (Figure 1).

## Ethical considerations

**Studies I and II** were secondary analyses of open-access survey data. Procedures for obtaining ethical approval and participant consent in these surveys are described in detail elsewhere.<sup>57, 58</sup> Access to DHS and MICS datasets is granted on two conditions: (i) that a research project description is submitted, and (ii) that data are used solely for the indicated purposes. **Studies III and IV** were conducted as part of a larger project, SAMSU (Strengthening Healthcare professionals' capability for effective Antimicrobial Stewardship, Consumption and Use in Uganda), which is aimed at improving antimicrobial stewardship in selected hospitals in Eastern Uganda. SAMSU received ethical approval from the Makerere University School of Health Sciences Institutional Review Board and Ethics committee (MakSHSREC-2020-21) and the Uganda National Council of Science and Technology (HS1155ES). For **Study III**, permission from District Health Offices at the local governments were obtained, which were presented to persons-in-charge at specific healthcare facilities for their acknowledgement and for record purposes. As **Study III** relied on records from outpatient registers, a waiver of written informed consent was granted by the MakSHSREC on the grounds that risks were minimal, and it was not practically possible to contact the caregivers of the children whose records were assessed. For **Study IV**, written informed consent for the study was obtained from all participants. The aim and purpose of the study were clearly explained, and participation was voluntary. All data were anonymised and kept confidential. Though confidentiality could not be guaranteed in FGDs, participants were asked to keep all group discussions confidential.

# Results

## Study I: Global trends in reported antibiotic use for sick children across LMICs in 2005-2017

Globally, LMICs saw a modest increase in reported antibiotic use for sick children during the study period, with a 17% relative increase from 36.8% (28.8-44.7) in 2005 to 43.1% (33.2-50.5) in 2017. Among WHO regions, South-East Asia and Africa with the lowest starting points also recorded the greatest relative increases in reported antibiotic use for sick children during the study period. In South-East Asia, the outcome increased 23% from 24.5% (16.3-34.3) in 2005 to 30.1% (20.3-42.0) in 2017. Similarly, in Africa, there was a 19% relative increase from 29.8% (22.3-38.0) in 2005 to 35.4% (29.8-41.4) in 2017. (Table 4) Yet, reported antibiotic use for sick children remained below the global LMIC average in Africa and South-East Asia throughout the study period. (Figure 3)

Compared to the other country income groups, LICs saw the greatest absolute (9.9%) and relative (34%) increases in the outcome during the study period, from 29.6% (21.2-41.1) in 2005 to 39.5% (32.9-47.6) in 2017. In contrast, the smallest gains in the outcome (1% absolute increase and 2% relative increase) were seen in LMICs-LM, from 40.7% (32.4-48.6) in 2005 to 41.7% (33.7-48.7) in 2017. (Table 4) Throughout the study period, reported antibiotic use for sick children remained highest and above global LMIC average in LMICs-UM. For LICs on the other hand, the outcome was consistently below global LMIC average in 2005-2017.

Among symptom complaints, the greatest absolute and relative increases in the outcome were seen among children with reported cough with fast or difficult breathing, from 41.4% (7.6-80.3) in 2005 to 49.6% (14.3-84.5) in 2017. (Table 4) This was also the group with the highest reported antibiotic use throughout the study period. The lowest reported antibiotic use throughout the study period was seen among children with reported diarrhoea symptoms. (Table 4)

Table 4: Reported antibiotic use for sick children across LMICs in 2005 and 2017 across LMICs globally, by WHO region, country income group, and symptom complaint.

	Proportion of reported antibiotic use for sick children, mean (Uncertainty Interval (UI) 2 <sup>nd</sup> and 98th percentile)			
	2005	2017	Absolute increase in mean 2005-2017	Relative increase in mean 2005-2017
Global LMIC	36.8 (28.8-44.7)	43.1 (33.2-50.5)	6.3%	17%
WHO region				
Africa	29.8 (22.3-38.0)	35.4 (29.8-41.4)	5.6%	19%
Americas	46.4 (27.6-64.4)	52.4 (36.0-65.9)	6.0%	13%
E. Mediterranean	42.0 (31.2-53.7)	45.4 (35.5-55.3)	3.4%	8%
European	60.6 (35.7-78.6)	67.7 (33.0-87.1)	7.1%	12%
South-East Asia	24.5 (16.3-34.3)	30.1 (20.3-42.0)	5.6%	23%
Western Pacific	53.3 (27.7-75.7)	61.7 (28.5-83.8)	8.4%	16%
Income group				
LIC	29.6 (21.2-41.1)	39.5 (32.9-47.6)	9.9%	34%
LMIC-LM	40.7 (32.4-48.6)	41.7 (33.7-48.7)	1.0%	2%
LMIC-UM	55.9 (34.9-73.2)	59.2 (35.3-76.3)	3.3%	6%
Symptom complaint				
Fever	38.8 (9.0-79.2)	43.7 (12.2-82.6)	4.9%	13%
Diarrhoea	34.7 (9.3-70.6)	33.4 (9.3-69.0)	-1.3%	-4%
Cough with fast or difficult breathing	41.4 (7.6-80.3)	49.6 (14.3-84.5)	8.2%	20%

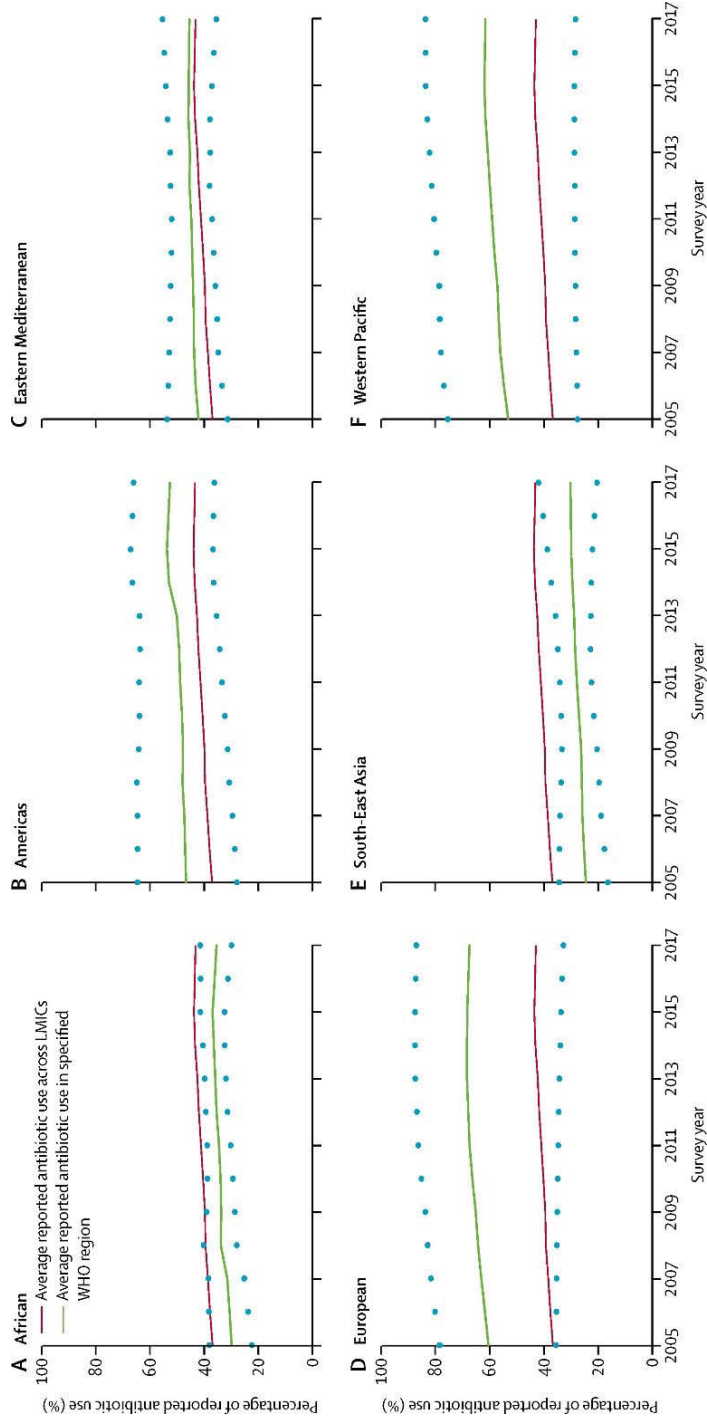


Figure 3: Trends in reported antibiotic use among sick children under 5 years of age across LMICs in 2005–17 by WHO regional groupings (A) African region. (B) Americas region. (C) Eastern Mediterranean region. (D) European region. (E) South-East Asia region. (F) Western Pacific region. The red line represents average antibiotic use across low- and middle-income countries (LMICs). The dots represent uncertainty intervals. (Source: Allwell-Brown et al, 2020.<sup>97</sup>)

# Study II: Global trends in reported antibiotic use for sick children in LMICs by user characteristics in 2005-2017

Across LMICs in 2005-2017, all user groups showed increasing trends in reported antibiotic use for sick children. (Figure 4) However, the outcome was consistently highest during the study period among urban residents, the richest, children having mothers with the highest education levels and those who sought care from the private medical sector. On the contrary, the lowest reported antibiotic use for sick children was consistently reported among the rural, poorest, children having mothers with the lowest education levels, and those who sought care from private informal sources or did not seek care.

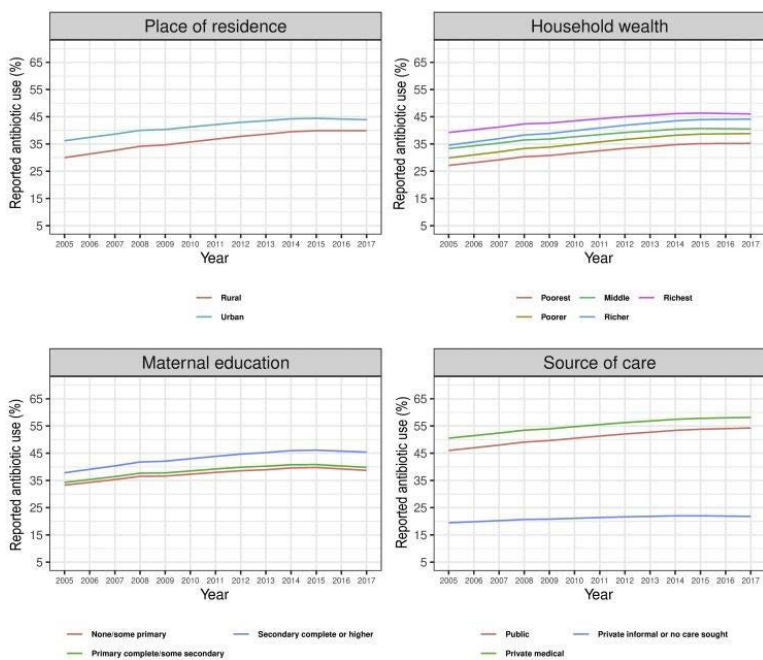


Figure 4: Trends in reported antibiotic use among sick under-five children across low- and middle-income countries in 2005-2017 by user characteristics. (Note: Lines represent mean values for reported antibiotic use in specified user groups. 10th-90th percentile uncertainty intervals for percentage of reported antibiotic use for sick children in 2005 and 2017 are presented in source paper (Allwell-Brown et al, 2021).<sup>98</sup>)



Greater absolute and relative increases in the outcome were seen in rural areas compared to urban areas, and among the poorest compared to the richest children across LMICs during the study period. (Table 5) Rural areas saw a 33% relative increase, from 30.0% (9.0-63.7) in 2005 to 39.9% (14.4-76.2) in 2017, compared to the 21% relative increase in urban areas from 36.2% (13.0-68.7) in 2005 to 43.9% (17.4-77.9) in 2017 (Table 5). Similarly, there was a 30% relative increase in the outcome among the poorest, from 27.1% (9.0-53.6) in 2005 to 35.2% (14.3-64.6) in 2017, compared to a 17% relative increase among the richest children. (Table 5)

Table 5: Reported antibiotic use among sick under-five children across LMICs in 2005 and 2017, by user characteristics.

