Evaluating the impact of a Lao language mobile phone antimicrobial use guideline application on antimicrobial prescribing in the Lao PDR



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Abstract

A major driver of antimicrobial resistance (AMR) is misuse of antimicrobials. This thesis aimed to enhance understanding of hospital antimicrobial use (AMU) in Laos, and explore improvements that could serve as a model for other low- and middle-income countries.

A situation analysis of AMU and AMR in humans, animals, and the environment in Laos from 1994-2020 (Chapter 1) revealed limited data, with most focused on human AMR. ESBL-producing *Escherichia coli* bacteraemia cases have risen rapidly over 16 years. The first systematic AMU surveys from 2017-2020 in six hospitals (Chapter 2) showed the highest percentage of AMU in inpatients in Southeast Asia (71%), largely due to inappropriate surgical and obstetrical prophylaxis.

These findings led to the antimicrobial stewardship study in Chapters 3 and 4, in which Lao antimicrobial prescribing guidelines were created and introduced, comparing delivery by pocketbook and mobile application. A stepped-wedge cluster randomized trial (NCT04914793) assessed guideline adherence in six hospitals, revealing adherence among inpatients in the App-based guideline group was 27% higher than the paper-based guideline group with no remarkable difference (aOR=1.27, 95% CI: 0.84-1.90, p=0.249). This small increase led to a qualitative study in Chapter 5, exploring how Lao prescribers made antimicrobial prescribing decisions and engaged with the guidelines. Prescribers mainly relied on clinical judgment. Guidelines were accessed infrequently as prescribers had memorized common recommendations.

Chapter 6 reviews the applicability of WHO AWaRe recommendations in Laos, comparing them to local guidelines. It emphasizes the importance of region-specific pathogens and antimicrobial susceptibility patterns, while noting that limited access to antibiotics may lead to inappropriate use.

This thesis presents crucial AMU data for Laos and introduces the country's first prescribing guidelines via a mobile app. The findings highlight gaps and challenges in implementing stewardship programs and offers key recommendations to improve AMU in Laos and similar settings.

Statement of impact of the Covid-19 pandemic

The fieldwork of my DPhil project was conducted during the Covid-19 pandemic which was challenging. I registered for my DPhil in mid-2019, and my fieldwork officially began in January 2021 when Covid-19 was not yet a major crisis in Laos, largely due to the strict border controls in place. However, the big epidemic wave hit Laos a few months later; this led to lockdowns and quarantines, forcing most doctors, including those at my study sites, to focus on Covid-19 and they were therefore less available to participate in my project.

Covid-19 led to delays of my intervention implementation. In addition, many prescribers at the participating hospitals were unavailable for training sessions because large gatherings were not allowed. To deal with these challenges I had to adapt my study procedures by delivering training and implementing interventions in smaller groups or one-on-one sessions. This adaptation increased the workload, extended the time required for each intervention implementation and outcome collection, as well as expanding the budget. Moreover, the number of patients at hospitals decreased, with mostly severely ill patients seeking care. This trend persisted until the final intervention implementation. However, the situation began to improve towards the end of my study. Furthermore, during this Covid-19 pandemic, many AMR activities were put on hold for the whole country. Despite these challenges I managed to fully implement my planned activities with good coverage at participating hospitals.

Statement of contributions

My supervisors, Elizabeth Ashley, Paul Newton, Paul Turner, Rogier van Doorn, Nicholas PJ Day, and Mayfong Mayxay provided methodological and scientific guidance throughout all stages of my DPhil. In addition, there were also essential contributors in each chapter as listed below:

Chapter 1: I conducted the literature search and gathered grey literature from various sectors. I drafted the manuscript for publication and served as the corresponding author. My supervisors, Paul Newton, Mayfong Mayxay, Rogier van Doorn and Elizabeth Ashley provided supervision. Manivanh Vongsouvath, Viengmon Davong, Tamalee Roberts and Risara Jaksuwan collaborated with me in gathering microbiological data. Bounxou Keohavong and Phouthavanh Inlorkham provided data from the Food and Drug Department, Ministry of Health, Laos. Phout Inthavong and Syseng Khounsy contributed data from animal health sectors. Sithixay Kaylath from the Faculty of Agriculture, National University of Laos assisted with data retrieval from the university library.

Chapter 2: I led the first antimicrobial use surveys in hospitals in Laos under the close supervision of Paul Newton, Elizabeth Ashley and Mayfong Mayxay. I formed and led the survey team with contributions from Danoy Chommanam and Anousone Douangnouvong in data collection. Tamalee Roberts supported data management early in the project. I analyzed the data and drafted the manuscript, with revisions from all supervisors and co-authors.

Chapter 3 and Chapter 4: I conceptualized the study along with my supervisors, and developed the first Lao antimicrobial prescribing guidelines under the supervision of Elizabeth Ashley, Paul Newton and Paul Turner. National and

international experts provided feedback on the guidelines. I transformed the guidelines into the MicroGuide mobile phone application format with support from Paul Turner and the MicroGuide team. Pimnara Peerawaranun and Mavuto Mukaka assisted with sample size calculation (Chapter 3). I led the training and data collection with Danoy Chommanam's support. Naomi Waithira and Chonticha Menggred assisted with data management. I analyzed data with input from Sue Lee and Mavuto Mukaka. The chapter was reviewed by all supervisors (Chapter 4).

Chapter 5: Elizabeth Ashley and I conceptualized the project with input from all supervisors. I conducted the interviews, with Anousone Douangnouvong assisting in scheduling and organizing documents. I analyzed the data, drafted the manuscript and finalized it based on feedback from supervisors and co-authors. The draft was reviewed by all before finalizing.

Chapter 6: Elizabeth Ashley and I conceptualized the project. I reviewed the literature and drafted the initial manuscript with feedback from all supervisors and co-authors.

Publications in relation to this thesis

Chapter 1:

Chansamouth V, Mayxay M, Dance DA, Roberts T, Phetsouvanh R, Vannachone B, Vongsouvath M, Davong V, Inthavong P, Khounsy S, Keohavong B, Keoluangkhot V, Choumlivong K, Day NP, Turner P, Ashley EA, van Doorn HR, Newton PN. Antimicrobial use and resistance data in human and animal sectors in the Lao PDR: evidence to inform policy. BMJ Glob Health. 2021 Nov;6(12):e007009. doi:10.1136/bmjgh-2021-007009. PMID:34853032; PMCID: PMC8638151.

Chapter 2:

Chansamouth V, Chommanam D, Roberts T, Keomany S, Paphasiri V, Phamisith C, Sengsavang S, Detleuxay K, Phoutsavath P, Bouthavong S, Douangnouvong A, Vongsouvath M, Rattana S, Keohavong B, Day NPJ, Turner P, van Doorn HR, Mayxay M, Ashley EA, Newton PN. Evaluation of trends in hospital antimicrobial use in the Lao PDR using repeated point-prevalence surveys-evidence to improve treatment guideline use. Lancet Reg Health West Pac. 2022 Jul 9;27:100531. doi:10.1016/j.lanwpc.2022.100531. PMID:35846979