		Proportion of reported antibiotic use for sick children, mean (Uncertainty Interval (UI) 10 <sup>th</sup> and 90 <sup>th</sup> percentile)			
		LMIC			
		2005	2017	Absolute increase in mean (2005-2017)	Relative increase in mean (2005-2017)
Place of residence	Rural	30.0 (9.0-63.7)	39.9 (14.4-76.2)	9.9%	33%
	Urban	36.2 (13.0-68.7)	43.9 (17.4-77.9)	7.7%	21%
Household wealth	Lowest	27.1 (9.0-53.6)	35.2 (14.3-64.6)	8.1%	30%
	Second	29.9 (10.2-57.8)	38.8 (16.1-68.8)	8.9%	30%
	Middle	33.3 (12.3-60.2)	40.5 (17.5-69.2)	7.2%	22%
	Fourth	34.6 (13.1-61.5)	44.2 (20.4-71.4)	9.6%	28%
	Highest	39.2 (17.0-65.0)	46.0 (22.5-72.4)	6.8%	17%
Maternal education	None/some primary	33.3 (8.9-70.4)	38.7 (12.5-77.7)	5.4%	16%
	Primary complete/some secondary	34.3 (10.3-67.4)	39.8 (15.6-73.3)	5.5%	16%
	Secondary complete or higher	37.8 (12.4-69.6)	45.4 (19.3-76.7)	7.6%	20%
Healthcare source visited	Public	46.0 (24.3-68.1)	54.3 (29.7-77.4)	8.3%	18%
	Private medical	50.5 (25.7-74.7)	58.2 (30.6-82.0)	7.7%	15%
	Private informal or no care sought	19.5 (7.6-39.0)	21.8 (8.6-45.4)	2.3%	12%

Similar trends as observed across LMICs globally were seen in Africa and South-East Asia. However, the increases in the outcome among user groups were greater in South-East Asia compared to Africa (Figure 5). For example, in South-East Asia in 2005-2017, there was an 81% relative increase in the outcome in rural areas from 25.9% (7.1-73.0) in 2005 to 46.8% (15.8-93.0) in 2017, compared to a 7% rise in South-East Asian urban areas. In comparison, rural African areas saw a 28% relative increase from 24.0% (5.7%-56.9) in 2005 to 30.8% (12.0-61.0) in 2017 compared to 19% rise in urban African areas.

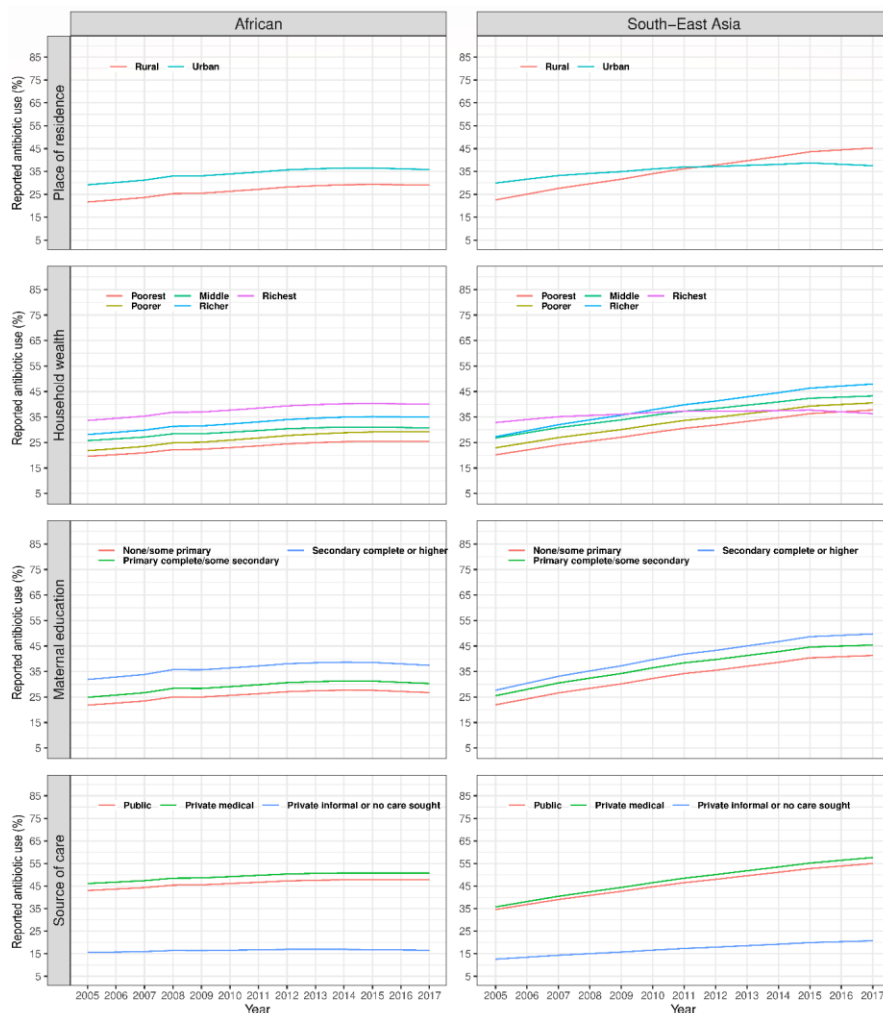


Figure 5: Trends in reported antibiotic use among sick under-five children in WHO regions Africa and South-East Asia in 2005-2017 by user characteristics. Note: Lines represent mean values for reported antibiotic use in specified user groups. 10th-90th percentile uncertainty intervals for percentage of reported antibiotic use for sick children in 2005 and 2017 are presented in source paper (Allwell-Brown et al, 2021)<sup>98</sup>

### Study III: Antibiotic prescribing patterns in Bugisu, Eastern Uganda

Antibiotics were prescribed for 62.2% of 3,471 febrile under-five outpatients that attended 37 public and PNFP primary and secondary healthcare facilities in Bugisu, Eastern Uganda between January 2019 and December 2020. There were a total of 2,478 antibiotic prescriptions of 22 antibiotic types: amoxicillin (52.2%), co-trimoxazole (14.7%), metronidazole (6.9%), gentamicin (5.7%), ceftriaxone (5.3%), ampicillin/cloxacillin (3.6%), penicillin (3.1%), and others (8.6%). (Figure 6). Febrile under-five outpatients received on average, 0.74 antibiotics per clinical encounter.

The commonest reported diagnoses were malaria (1,414 (39.3%)), acute upper respiratory tract infection, AURTI (1,381 (38.4%)), diarrhoea (548 (15.2%)), pneumonia (370 (10.3%)), skin infections (227 (6.3%)), non-specific bacterial infections (“bacteraemia”, “septicaemia”, “sepsis”, and “bacterial infection”) in 200 (5.6%), and helminthiasis in 154 (4.3%) children. AURTI was the commonest single indication for antibiotic prescribing. Of 676 children with AURTI as the only documented diagnosis, 516 (76.3%) received antibiotics.

Of 314 children aged 2-59 months diagnosed with non-severe pneumonia, almost all (303 (96.5%)) received at least one antibiotic prescription. Of these, 226 (72.0%) received prescriptions for amoxicillin, with only 29 children (9.2%) receiving a prescription for amoxicillin at the appropriate dose for up to five days, in accordance with national guidelines. One-hundred-and-three (15.2%) of 680 children with malaria as the only documented diagnosis, and 77 (40.1%) of 192 children with acute watery diarrhoea as the only documented diagnosis received antibiotics.

All 13 children with dysentery, and all 30 children with severe pneumonia diagnosis received at least one antibiotic. In these cases, the choice and combinations of antibiotics prescribed varied, and in almost all cases did not match guideline recommendations.

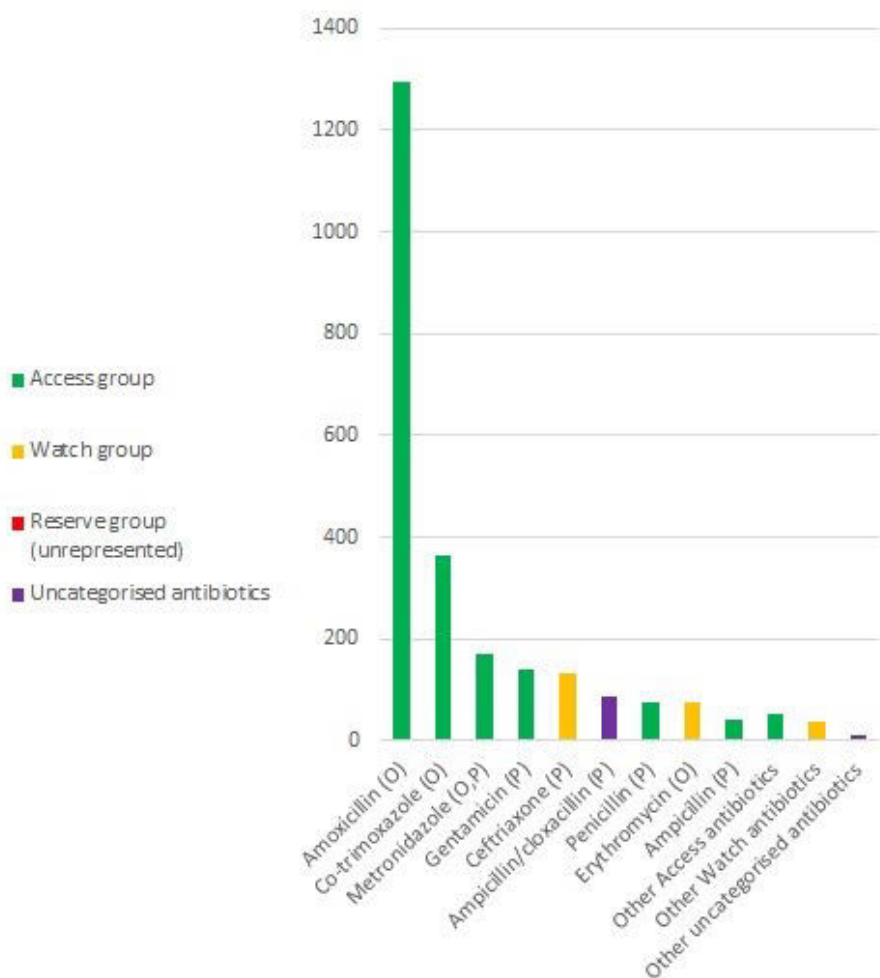


Figure 6: Frequency of antibiotic prescriptions for febrile under-five children attending lower-level healthcare facilities in Bugisu, Eastern Uganda in 2019 and 2020 by AWARe classification

### *Contextual determinants of antibiotic prescribing*

After adjusting for patient-level variables (Level-1), 22.0% of the variation in antibiotic prescribing for febrile under-five outpatients was attributed to between-healthcare facility differences. (Model 2, Table 6). In the final model, 11.4% of this variation remained unexplained. (Model 3, Table 6).

Higher health centre levels compared to HC-II facilities, and PNFP ownership (Adjusted Odds Ratio, 4.30; 95% Confidence Interval, 1.91-9.72) (Model 3, Table 6) were significant contextual determinants of antibiotic prescribing. A higher patient-to-prescriber ratio and physical presence of Uganda Clinical Guidelines at healthcare facilities showed no significant association with antibiotic prescribing. (Model 3, Table 6).

Table 6: Patient- and healthcare facility-level determinants of ATC J01/P01AB antibiotic prescribing for febrile under-five outpatients at surveyed healthcare facilities in Bugisu, Eastern Uganda. **Model 1** is the null model; **Model 2** includes Level-1 variables; **Model 3** includes Level-1 and Level-2 variables.

	<b>Model 1</b>	<b>Model 2</b>	<b>Model 3</b>
	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
<b>Child's age</b>			
<6months	-	Ref	Ref
6-24 months	-	1.04 (0.69-1.56)	1.04 (0.69-1.57)
>24 months	-	1.07 (0.70-1.64)	1.09 (0.71-1.68)
<b>Child's sex</b>			
Male	-	Ref	Ref
Female	-	0.97 (0.79-1.19)	0.97 (0.79-1.19)
<b>Date of presentation</b>			
Jan-Mar 2019	-	Ref	Ref
Apr-Jun 2019	-	0.94 (0.63-1.39)	0.91 (0.61-1.36)
Jul-Sep 2019	-	0.90 (0.60-1.35)	0.90 (0.60-1.35)
Oct-Dec 2019	-	0.70 (0.45-1.10)	0.70 (0.44-1.10)
Jan-Mar 2020	-	0.87 (0.58-1.29)	0.85 (0.57-1.27)
Apr-Jun 2020	-	0.94 (0.61-1.44)	0.95 (0.61-1.46)
Jul-Sep 2020	-	0.55 (0.36-0.84)*	0.56 (0.36-0.86)*
Oct-Dec 2020	-	0.82 (0.54-1.23)	0.81 (0.54-1.22)
<b>Malaria test result</b>			
Positive	-	Ref	Ref
Negative	-	4.88 (3.80-6.26)*	4.80 (3.74-6.16)*
<b>Pneumonia<sup>a</sup></b>			
No	-	Ref	Ref
Yes	-	42.99 (21.86-84.54)*	44.80 (22.01-91.22)*
<b>AURTI</b>			
No	-	Ref	Ref
Yes	-	4.96 (3.92-6.27)*	5.18 (4.09-6.57)*
<b>Acute watery diarrhoea<sup>b</sup></b>			
No	-	Ref	Ref
Yes	-	0.71 (0.53-0.96)*	0.75 (0.56-1.01)
<b>Skin infection</b>			
No	-	Ref	Ref
Yes	-	5.00 (2.75-9.12)*	5.11 (2.78-9.41)*
<b>Non-specific bacterial infection<sup>c</sup></b>			
No	-	Ref	Ref
Yes	-	22.62 (9.45-54.10)*	22.42 (9.39-53.56)*
<b>Helminthiasis</b>			
No	-	Ref	Ref
Yes	-	0.60 (0.37-0.99)*	0.61 (0.37-0.99)*
<b>Health centre level</b>			
HC II	-	-	Ref
HC III	-	-	4.56 (2.43-8.55)*
HC IV	-	-	2.44 (1.23-4.82)*
General hospital	-	-	6.82 (1.42-32.82)*
<b>Healthcare facility ownership</b>			
Public	-	-	Ref
PNFP	-	-	4.30 (1.91-9.72)*
<b>Uganda Clinical Guidelines available</b>			
No	-	-	Ref
Yes	-	-	0.59 (0.27-1.29)
<b>Patient/prescriber ratio</b>	-	-	1.04 (1.00-1.09)

Model measures of clustering			
Healthcare facility-level variance (Standard Error)	.931 (0.248)	0.929 (0.266)	0.425 (0.140)
Proportional change in variance	-	0.21%	54.25%
Intra-class correlation	0.221	0.220	0.114
Median Odds Ratio	2.51	2.51	1.86

<sup>a</sup> Includes 526 cases of acute watery diarrhoea, 14 cases of dysentery and 8 cases of persistent diarrhoea

<sup>b</sup> Includes 337 cases of non-severe pneumonia and 33 cases of severe pneumonia

<sup>c</sup> “Non-specific bacterial infection” refers to the following diagnoses: “bacteraemia”, “septicaemia”, “sepsis”, and “bacterial infection”.

## Study IV: Healthcare providers’ considerations in antibiotic prescribing for febrile under-five patients

FGDs and in-depth interviews were conducted with a total of 85 participants from 16 primary and secondary healthcare facilities in Bugisu, Eastern Uganda. Participants had a mean age of 36.8 years, and were mostly females (64/85), from public (61/85) and secondary (54/85) healthcare facilities.

Results of data analysis are presented at five levels, in accordance with the theoretical framework guiding this thesis (Figure 1): (i) Individuals, households and communities, (ii) Service delivery, (iii) Health sector, (iv) Governance at national and sub-national levels, and (v) International level

### Level I: Individuals, households and communities

Care-seeking from healthcare facilities was described as heavily influenced by availability of medicines, with high attendance rates when medicines were available, and low attendance during medicine stock-outs. Community members were said to be generally aware of the status of medicine stocks at local healthcare facilities, and came with high expectations of receiving medicines, including antibiotics.

*OLP: So you become busy when there is stock? How do they (the community) know that there is stock?*

*R: [Audible reactions in the group]*

*R6: Yeah, they will know of course! Like ‘Let me come and get- they brought medicine’, so they come.*

*R3: There are those who know the vehicle, they see the vehicle coming.*

*R1: Even if the vehicle comes today at this time, the people will be here, and when indeed they are sick.*

*OLP: So at this point in time they are not sick?*

*R1: They are sick, they are sick. And there are few now who are buying [medicines], and there are those who are just at home. They are waiting for the government drugs.*

*FGD 6 (Public and PNFP HC-II nurses)*

When antibiotics were not available at healthcare facilities, affordability was said to be a challenge for many. Participants described that some caregivers would rather wait at home with sick children, than buy antibiotics or go to a referral centre.

*R6: You tell this mother, 'I would have loved to give you ABCD but I don't have [...]. Go to the referral'. They will tell you 'I will not'. [...] The following day they will come back, 'Musawo (doctor) have they brought the drugs?' - just like that!*

*FGD 4 (Nurses, public secondary healthcare facility)*

Participants stated that sometimes caregivers came to the healthcare facilities, giving false medical histories, or presenting several children in a single visit so as to obtain medicines (including antibiotics) for later use.

*R6: ...that's why you see that the number (patient load) is always big here, because the mother will come with her seven children and I cannot chase her away. And maybe her target is just to get some first aid and keep at home...*

*FGD 8 (Nurses, public HC-III)*

## Level II: Service delivery

### **Availability of diagnostics and antibiotics**

Participants from public healthcare facilities felt that, by regulation, they were expected to prescribe antibiotics available within their healthcare facilities, which patients should receive free-of-cost. They reported adhering to these regulations when antibiotic stocks were available, but were forced to ask patients to buy antibiotics from external sources during stock-outs. Sometimes stock-outs provided an opportunity to prescribe outside the range of antibiotics normally supplied to the healthcare facilities.

Furthermore, diagnostic tests or other materials to facilitate testing (such as gloves, reagents, vacutainers, etc.) were not always available. Malaria rapid diagnostic tests (mRDTs) were reported as routinely performed across all health centre levels, while microscopy was available at some HC-III and above, and complete blood count (CBC) was available in some HC-IV and General Hospital level facilities. Patients thought to require culture and sensitivity testing were referred, or [less commonly] had their samples sent to the Regional Referral Hospital. During stock-outs of mRDTs and other supplies, respondents asked patients to procure test kits from private markets, referred the patient, or gave symptom-based treatment often covering for both malaria and “bacterial infection”.

Participants, especially those from public primary healthcare centres, reported feeling limited in terms of antibiotic choices, as they were only supplied with “one drug”- amoxicillin. They felt constrained to prescribe the

“same drug” even when the patient had already been exposed to it, or was in their opinion, clearly not responding to amoxicillin treatment.

At PNFPs [and public healthcare facilities during stock-outs], affordability of antibiotics was an important consideration in prescribing.

*R1: ...The cost of the drug also influences my prescription. I may want to give someone ceftriaxone (an antibiotic), but this person tells me, 'I only came with 2000 [Ugandan Shillings]'. So I will automatically opt for a cheaper drug and we look at Amoxil (amoxicillin). So the availability and the cost [are considerations] for us the PNFPs.*

*FGD 6 (Nurses, PNFP and public HC-II)*

## **Health Financing**

Participants expressed that financing for medicines and supplies to their healthcare facilities was insufficient, and that stocks ran out soon after supplies were received.

*R1: As you sit down as Health Centre III's and budget, you realize that because we have very many demands, we normally go beyond the money we are given. So you have to sit down and reduce certain things; that's why we always come to a limited number [...]. So, for example if you are saying we need 100 boxes of Amoxikid (amoxicillin) and it goes beyond, you have to reduce and reduce until maybe like now we are getting 40. So that's the challenge we normally get. It's the money that we are assigned to as Health Centre III that limits us.*

*FGD 8 (Public HC-III nurses)*

*R1: ...we last received drugs in May (three months ago) and up to now, we have not received, and most of the drugs are out of stock. What they also give us is very little compared to the number of patients we are handling, it can take us less than even a month and the drugs get out of stock. So, stock-outs are very common.*

*FGD 5 (Public HC-III nurses)*

Laboratory staff at public primary healthcare facilities described that their limited budget was spent mainly on mRDTs, giving little room for other diagnostic tests, even when they desired and felt capable of providing a wider range of diagnostic services, for example, microscopy.

*Of course now I cannot put a microscope there (on the list of supplies to be ordered), I can't. [...] When you make a budget, they want you to use 1,800,000 [Ugandan Shillings] in a year [...] When you look at the RDT, government buys it 45,000 a box. Now government is looking at the high prevalence of malaria, so for them they will finish the whole budget on malaria. When you see their consignment, it is full of RDTs.*

*IDI 7 (Laboratory technician, public HC-III)*



Results-based financing (RBF) was desirable among participants, as healthcare facilities with RBF funds had greater autonomy in procurement of medicines, and could access a wider range of antibiotics. Also, the effect of stock-outs of medicines from the National Medical Stores (NMS) in these facilities were said to be mitigated by RBF funds.

*JNS: So when the medicines are out of stock before [the end of the quarter], are you able to make a request to have them delivered?*

*R: Like with NMS, you wait for the cycle to come, except for those RBF facilities [...]. You breach the gap by using RBF funds, and then you buy some commodities to make you run as you wait for NMS to deliver. But here there is nothing like that, they just wait- no RBF.*

*IDI 4 (Clinical Officer, public HC-II)*

### **Health information**

Participants from public primary healthcare facilities described that patients were expected to be responsible for their own medical records keeping. Each patient should keep notebook where their medical records are documented, and present this at each visit to the healthcare facility. Participants however reported that a common practice among caregivers was to re-use the same notebook for several members of the same family, tearing out used pages so the book appears new at each visit. This presented challenges in following up antibiotic treatment trails, and health workers often had to rely on memory to identify and manage follow-up patients, or start antibiotic treatment afresh.

### **Health infrastructure**

Health workers described that referral of patients was challenging, as caregivers were generally reluctant to be referred. Even though diagnostic tests and treatment were available free-of-cost at public referral centres, distance and transportation costs were cited as major barriers to referral.

*R2: Another challenge that I see it is the referral system. If you get a very ill patient referral is very hard. Like if you want to get like a special vehicle it's 100,000 Shillings; whereby people are very poor- they can't afford. So most of the people carry their people home and they go to die there. [...] Let's say you use a vehicle from here in the main taxi you can take four hours on the way. So if someone is very ill and you want emergency, the transport is very hard.*

*FGD 10 (PNFP HC-IV nurses)*

As such, health workers sometimes took personal measures to expand services within their healthcare facilities as an alternative to referral.

*JNS: Do you normally have or stock any injectable medicines here?*

*R: We as a health centre II, we have not been stocking them and the district does not give them to us. But if there are conditions which require us to use them, we go to other health centre IVs [...]. We can go there and ask if we need drugs like Artesunate, ampicillin, and we use them in babies and in severe malaria, but we don't get them as health centre II's.*

*IDI 8 (Clinical Officer, public HC-II)*

## **Human resources**

### *Healthcare worker roles*

The task of antibiotic prescribing was described as primarily that of Clinical Officers and Medical Officers, but nurses and nursing assistants reported taking on this role in their absence, or in facilities that lacked these cadres. Some reported that in such instances, lack of clinical support in situations of diagnostic uncertainty affected prescribing behaviour.

*R1: ... since health centre II's don't have Clinical Officers, we handle prescriptions as nurses. Yet for some situations we require some consultation, and since that immediate supervisor of a Clinical Officer is not around, you end up fidgeting with the prescription.*

*Female, FGD 9 (Nurses, PNFP and public HC-II)*

Heavy patient load especially at public secondary healthcare facilities was reported as leading to inadequate time for proper history and examination, long waiting times for lab results, missed doses for parenteral antibiotics, and over-prescribing of ceftriaxone because of its convenient, once-daily dosing.

Participants from public primary healthcare facilities expressed dissatisfaction that their capacities were being under-used at their healthcare facilities, and that working at these lower-level healthcare facilities led to a deterioration of clinical skills. Some also expressed a sense of loss of prestige among caregivers as a result of the limited range of medicines or procedures they were allowed to prescribe or carry out. Administering medicines (including antibiotics) outside the recommended range for their health centre level sometimes provided an opportunity to demonstrate their skills and gain prestige among caregivers.

*R6: ... I hope the government would at least add in more drugs, rather than giving us only one type of drug because these patients, they don't suffer from the same illness or suffer from the same sickness whereby always one drug, one drug! It is a bit challenging.*

*R5: It is challenging.*

*R6: And some patients may think that these nurses do not know, yet that's all.*

*R1: That's why they give them one type of drug.*

*[...]*

*R1: No injectable, no emergency drugs, the boy then starts convulsing, we just look [...]*

*R5: Actually it is true because these people go and buy drugs- the injectables- and they come here, and they first ask you: "doctor do you know how to administer and you help me?"*

*(All laugh)*

*[...]*

*R1: I have spent five years here without cannulation.*

*OLP: No wonder they come and ask you if you can put cannulas*

*R3: They always come; and they will see- if they give you their time and you attend to them, that is when they will realize that these people also know.*

*FGD 6 (Nurses, public and PNFP HC-II)*

### *Health worker motivations*

#### *Empathy*

Sometimes, participants were motivated by empathy to prescribe antibiotics, due to perceived or expressed caregiver social constraints; for example, inability to afford diagnostics or medicines when stocks were out, or real or perceived reluctance to be referred due to financial constraints or transportation difficulties.

*"...the reason why the patient has come to you is because there is need for a service but they lack the money to avail the service, so the only option is you at the facility. So, if you cannot be able to help them in a way that you are not able to give them that antibiotic, then definitely it will make them feel bad..."*

*IDI 3 (Clinical Officer, public HC-III)*

*"...there is a low supply from the National Medical Stores- it is not sufficient to our [healthcare facility], but the policy stipulates that we are not supposed to tell the patients to go out to buy the drugs [...]. But we always endeavour. We feel. We are parents. We find ourselves saying 'please go and buy' and sometimes we sacrifice because the child is very ill and convulsing, and you sacrifice your 1000 [Ugandan Shillings] – 'please you go and buy this'."*

*FGD 2 (Nurses, public secondary healthcare facility)*

#### *Financial gain*

One participant from a PNFP primary healthcare facility described financial gain as a motivation for antibiotic prescribing, as health worker salary where she worked was directly correlated with revenue generated at individual level.

*"...If a month ends and I only raised 20,000 a month, questions and worries may come. What's happening? So, I may opt for bigger drugs to fetch in some bigger money..."*

*FGD 6 (Nurses, PNFP and public HC-II)*

In a public secondary healthcare facility, participants in a FGD of nurses described “*motivation*” from medicine sales reps as influencing prescribing behaviour.

### Level III: Health sector

Caregivers were commonly reported to have administered antibiotics to their children before seeking care at healthcare facilities, either by self-medication (sometimes based on older prescriptions), or through prior care-seeking from private drug shops, pharmacies or clinics. Participants expressed that the private retail sector was in dire need of regulation, as antibiotics could easily be obtained over-the-counter at drug shops, and quantities bought were based on “*how much they had in the pocket*”, rather than quantities needed. Oftentimes, patients having received prior medications came to healthcare facilities without documentation, so that health workers needed to guess what antibiotics they had received, or simply disregard any prior antibiotic use.

*R5: They just buy from some clinics or drug shops but they do not prescribe, they do not write anything down so you guess what this would have been. This very tablet or this coloured capsule- you don't know exactly what they have given, so that's the dilemma we are in.*

*FGD 1 (Clinical Officers, public secondary healthcare facility)*

Sometimes, more well-off caregivers brought children to public healthcare facilities, having already administered “higher-class” antibiotics. They thus expressed a sense of distrust in the government-provided antibiotics, which they perceived to be of inferior quality. Health workers were sometimes also of the opinion that more expensive antibiotic brands were of higher quality, and that changing of brands of the same antibiotics affected treatment.

*R6: ...German Fansidar (antimalarial) was at 3000 Shillings while Ugandan Fansidar was at 600, meaning that the other one was more effective than the Ugandan one. Even ceftriaxone- there is a type that is at 9000 Shillings and another one that is at 2000, meaning that the effectiveness of some of these drugs is not all that good, depending on the manufacturers.*

*FGD 1 (Clinical Officers, public secondary healthcare facility)*

*R6: ...You will find that a patient may not respond to the “Cef” (ceftriaxone) from India that we stock. Yet, if you give them the “Cef” from Egypt, it will be more effective- and the one from Germany will also work better.*

*FGD 4 (Nurses, public secondary healthcare facility)*

## Level IV: Governance at national and sub-national levels

### Local government and word in the community

Caregiver reports about quality of services provided were described as influencing antibiotic prescribing among participants from both public and PNFP facilities. While PNFP participants' concerns were mainly related to revenue generation, participants from public healthcare facilities expressed that failure to provide satisfactory services (including the provision of antibiotics) could be met with negative comments about poor service delivery spread in the community, or reports made to local government officials which could impact their employment. For instance, when under-aged children came to healthcare facilities as guardians of younger children, health workers feared that turning them back and asking them to return with an adult (who could give a proper clinical history and better understand treatment instructions) could lead to exaggerated or false reports at the sub-county.

*R7: Sometimes you send them back to call the parents, but before coming here, she first goes to the sub-county, 'they have sent my children back, they have not offered them any services'.*

*JNS: The parent?*

*R7: Yes, she first goes to the sub-county and reports, then she will come back.*

*JNS: After reporting?*

*R7: Yes.*

*R6: And the councillor will come for you!*

*FGD 8 (Nurses, public HC-III)*

### National clinical guidelines

National clinical guidelines were cited as a common consideration in antibiotic prescribing across all FGDs and in-depth interviews. However, these were sometimes said to be physically unavailable, in short supply, or outdated. A few participants expressed doubt in the guidelines, regarding the prescribing of ciprofloxacin for dysentery, and gentamicin in children

## Level V: International context

In some PNFPs, support from foreign development partners was said to contribute to the sustained availability of available medicine stocks in the facilities, although diagnostics availability remained a challenge. And, in one public secondary healthcare facility, it was reported that support from foreign implementing partners during the COVID-19 pandemic with the provision of pulse oximeters helped to broaden the diagnostic capacity at the facility.

# Discussion

The discussion of study findings is divided into two main parts: *Part I* is a discussion of the LMIC trends in reported antibiotic use for sick under-five children in relation to findings from other global trend analyses on antibiotic consumption since 2000. *Part II* discusses the determinants of antibiotic prescribing for febrile under-five patients in the Ugandan context, based on the framework guiding this thesis (Figure 1). *Parts I* and *II* findings are later integrated under the title “Implications of study findings” in the Conclusion section of the thesis.

## Part I: Reported antibiotic use for sick under-five children in LMICs

We found a modest increase (17% relative increase) in reported antibiotic use for sick under-five children across LMICs in 2005-2017. And, in 2017, about 43% of sick under-five children in LMICs reportedly received antibiotics for fever, diarrhoea, or cough with fast or difficult breathing. LICs, African and South-East Asian countries recorded the greatest relative increases in the outcome during the study period, but also consistently recorded the lowest reported antibiotic use for sick under-five children. Within LMICs, reported antibiotic use for sick under-five children increased across all user groups. The greatest gains (yet consistently lowest reported antibiotic use for sick under-five children) were seen among the poorest children, those living in rural areas, and having mothers with the lowest education levels. Conversely, the outcome remained highest among the wealthiest children, those living in urban areas, and having mothers with the highest education levels.

The global LMIC increase in the outcome reported in **Studies I** and **II** is much less pronounced than those reported by earlier studies, which could have been as a result of different methodological approaches, or differences in countries included and population groups studied. For instance, while LICs and LMICs-LM were under-represented in earlier studies,<sup>31, 36, 37</sup> they were the main feature of our studies. An earlier study attributed 76% of the global increase in antibiotic consumption to five countries: Brazil, Russia, India, China and South Africa.<sup>37</sup> Of these countries, only India featured in our studies and drove

South-East Asia trends, where we found the greatest increases in reported antibiotic use for sick under-five children across user groups. Yet, despite the large increases in total antibiotic consumption in India documented in earlier studies,<sup>31, 36, 37, 99</sup> antibiotic consumption rates (consumption per person) in India remain lower than the European average.<sup>99</sup> This supports our finding that proportion of reported antibiotic use for sick under-five children in South-East Asia remained below global LMIC average in 2005-2017.

The only study prior to **Studies I** and **II** that estimated global trends in paediatric antibiotic consumption in 2011-2015 (using consumption of child appropriate formulations as proxy) also reported a “slight increase”,<sup>40</sup> supporting our findings of a modest increase in the paediatric population. However, the time frame studied was shorter than ours, which may have also explained the modest increase the study was able to demonstrate. A more recent study combined pharmaceutical sales data (used in previous global analyses) with DHS and MICS data to provide estimated antibiotic consumption trends globally in 2000-2018.<sup>100</sup> Though our results are not directly comparable (due to differences in methodology, and regional groupings used), their finding that antibiotic consumption rates in Sub-Saharan Africa, and in South-East Asia, East Asia and Oceania were lower than the LMIC average are in line with our findings.

In LMICs, rising antibiotic consumption is positively correlated with economic growth (specifically Gross Domestic Product per capita).<sup>31, 37</sup> This supports our findings that within LMICs, proportion of reported antibiotic use for sick under-five children tended to increase with higher country income group, and remained above global LMIC average in wealthier WHO regions (all regions except Africa and South-East Asia). In addition, **Study II** findings suggest that the same “wealth effect” on antibiotic consumption may apply at individual and household levels within LMICs. Contrary to these LMIC trends that we report, antibiotic use tends to be higher among poorer population groups in high-income countries with universal health coverage.<sup>101</sup>

LMICs are an immensely diverse group of countries, and it would be misleading to draw generalised conclusions on the implications of **Studies I** and **II** without contextualised evidence. Moreover, as these studies did not provide information on specific antibiotic types reportedly used, their dosages or aetiologies of illness symptoms, it is difficult to evaluate the appropriateness of reported antibiotic usage based on these studies alone. **Studies III** and **IV** conducted in Eastern Uganda (a low-income setting), provide a deeper understanding of some of the everyday realities underlying the global trends reported.

In the following paragraphs, I discuss contextual determinants of antibiotic prescribing at public and PNFP, primary and secondary healthcare facilities,

in Bugisu, Eastern Uganda, using the conceptual framework guiding this thesis (Figure 1). I have deliberately taken a comprehensive approach that covers the entire framework, to emphasize the potential of all parts of the health system to influence antibiotic prescribing and access, thus creating opportunities for interventions. Since **Study IV** is the only study that cuts across all levels of the framework, its findings will guide the general discussion, with elements of other component studies drawn upon where relevant.

## Part II: Contextual determinants of antibiotic prescribing in Eastern Uganda

### Level-I: Individuals, households and communities

Caregiver expectations and demands were important influences on antibiotic prescribing among both public and PNFP study participants. And, in public healthcare facilities, when antibiotics were not available, affordability was reported as being a problem for many. This is a plausible finding, given the high level of poverty in the region,<sup>93</sup> and that poorer populations in Uganda have a greater tendency to use public healthcare facilities where services are free.<sup>102</sup> Participants reported that even when antibiotics may have been available at referral centres, distance and transport barriers made caregivers reluctant towards referral. Similar findings about distance and cost barriers to referral have been reported in Wakiso, a densely-populated district bordering Kampala, Uganda's capital.<sup>103</sup>

Medicines (including antibiotics) could not always be guaranteed to be available at public healthcare facilities. Therefore, while there were available medicine stocks, caregivers were described as going to various lengths (such as giving false medical histories, and presenting several children at a time who were suspected not to be ill) to procure medicines, presumably for home storage in case of eventual illness. Inevitably, this community behaviour contributes to an overload of the public healthcare system, and a drain on already strained resources, perpetuating a vicious cycle of lack of access to diagnostics and antibiotics, and lack of trust in the public healthcare system.

### Level-II: Service delivery

#### **Medicines and technologies: availability of diagnostics**

**Studies III** and **IV** demonstrated an uneven availability of diagnostic tests within and between health centre levels. mRDT was the only test reported to be routinely performed across all healthcare facilities regardless of level. Yet, stock-outs of malaria test kits were common, and even in facilities where other types of diagnostic tools (e.g. microscopy, CBC) were said to be available, lack of other materials such as gloves or reagents, and frequent breakdown of



equipment commonly hindered their use. Lack of adequate diagnostic capacity at primary and secondary healthcare facility levels is not uncommon in Uganda and similar LMIC contexts. One study found that median availability of diagnostics across 10 LMICs including Uganda was 19.1% at basic primary healthcare facilities, and 49.2% in advanced primary care level.<sup>104</sup> Another study in Uganda found that laboratory tests were performed in less than 30% of patients attending primary healthcare facilities with diagnoses requiring investigations.<sup>105</sup> When health workers were unable to perform diagnostic tests, caregivers were generally described as being unable or unwilling to procure diagnostic services from private sources, or to be referred. This commonly led to empirical prescribing of both antimalarials and antibiotics.

Findings from **Study III** suggested an over-prescribing of antibiotics, with 62.2% of febrile under-five outpatients receiving an antibiotic prescription. This rate is similar to the 60.1% and 62.7% antibiotic prescribing proportions reported on average across other LMIC settings, including Uganda.<sup>45, 46</sup> Given the relatively low prevalence of conditions with clear clinical indications for antibiotic prescriptions in **Study III** (dysentery (0.39%) and pneumonia (10.3%)), the 62.2% antibiotic prescribing proportion we found is likely high. There were other, more “generic” diagnoses reported in **Study III** that may have warranted antibiotic prescriptions (skin infections, and non-specific bacterial infections). Yet, even if all of these patients, including those with dysentery and pneumonia, required antibiotics for each condition separately, their total prevalence (22.6%) would still be well-below the antibiotic prescribing proportion of 62.2% that we found. The high antibiotic prescribing rate could at least be partly attributed to the lack of diagnostic support for non-malarial fevers that has been described in other studies.<sup>44, 106</sup>

Even in the absence of affordable, context-appropriate point-of-care diagnostic tools for non-malarial fevers, there are some relatively high-impact, “low-hanging fruits” that could be addressed in LMICs. **Study III** found antibiotic prescribing for AURTI, malaria, and acute watery diarrhoea, even when these were the only reported diagnoses; and in **Study I**, about one-third of children across LMICs with diarrhoea received antibiotics in 2017, despite only a small proportion of diarrhoea cases requiring antibiotic treatment. Similar reports of antibiotic prescribing for AURTI, malaria, and acute watery diarrhoea have been made in other studies in LMIC contexts;<sup>45, 46, 107-109</sup> yet, these prescriptions may to a large extent be considered unnecessary.<sup>110</sup> Given the high prevalence of these conditions in Uganda and similar settings, interventions to minimise antibiotic prescribing for these conditions could greatly reduce antibiotic consumption in these populations.

## **Medicines and technologies: availability of antibiotics**

**Study III** found that the main antibiotics being prescribed for febrile under-five outpatients at primary and secondary healthcare facilities were amoxicillin and co-trimoxazole of the Access group. These were also the top two antibiotics distributed by Uganda's National Medical Stores to public secondary and tertiary healthcare facilities in 2019.<sup>111</sup> **Study III** also found that, co-trimoxazole and ampicillin/cloxacillin were commonly prescribed, despite their not being indicated in any of the reported diagnoses in the study.<sup>110</sup>

Availability of antibiotics within public healthcare facilities was cited as perhaps the strongest consideration in antibiotic choice among healthcare workers, as health workers felt they were required by regulation to prescribe antibiotics available within the healthcare facility, which could be obtained free-of-cost by patients. Participants from public primary healthcare facilities felt particularly constrained by the limited range of antibiotics they were supplied, and were therefore expected to prescribe. Similar to our findings at lower level facilities, availability of antibiotics within tertiary healthcare facilities in Uganda has also been shown to be a key influence on prescribing practices.<sup>112</sup>

## **Health information**

Patient record keeping and follow-up is important in monitoring antibiotic treatment response or suspected resistance. As observed in **Study III** (manuscript), surveyed primary healthcare facilities lacked the capacity (human and material resources) to maintain patient records. Indeed, **Study IV** found that patients were expected to be responsible for their own medical records keeping – caregivers visiting public primary healthcare facilities were expected to buy a notebook (one per patient) for their medical records, and presenting the book was considered a prerequisite to being attended to at the healthcare facility. To save cost, caregivers re-used books for other children or family members, tearing off old documentation so as to give the appearance of a new book at each visit. This presented a challenge to follow-up so that health workers often needed to rely on memory or start antibiotic treatment afresh with each patient visit. This may be an under-investigated area, as no studies were found that reported similar findings. Perhaps allowing caregivers to keep a “family book” instead of a book per patient may facilitate adherence in this population.

## **Health financing**

Funding for medicines and supplies was generally described as insufficient, especially at public healthcare facilities. However, participants from PNFPs and public healthcare facilities with access to RBF enjoyed access to a wider range of antibiotics within their healthcare facilities. Some PNFP participants in addition had the possibility to source for unavailable medicines on behalf

of patients. PNFPs are partially funded by out-of-pocket payment, in addition to foreign development partner support and government contributions,<sup>78</sup> which could explain their access to a wider range of medicines and the significantly higher antibiotic prescribing in PNFPs compared to public healthcare facilities that was seen in **Study III**.

RBF was generally considered desirable among participants from public healthcare facilities, as the additional funds helped to mitigate the effects of medicine stock-outs and increased their autonomy in medicines procurement. RBF refers to a “cash payment or non-monetary transfer made to a national or sub-national government, manager, provider, payer or consumer of health services after attainment and verification of predefined results”.<sup>113</sup> Though recognised and promoted in Uganda as an innovative means to improve health systems performance, national uptake and implementation of RBF has been slow, mainly due to perceived difficulties with integration into public health systems.<sup>114</sup> Similar to our findings, RBF has been reported to increase healthcare facility autonomy and perceived access to essential medicines in similar LMIC contexts.<sup>115, 116</sup> Yet RBF as currently implemented in many contexts has been criticised as an unsustainable donor fad, possibly doing more harm than good to health systems in LMICs.<sup>117</sup> Nevertheless, recent renewed policy interest in RBF adoption in Uganda has been attributed, among other factors, to the incentive of foreign funding.<sup>118</sup>

### **Human resources for health**

A key factor influencing antibiotic prescribing behaviour, especially at public primary healthcare facilities, was the sense of prestige that came with prescribing or administering antibiotics that were typically out-of-supply-range for the healthcare facility level. To the health workers, the availability of “one drug” at their facilities gave an impression to caregivers that their knowledge about alternatives was as limited as the range of supplies they received. Moreover, some health workers took personal measures to expand services for patients within their healthcare facilities instead of referral, such as collecting antibiotics from other healthcare facilities that were not normally supplied at their health centre level. This behaviour was partly driven by a sense of personal capability to handle more complicated conditions than what was expected for their facility level. Indeed, health workers with sufficient training may be capable of providing a wider range of services, which could be life-saving in some instances where access to alternative healthcare services is limited. However, in the absence of clear regulations (with effective monitoring) on what cadres are allowed to prescribe specific antibiotic types, such actions could perpetuate or worsen poor antibiotic prescribing practices. Our findings highlight the need for greater investment in human resources for health, and improved alignment of health worker capacities with community health needs.<sup>119</sup>

### Level-III: Health sector

Study participants felt that there was a dire need for regulation and oversight in Uganda's private retail pharmaceutical sector. Children were often brought to facilities, having already taken some antibiotics, yet, the types or appropriateness of prior antibiotic use could not always be ascertained, given the lack of documentation and poor dispensing practices at drug shops and private clinics. Furthermore, the availability and exposure of patients to "superior" antibiotic classes from the private retail sector was seen as causing caregivers to lose respect for public healthcare workers and the medicines they provided, which were seen as being of inferior quality.

Indeed, the private sector is the dominant source of care-seeking for childhood illnesses in LMICs<sup>120</sup> (also observed in **Study II**). Populations in these settings often prefer to seek care from private sources (particularly informal sources), given their faster services, nearness, and flexibility, among other reasons.<sup>121</sup> The potential of the private sector to contribute to expanding national child health services coverage in LMICs, [while also helping to relieve public healthcare services] is well-recognised.<sup>122</sup> Yet, antibiotic dispensing practices at private drug shops in Uganda and other LMIC settings remain sub-optimal.<sup>123-126</sup> For instance, one study in Uganda based on 428 exit interviews with care-givers of under-five children found that appropriate antibiotics were dispensed in only 4% of cases.<sup>127</sup> Nevertheless, another study suggests that achieving high-levels of adherence to childhood illness treatment guidelines in drug shops may be possible in Uganda.<sup>128</sup>

Among healthcare workers, not all brands of antibiotics (of the same type) were equal. More expensive, often foreign brands were perceived as being of higher quality, and some participants felt that changing brands of the same antibiotic type during the course of treatment influenced treatment outcomes. Antibiotic brand scepticism is not limited to LMIC healthcare practitioners,<sup>129</sup> and concerns expressed by health workers in LMICs may be even more legitimate, given the ubiquity of sub-standard and falsified medicines (including antibiotics) in these settings.<sup>130</sup> Studies comparing generic antibiotics to branded forms are limited and varied in outcomes (for example<sup>131-135</sup>), and a literature review on the efficacy of generic antibiotics was inconclusive.<sup>136</sup> This is an area warranting investigation, especially in LMICs where availability of generics is crucial to achieving universal antibiotic access.

### Level-IV: Governance at national and sub-national levels

Caregiver demands have been cited as a determinant of antibiotic prescribing.<sup>137</sup> Yet, our findings suggest that public health workers in this setting may be under even greater pressure to satisfy patient demands by prescribing antibiotics than in other settings, given the impact caregiver complaints could

have on their employment. Since 2001, Uganda has had a “free healthcare” policy, stipulating that public healthcare services (including diagnostic tests and medicines) be provided free-of-cost to patients.<sup>76</sup> Caregivers in our study (as described by participants) saw free medicines as a right, and a yardstick for quality of service. And when this was denied (even if reasonably so), they expressed dissatisfaction that they were being “chased away”, or that the health worker “refused to give them medicines”. And, local politicians tended to take sides with the community when complaints were made against public health workers.

Uganda’s “free healthcare” policy has been criticised – described as a mere political ploy to secure votes.<sup>76</sup> According to participant reports in one study, the government clearly cannot afford it; and yet, when shortcomings become obvious to the public, the blame is shifted onto health workers.<sup>138</sup> Public health workers, on the other hand, are also not completely blameless. Given the history of corruption in Uganda’s public health sector,<sup>139</sup> caregivers may have good reason to doubt their intentions when antibiotics are withheld.

Our study highlights a priority need for improved trust between communities and health workers in this setting, to improve appropriate access to antibiotics. Communities need to be sensitised on the impact of unnecessary antibiotic demand and consumption on resistance development and availability of antibiotics for patients with genuine need. Conserving antibiotics should be seen as a collective public responsibility, and promoted as a positive social norm. At the same time, health workers also need to be supported (for example through improved diagnostic capacity, locally relevant guidelines, and support supervision) to confidently decline giving antibiotics when deemed unnecessary. Furthermore, opportunities for interactions between public health workers, communities and local politicians should be encouraged, in an atmosphere that fosters mutual trust rather than blame. And, importantly, community members could use their political power to make demands for better quality of care both from local politicians and health workers.

## Level-V: International context

Assistance from foreign development partners was described as a key factor contributing to regularity and a wider range of antibiotic stocks in PNFPs compared to public healthcare facilities. And, in a public healthcare facility, support from foreign partners during the COVID-19 pandemic was described as having helped to broaden diagnostic capacity. Foreign aid continues to form a large part of Uganda’s health spending,<sup>80</sup> and Uganda’s foreign Health Development Partners (HDPs) remain key influencers (even drivers) of national health priority-setting, given their financial muscle to fund policies.<sup>138</sup> Support from Uganda’s HDPs, if secured, could be leveraged to prioritise improved antibiotic access and appropriate use in Uganda.

# Methodological considerations

## Study limitations

In **Studies I and II**, data were not available for every country-year, and modelling of the outcome was required to fill data gaps. Thus, uncertainty intervals generated for the mean proportions of reported antibiotic use for sick under-five children were wide and overlapping, and even more so in **Study II** where data were further disaggregated by user characteristics. Interpretations are therefore made with caution. Nevertheless, these studies based on DHS and MICS data were the first since 2000 to provide evidence on reported antibiotic use for sick under-five children across LMICs, particularly LICs and LMICs-LM which have otherwise been under-represented in global analyses. The only study after ours that also analysed reported antibiotic use in the same populations was based on the same data sources. Second, participants may have been prone to recall bias, and may not correctly report or classify the treatment given to their children in the two weeks prior to the survey interviews. However, caregivers are encouraged to show the treatment packaging and report trade names of administered medicines, which medically trained personnel in the data collection team could appropriately classify. Third, there was a lack of information on specific antibiotic type, dosage, duration of treatment and illness symptom aetiology in the DHS and MICS. Hence appropriateness of reported antibiotic use could not be determined.

**Study III** was based on outpatient register data, and analyses could have been compromised by missing data. Nevertheless, we did not find any systematic bias attributable to records that were not available at data collection. Second, while the analytical statistics took into account the survey and cluster structure of the data by using the mixed-effect approach, the descriptive statistics did not apply weights to account for unequal probabilities of selection due to different client quality data volumes at sampled facilities. Despite the large sample and high response rate, which should reduce the selection bias, results of the descriptive statistical analysis should be interpreted with caution. Third, the study focused on antibiotic prescribing patterns, which may not directly correspond to usage.

**Study IV** was based solely on reports from health workers. Thus, it was possible that they emphasized challenges while underplaying their own negative

attitudes and behaviours that may promote poor antibiotic management. Secondly, one of the interviewers had had prior contact with study participants during trainings on antibiotic stewardship, which may have led responses to be influenced by social desirability bias. However, this is unlikely as the aim was not to test participants' knowledge on antimicrobial stewardship. On the contrary, I consider this an advantage, as participants, already being familiar with one of the interviewers may have felt more at ease to discuss every-day dilemmas in antibiotic prescribing for young children.

## Trustworthiness (Study IV)

*Credibility* refers to measures taken by the researcher to ensure rigorous collection of high quality data that will be analysed in such a way as to give accurate representation of the study participants' reports. In our study, credibility was enhanced by data collection triangulation and researcher triangulation. Data collection tools were developed with input from Ugandan and non-Ugandan researchers, with backgrounds in medicine, pharmacy and social sciences. Data collection tools were pilot-tested and adapted accordingly. Data were collected by two Ugandan researchers with backgrounds in pharmacy and social sciences, and participant responses were regularly compared within and across healthcare facilities. Data coding was done by three researchers: (i) a pharmacist with qualitative research experience who also collected the data, (ii) another Ugandan pharmacist and lecturer who is currently a doctoral student in the United Kingdom, and (iii) myself, a Nigerian doctoral student in Sweden, with a medical education and clinical experience in a Nigerian tertiary hospital and general outpatient setting, and no prior practical experience with qualitative research.

Field notes from data collection were reviewed during analysis for any discrepancies or important themes that may have been missed. The data coding and analysis process was recursive, with regular discussions between researchers coding the data, and the principal investigator (a Ugandan pharmacist and senior lecturer in health systems pharmacy), with guidance from another researcher with specific qualitative research expertise in the field of AMR. Other researchers on the team, with knowledge and experience within health systems in African LMICs brought subject matter expertise and "outsider" perspectives.

*Transferability* refers to the generalisability of study findings, which is a judgement for individual readers to make. Nevertheless, the purposive selection of participants across public and PNFP healthcare facilities at HC-II, -III, IV and General Hospital, rural and urban areas, multiple cadres, and the mix of data collection strategies (in-depth interviews, and especially the use of FGDs), may enhance transferability of our findings. *Dependability* refers to the "auditability" of a qualitative study. This was addressed in our study by

the use of field notes and memos. In addition, data were analysed using a qualitative data analysis software programme (Nvivo), with all themes clearly traceable to source codes and quotes. This also partly addresses *confirmability*, which refers to how well the results link to the raw data. The use of illustrative quotes throughout reporting also improves the confirmability of our findings.



# Conclusions

## Summary of key findings

There was a modest increase (17% relative increase) in reported antibiotic use for sick under-five children across LMICs in 2005-2017. In 2017, about 43% of sick under-five children in LMICs reportedly received antibiotics for fever, diarrhoea, or cough with fast or difficult breathing. LICs, African and South-East Asian countries saw the greatest relative increases in the outcome during the study period, but also consistently recorded the lowest reported antibiotic use for sick under-five children. **(Study I)**

Within LMICs, reported antibiotic use for sick children increased across all user groups. The greatest gains (yet consistently lowest reported antibiotic use for sick under-five children) were seen among the poorest children, those living in rural areas, and having mothers with the lowest education levels. Conversely, the outcome remained highest among the wealthiest children, those living in urban areas, and having mothers with the highest education levels. **(Study II)**

In the Ugandan context, 62.2% of febrile under-five outpatients attending primary and secondary healthcare (public and PNFP) facilities in Bugisu, Eastern Uganda received antibiotic prescriptions in 2019-2020. Yet a narrow range of antibiotics was prescribed, with amoxicillin and co-trimoxazole accounting for two-thirds of all antibiotic prescriptions. Co-trimoxazole and ampicillin/cloxacillin were prescribed, despite not being indicated in any of the reported conditions in Study III. Higher health centre levels, (compared to HC-II), and PNFP ownership were significant contextual determinants of antibiotic prescribing. **(Study III)**

Among other interrelated factors across multiple levels of the health system, availability of antibiotics and diagnostics within healthcare facilities, caregiver demands, and governance at national and sub-national levels were important considerations in antibiotic prescribing for febrile under-five children in primary and secondary healthcare facilities in Bugisu, Eastern Uganda. **(Study IV)**

## Implications of study findings

Access to appropriate and effective antibiotics remains a challenge in LMICs. While global antibiotic consumption trend analyses indicate that LMICs have driven most of the global increases in antibiotic consumption since 2000, such generalisation must be applied with caution. Indeed, 76% of the global increase in antibiotic consumption in 2000-2010 was attributed to only five LMICs,<sup>37</sup> meaning the vast majority of LMICs may not share the same experience. This view is supported by our studies that provide evidence especially from LICs and LMICs-LM that were under-represented in previous global analyses of antibiotic consumption trends, and reinforced by our in-depth field studies in Uganda. Furthermore, our finding that reported antibiotic use for sick under-five children remained directly proportional to regional, national and household wealth suggest that inequities in antibiotic access persist between and within LMICs.

Yet, as demonstrated in the Ugandan context, the pervasive misuse of antibiotics and their wastage in the midst of scarcity thrives in LMICs, side-by-side with inadequate antibiotic access. This is partly due to weak and porous health systems, with a diverse and extensive, yet often poorly regulated network of antibiotic “gatekeepers”, among other multi-level health system factors identified in these studies. Indeed, the double burden of lack of access and inappropriate (even excessive) exposure to antibiotics in LMICs is likely greatest among the poorest populations, since these are the same groups with the greatest infectious diseases burden and lack of access to quality health services. In essence, the greatest need for antibiotic stewardship in LMICs may be among the same groups with the greatest need for improved access to antibiotics, requiring a health systems strengthening approach to improve both antibiotic stewardship and overall quality of care.

## Recommendations and research priorities

Health systems may be considered as complex adaptive systems, meaning that interventions in one part of the system could have effects on all parts. And indeed, as outlined in the discussion, there are opportunities for interventions across all parts of the health system that could impact appropriate antibiotic access and use, even if not directly linked to the “Medicines and Technologies” block of the framework (Figure 1). Nevertheless, I propose four recommendations, inspired by study findings in the Ugandan context, but which could have broader application in similar LMIC contexts:

- i) **Bottom-up approach to antibiotic stewardship:** There is a need for improved awareness among communities (and local politi-

cians) on how individual actions could promote antibiotic resistance, and the potential impact of this on individual and community health and economy. Communities, health workers and local government officials should see themselves as partners and key players in the health system, and embrace the common goal of improving community (and ultimately national) health outcomes, including appropriate access to effective antibiotics. Communities could capitalise on their democratic power to make demands for improved healthcare services from health workers and local politicians.

- ii) **Targeting “low-hanging fruits”** as opportunities to significantly cut down inappropriate antibiotic consumption in LMICs. By this I refer to conditions of public health significance where there are clear indications to safely *not* prescribe antibiotics, but where antibiotics are still being prescribed – particularly acute watery diarrhoea, AURI and malaria. Strengthening and dissemination of supportive evidence, and regular training and support from paediatricians could help less-experienced health workers make safe, yet confident treatment choices, even while affordable point-of-care diagnostics for non-malarial fevers are still lacking.
- iii) **Stronger focus on health promotion and prevention of infectious diseases** by vaccination, promoting basic hygiene, clean water and sanitation in communities, adequate nutrition, and other basic infrastructure to promote population well-being. These could contribute to reducing infectious disease burden and frequency of febrile illness in under-five children, thus lessening the risk of exposure to antibiotics.
- iv) Finally, I suggest two **research priority areas** which may contribute to improved appropriate access to antibiotics in LMICs. First, recognising that people are central to health systems functions, and are generally the vehicles of interaction within health systems, research integrating *health systems and social sciences* are needed to improve health system outcomes. Second, issues of inadequate financing underlie most (if not all) of the identified health systems challenges. Therefore, research *into innovative health financing modalities* that allow contribution from the informal sector is another suggested research priority for LMICs.

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# References

1. Murray CJL, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet* 2022; **399**: 629-55.
2. O'Neill J. Tackling drug-resistant infections globally: final report and recommendations. London, 2016.
3. Laxminarayan R, Matsoso P, Pant S, et al. Access to effective antimicrobials: a worldwide challenge. *The Lancet* 2016; **387**: 168–75.
4. Holmes AH, Moore LSP, Sundsfjord A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet* 2016; **387**: 176-87.
5. WHO. Global action plan on antimicrobial resistance. Geneva, Switzerland: WHO; 2015.
6. WHO. Fifty-first World Health Assembly Resolutions and decisions, annexes-document WHA51/1998/REC/1 Geneva, 1998.
7. WHO. WHO Global Strategy for Containment of Antimicrobial Resistance. 2001.
8. Our story – About us – ReAct.
9. World Economic Forum. Global Risks 2013 Eighth Edition. 2013.
10. WHO. Sixty-seventh World Health Assembly- Resolutions and decisions annexes. Geneva, 2014.
11. Assembly UNG. Political Declaration of the high-level meeting of the General Assembly on antimicrobial resistance: draft resolution / submitted by the President of the General Assembly. 2016.
12. WHO. Supporting countries with national action plan implementation. <https://www.who.int/activities/supporting-countries-with-national-action-plan-implementation> (13/03/2022).
13. Laxminarayan R, Van Boeckel T, Frost I, et al. The Lancet Infectious Diseases Commission on antimicrobial resistance: 6 years later. *Lancet Infect Dis* 2020; **20**: e51-e60.
14. Mpundu M. Moving from paper to action – The status of National AMR Action Plans in African countries. <https://revive.gardp.org/moving-from-paper-to-action-the-status-of-national-amr-action-plans-in-african-countries/> (15/10/2021).
15. O'Neill J. Securing new drugs for future generations: the pipeline of antibiotics. 2015.
16. Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance- the need for global solutions. *Lancet Infect Dis* 2013; **13**: 1057-98.
17. CIDRAP. Report highlights 'fragile and failing' antibiotic pipeline | CIDRAP. <https://www.cidrap.umn.edu/news-perspective/2022/02/report-highlights-fragile-and-failing-antibiotic-pipeline>
18. WHO. Antimicrobial stewardship programmes in health-care facilities in low-and middle-income countries. A practical toolkit. Geneva: World Health Organization; 2019.



19. Årdal C, Outtersen K, Hoffman SJ, et al. International cooperation to improve access to and sustain effectiveness of antimicrobials. *Lancet* 2016; **387**: 296-307.
20. Heyman G, Cars O, Bejarano M-T, Peterson S. Access, excess, and ethics--towards a sustainable distribution model for antibiotics. *Ups J Med Sci* 2014; **119**: 134-41.
21. Daulaire N, Bang A, Tomson G, Kalyango JN, Cars O. Universal Access to Effective Antibiotics is Essential for Tackling Antibiotic Resistance. *The Journal of law, medicine & ethics : a journal of the American Society of Law, Medicine & Ethics* 2015; **43 Suppl 3**: 17-21.
22. Merrett GL, Bloom G, Wilkinson A, MacGregor H. Towards the just and sustainable use of antibiotics. *J Pharm Policy Pract* 2016; **9**: 31.
23. WHO. Global antimicrobial resistance and use surveillance system (GLASS) report 2021. Geneva: World Health Organization, 2021.
24. Sharland M, Gandra S, Huttner B, et al. Encouraging AWARe-ness and discouraging inappropriate antibiotic use-the new 2019 Essential Medicines List becomes a global antibiotic stewardship tool. *The Lancet Infectious diseases* 2019; **19**: 1278-80.
25. World Health Organization Model List of Essential Medicines – 22nd List, 2021. Geneva, 2021.
26. Sharland M, Pulcini C, Harbarth S, et al. Classifying antibiotics in the WHO Essential Medicines List for optimal use-be AWARe. *The Lancet Infectious diseases* 2018; **18**: 18-20.
27. WHO. Adopt AWARe: Handle antibiotics with care. [www.adoptaware.org](http://www.adoptaware.org)
28. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infectious Diseases* 2014; **14**: 13.
29. Laxminarayan R, Van Boeckel TP. The value of tracking antibiotic consumption. *Lancet Infect Dis* 2014; **14**: 360-1.
30. WHO. WHO methodology for a global programme on surveillance of antimicrobial consumption Version 1.0.
31. Klein EY, Van Boeckel TP, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci USA* 2018; **115**: E3463-e70.
32. WHO. Global antimicrobial resistance surveillance system (GLASS) report: early implementation 2020. Geneva, 2020.
33. WHO. GLASS manual on the management of antimicrobial consumption data. Geneva: World Health Organization, 2020.
34. Versporten A, Zarb P, Caniaux I, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. *Lancet Glob Health* 2018; **6**: e619-e29.
35. WHO. WHO methodology for point prevalence survey on antibiotic use in hospitals. 2018.
36. Klein EY, Milkowska-Shibata M, Tseng KK, et al. Assessment of WHO antibiotic consumption and access targets in 76 countries, 2000-15: an analysis of pharmaceutical sales data. *Lancet Infect Dis* 2020.
37. Van Boeckel TP, Gandra S, Ashok A, et al. Global antibiotic consumption 2000 to 2010: An analysis of national pharmaceutical sales data. *Lancet Infect Dis* 2014; **14**: 742-50.
38. Morgan DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg S. Non-prescription antimicrobial use worldwide: A systematic review. *Lancet Infect Dis* 2011; **11**: 692-701.

39. Padget M, Guillemot D, Delarocque-Astagneau E. Measuring antibiotic consumption in low-income countries: a systematic review and integrative approach. *International Journal of Antimicrobial Agents* 2016; **48**: 27–32.
40. Jackson C, Hsia Y, Bielicki JA, et al. Estimating global trends in total and childhood antibiotic consumption, 2011-2015. *BMJ Glob Health* 2019; **4**: e001241.
41. Källander K, Nsungwa-Sabiiti J, Peterson S. Symptom overlap for malaria and pneumonia—policy implications for home management strategies. *Acta Tropica* 2004; **90**: 211-4.
42. Sey ICM, Ehimiyein AM, Bottomley C, Riley EM, Mooney JP. Does Malaria Cause Diarrhoea? A Systematic Review. *Frontiers in medicine* 2020; **7**.
43. Baltzell K, Elfving K, Shakely D, et al. Febrile illness management in children under five years of age: a qualitative pilot study on primary health care workers' practices in Zanzibar. *Malaria journal* 2013; **12**: 37-.
44. Baltzell K, Kortz TB, Scarr E, et al. 'Not All Fevers are Malaria': a Mixed Methods Study of Non-Malarial Fever Management in Rural Southern Malawi. *Rural and Remote Health* 2019; **19**.
45. Fink G, D'Acremont V, Leslie HH, Cohen J. Antibiotic exposure among children younger than 5 years in low-income and middle-income countries: a cross-sectional study of nationally representative facility-based and household-based surveys. *Lancet Infect Dis* 2020; **20**: 179-87.
46. Knowles R, Sharland M, Hsia Y, et al. Measuring antibiotic availability and use in 20 low- and middle-income countries. *Bull World Health Organ* 2020; **98**: 177-87c.
47. Gyssens IC, Wertheim HF. Editorial: Antimicrobial Stewardship in Low- and Middle-Income Countries. *Front Public Health* 2020; **8**.
48. So AD, Bigdeli M, Tomson G, Woodhouse W, Ombaka E, Peralta AQ. Part 5: The access and excess dilemma. "Antibiotic resistance—the need for global solutions". *Lancet Infect Dis* 2013; **13**: 1057-98.
49. Bigdeli M, Jacobs B, Tomson G, et al. Access to medicines from a health system perspective. *Health Policy Plan* 2013; **28**: 692-704.
50. Tomson G, Vlad I. The need to look at antibiotic resistance from a health systems perspective. *Ups J Med Sci* 2014; **119**: 117-24.
51. Cars O, Chandy SJ, Mpundu M, Peralta AQ, Zorzet A, So AD. Resetting the agenda for antibiotic resistance through a health systems perspective. *Lancet Glob Health* 2021; **9**: e1022-e7.
52. The DHS Program - DHS Methodology.
53. International I. Demographic and Health Survey Sampling and Household Listing Manual. MEASURE DHS, Calverton, Maryland, U.S.A: ICF International; 2012.
54. UNICEF MICS. Manual for mapping and household listing. 2013.
55. The DHS Program - DHS Survey Design: Sample Size.
56. The DHS Program - Survey Process.
57. DHS. Demographic and Health Surveys. <https://www.dhsprogram.com>
58. UNICEF. Multiple Indicator Cluster Surveys. <https://mics.unicef.org/> (25 June 2018).
59. Sultana M, Sarker AR, Sheikh N, et al. Prevalence, determinants and health care-seeking behavior of childhood acute respiratory tract infections in Bangladesh. *PLoS ONE* 2019; **14**.
60. Yaya S, Uthman OA, Okonofua F, Bishwajit G. Decomposing the rural-urban gap in the factors of under-five mortality in sub-Saharan Africa? Evidence from 35 countries. *BMC Public Health* 2019; **19**: 616.

61. Van Malderen C, Amouzou A, Barros AJD, Masquelier B, Van Oyen H, Speybroeck N. Socioeconomic factors contributing to under-five mortality in sub-Saharan Africa: a decomposition analysis. *BMC Public Health* 2019; **19**: 760.
62. Petrie A, & Sabin, C. Medical statistics at a glance. Third ed. Oxford: WILEY Blackwell; 2009.
63. Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health* 2019; **7**: e37-e46.
64. Moller A-B, Petzold M, Chou D, Say L. Early antenatal care visit: a systematic analysis of regional and global levels and trends of coverage from 1990 to 2013. *Lancet Glob Health* 2017; **5**: e977–e83.
65. UNDP. Human development indices and indicators: 2018 statistical update. New York: UNDP, 2018.
66. UN-DESA. World population prospects: the 2017 revision. New York: United Nations Population Division, 2017.
67. Roth GA, Abate D, Abate KH, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* 2018; **392**: 1736-88.
68. WHO. Global health expenditure database. Geneva: World Health Organization, 2018.
69. World Bank. Population, total - Uganda. <https://data.worldbank.org/indicator/SP.POP.TOTL?locations=UG> (14/03/2022).
70. World Bank. Rural population (% of total population). <https://data.worldbank.org/indicator/SP.RUR.TOTL.ZS?locations=UG>
71. World Bank. Fertility rate, total (births per woman) - Uganda. <https://data.worldbank.org/indicator/SP.DYN.TFRT.IN?locations=UG> (14/03/2022).
72. World Bank. Population ages 0-14 (% of total population) - Uganda. <https://data.worldbank.org/indicator/SP.POP.0014.TO.ZS?locations=UG>
73. UNICEF. Uganda key demographic indicators. <https://data.unicef.org/country/uga/>
74. Unicef Uganda. Child and maternal health. <https://www.unicef.org/uganda/what-we-do/child-survival-development> (14/03/2022).
75. Ministry of Health Uganda. Health sector development plan 2015/16-2019/20. 2015.
76. Nannini M, Biggeri M, Putoto G. Health Coverage and Financial Protection in Uganda: A Political Economy Perspective. *International journal of health policy and management* 2021.
77. Facts and figures of the PNFPs. Uganda, 2007.
78. Ssenyonjo A, Namakula J, Kasyaba R, Orach S, Bennett S, Ssengooba F. Government resource contributions to the private-not-for-profit sector in Uganda: Evolution, adaptations and implications for universal health coverage. *International journal for equity in health* 2018; **17**.
79. Amone J, Asio S, Cattaneo A, et al. User fees in private non-for-profit hospitals in Uganda: a survey and intervention for equity. *International journal for equity in health* 2005; **4**: 6.
80. Uganda Ministry of Health. A Roadmap Towards Universal Health Coverage In Uganda 2020/21 to 2029/30 | Ministry of Health Knowledge Management Portal. 2020.

81. Ministry of Health. National Health Facility Master List 2018: A complete list of all health facilities in Uganda. Kampala, Uganda: Ministry of Health, 2018.
82. Uganda National Malaria Control Division (NMCD) UBOSU, and ICF,. Uganda Malaria Indicator Survey 2018-19. Kampala, Uganda, and Rockville, Maryland, USA: NMCD, UBOS, and ICF, 2020.
83. Uganda Health Sector Strategic and Investment Plan 2010/11-2014-15. 2010.
84. Katende D, Mutungi G, Baisley K, et al. Readiness of Ugandan health services for the management of outpatients with chronic diseases. *Tropical medicine & international health : TM & IH* 2015; **20**: 1385-95.
85. UNAS C, GARP-Uganda, Mpairwe, Y., & Wamala, S. Antibiotic Resistance in Uganda: Situation Analysis and Recommendations. Kampala, Uganda, 2015.
86. Government of Uganda Antimicrobial Resistance National Action Plan 2018-2023.
87. Lanyero H, Ocan M, Obua C, et al. Antibiotic use among children under five years with diarrhea in rural communities of Gulu, northern Uganda: a cross-sectional study. *BMC Public Health* 2021; **21**: 1254.
88. Lanyero H, Eriksen J, Obua C, et al. Use of antibacterials in the management of symptoms of acute respiratory tract infections among children under five years in Gulu, northern Uganda: Prevalence and determinants. *PLoS ONE* 2020; **15**.
89. Buchner DL, Kitutu FE, Cross DE, Nakamoga E, Awor P. A cross-sectional study to identify the distribution and characteristics of licensed and unlicensed private drug shops in rural Eastern Uganda to inform an iCCM intervention to improve health outcomes for children under five years. *PLoS One* 2019; **14**: e0209641.
90. Mbonye AK, Buregyeya E, Rutebemberwa E, et al. Prescription for antibiotics at drug shops and strategies to improve quality of care and patient safety: A cross-sectional survey in the private sector in Uganda. *BMJ Open* 2016; **6**.
91. Uganda Bureau of Statistics. Population projections by district 2015 to 2021. <https://www.ubos.org/explore-statistics/20/>
92. Uganda Bureau of Statistics (UBOS) and ICF. Uganda Demographic and Health Survey 2016. Kampala, Uganda and Rockville, Maryland, USA, 2018.
93. UNICEF. Multidimensional child poverty and deprivation in Uganda: Volume 1. 2019.
94. Kish L. Survey Sampling. New York, London: John Wiley & Sons, Inc.; 1965.
95. Gwimile JJ, Shekalaghe SA, Kapanda GN, Kisanga ER. Antibiotic prescribing practice in management of cough and/or diarrhoea in Moshi Municipality, Northern Tanzania: cross-sectional descriptive study. *Pan Afr Med J* 2012; **12**: 103-.
96. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology* 2006; **3**: 77-101.
97. Allwell-Brown G, Hussain-Alkhateeb L, Kitutu FE, Strömdahl S, Mårtensson A, Johansson EW. Trends in reported antibiotic use among children under 5 years of age with fever, diarrhoea, or cough with fast or difficult breathing across low-income and middle-income countries in 2005-17: a systematic analysis of 132 national surveys from 73 countries. *Lancet Glob Health* 2020; **8**: e799-e807.

98. Allwell-Brown G, Hussain-Alkhateeb L, Sewe MO, et al. Determinants of trends in reported antibiotic use among sick children under five years of age across low-income and middle-income countries in 2005–17: A systematic analysis of user characteristics based on 132 national surveys from 73 countries. *International Journal of Infectious Diseases* 2021; **108**: 473-82.
99. Farooqui HH, Selvaraj S, Mehta A, Heymann DL. Community level antibiotic utilization in India and its comparison vis-à-vis European countries: Evidence from pharmaceutical sales data. *PLoS ONE* 2018; **13**.
100. Browne AJ, Chipeta MG, Haines-Woodhouse G, et al. Global antibiotic consumption and usage in humans, 2000&#x2013;18: a spatial modelling study. *The Lancet Planetary Health* 2021; **5**: e893-e904.
101. Schmiede D, Evers M, Kistemann T, Falkenberg T. What drives antibiotic use in the community? A systematic review of determinants in the human outpatient sector. *International Journal of Hygiene and Environmental Health* 2020; **226**: 113497.
102. Kiwanuka SN, Ekirapa EK, Peterson S, et al. Access to and utilisation of health services for the poor in Uganda: a systematic review of available evidence. *Transactions of The Royal Society of Tropical Medicine and Hygiene* 2008; **102**: 1067-74.
103. Musoke D, Namata C, Lubega GB, et al. Access, use and disposal of antimicrobials among humans and animals in Wakiso district, Uganda: a qualitative study. *J Pharm Policy Pract* 2021; **14**: 69.
104. Yadav H, Shah D, Sayed S, Horton S, Schroeder LF. Availability of essential diagnostics in ten low-income and middle-income countries: results from national health facility surveys. *Lancet Glob Health* 2021; **9**: e1553-e60.
105. Mbonye MK, Burnett SM, Colebunders R, et al. Disease diagnosis in primary care in Uganda. *BMC Fam Pract* 2014; **15**: 165.
106. Hopkins H, Bruxvoort KJ, Cairns ME, et al. Impact of introduction of rapid diagnostic tests for malaria on antibiotic prescribing: Analysis of observational and randomised studies in public and private healthcare settings. *BMJ (Online)* 2017; **356**.
107. Rogawski ET, Platts-Mills JA, Seidman JC, et al. Use of antibiotics in children younger than two years in eight countries: A prospective cohort study. *Bull World Health Organ* 2017; **95**: 49–61.
108. Huth PFB, Addo M, Daniel T, et al. Extensive Antibiotic and Antimalarial Prescription Rate among Children with Acute Febrile Diseases in the Lake Victoria Region, Tanzania. *Journal of Tropical Pediatrics* 2021; **67**.
109. Fomba S, Koné D, Doumbia B, et al. Management of uncomplicated malaria among children under five years at public and private sector facilities in Mali. *BMC Public Health* 2020; **20**: 1888.
110. Ministry of Health. Uganda Clinical Guidelines 2016. Kampala, Uganda 2016.
111. Namugambe JS, Delamou A, Moses F, et al. National antimicrobial consumption: Analysis of central warehouses supplies to in-patient care health facilities from 2017 to 2019 in Uganda. *Tropical Medicine and Infectious Disease* 2021; **6**.
112. Kagoya EK, Royen KV, Waako P, et al. Experiences and views of healthcare professionals on the prescription of antibiotics in Eastern Uganda: A qualitative study. *Journal of global antimicrobial resistance* 2021; **25**: 66-71.
113. Musgrove P. Financial and Other Rewards for Good Performance or Results: A Guided Tour of Concepts and Terms and a Short Glossary. 2011.

114. Ssenyonjo A, Ekirapa-Kiracho E, Musila T, Ssengooba F. Fitting Health Financing Reforms to Context: Examining the Evolution of Results-Based Financing Models and the Slow National Scale-Up in Uganda (2003-2015). *Global health action* 2021; **14**: 1919393-.
115. Chama-Chiliba CM, Hangoma P, Chansa C, Mulenga MC. Effects of performance based financing on facility autonomy and accountability: Evidence from Zambia. *Health Policy OPEN* 2022; **3**: 100061.
116. Sieleunou I, Turcotte-Tremblay A-M, De Allegri M, et al. How does performance-based financing affect the availability of essential medicines in Cameroon? A qualitative study. *Health Policy and Planning* 2019; **34**: iii4-iii19.
117. Paul E, Albert L, Bisala BNS, et al. Performance-based financing in low-income and middle-income countries: isn't it time for a rethink? *BMJ Glob Health* 2018; **3**: e000664.
118. Ssengooba F, Ssenyonjo A, Musila T, Ekirapa-Kiracho E. Momentum for policy change: alternative explanations for the increased interest in results-based financing in Uganda. *Global health action* 2021; **14**: 1948672.
119. WHO. Global strategy on human resources for health: Workforce 2030. Geneva 2016.
120. Grépin KA. Private Sector An Important But Not Dominant Provider Of Key Health Services In Low- And Middle-Income Countries. *Health affairs (Project Hope)* 2016; **35**: 1214-21.
121. Sudhinaraset M, Ingram M, Lofthouse HK, Montagu D. What is the role of informal healthcare providers in developing countries? A systematic review. *PloS one* 2013; **8**: e54978-e.
122. Awor P, Peterson S, Gautham M. Delivering child health interventions through the private sector in low and middle income countries: challenges, opportunities, and potential next steps. *BMJ* 2018; **362**: k2950.
123. Nahar P, Unicomb L, Lucas PJ, et al. What contributes to inappropriate antibiotic dispensing among qualified and unqualified healthcare providers in Bangladesh? A qualitative study. *BMC Health Serv Res* 2020; **20**: 656.
124. Horumpende PG, Sonda TB, van Zwetselaar M, et al. Prescription and non-prescription antibiotic dispensing practices in part I and part II pharmacies in Moshi Municipality, Kilimanjaro Region in Tanzania: A simulated clients approach. *PloS one* 2018; **13**: e0207465-e.
125. Basu S, Copana R, Morales R, Jr., et al. Keeping It Real: Antibiotic Use Problems and Stewardship Solutions in Low- and Middle-income Countries. *The Pediatric Infectious Disease Journal* 2022; **41**.
126. Afari-Asiedu S, Oppong FB, Tostmann A, et al. Determinants of Inappropriate Antibiotics Use in Rural Central Ghana Using a Mixed Methods Approach. *Front Public Health* 2020; **8**.
127. Mayora C, Kitutu FE, Kandala NB, Ekirapa-Kiracho E, Peterson SS, Wamani H. Private retail drug shops: What they are, how they operate, and implications for health care delivery in rural Uganda. *BMC Health Serv Res* 2018; **18**.
128. Awor P, Wamani H, Tylleskar T, Peterson S. Drug seller adherence to clinical protocols with integrated management of malaria, pneumonia and diarrhoea at drug shops in Uganda. *Malaria journal* 2015; **14**: 277.
129. Dietze J, Priluck A, High R, Havens S. Reasons for the Underutilization of Generic Drugs by US Ophthalmologists: A Survey. *Ophthalmology and Therapy* 2020; **9**: 955-70.
130. McManus D, Naughton BD. A systematic review of substandard, falsified, unlicensed and unregistered medicine sampling studies: a focus on context, prevalence, and quality. *BMJ Glob Health* 2020; **5**: e002393.

131. Ordóñez K, Feinstein MM, Reyes S, Hernández-Gómez C, Pallares C, Villegas MV. Clinical and economic impact of generic versus brand name meropenem use in an intensive care unit in Colombia. *Brazilian Journal of Infectious Diseases* 2019; **23**: 237-45.
132. Lin YS, Jan IS, Cheng SH. Comparative analysis of the cost and effectiveness of generic and brand-name antibiotics: the case of uncomplicated urinary tract infection. *Pharmacoepidemiology and Drug Safety* 2017; **26**: 301-9.
133. Pathak P, Dawane J. In vitro comparison of generic and branded preparations of amoxicillin with potassium clavulanate. *Journal of Clinical and Diagnostic Research* 2016; **10**: FC07-FC9.
134. Piovani D, Clavenna A, Cartabia M, et al. Comparing recurrent antibiotic prescriptions in children treated with a brand name or a generic formulation. *Pharmacoepidemiology and Drug Safety* 2015; **24**: 121-8.
135. Punpanich W, Srisarang S, Prachantasen U. Therapeutic effectiveness of the generic preparation of meropenem (Mapenem®) in the treatment of moderate to severe infection in children. *Journal of the Medical Association of Thailand* 2012; **95**: 895-902.
136. Tattevin P, Crémieux AC, Rabaud C, Gauzit R. Efficacy and quality of antibacterial generic products approved for human use: A systematic review. *Clinical Infectious Diseases* 2014; **58**: 458-69.
137. Krockow EM, Colman AM, Chattoe-Brown E, et al. Balancing the risks to individual and society: a systematic review and synthesis of qualitative research on antibiotic prescribing behaviour in hospitals. *Journal of Hospital Infection* 2019; **101**: 428-39.
138. Mukuru M, Kiwanuka SN, Gilson L, Shung-King M, Ssengooba F. The actor is policy: Application of elite theory to explore actors' interests and power underlying maternal health policies in Uganda, 2000-2015. *International journal of health policy and management* 2021; **10**: 388-401.
139. Caryn Peiffer RA, Heather Marquette. Uganda's Health Sector as a 'Hidden' Positive Outlier in Bribery Reduction. Birmingham, UK, 2018.

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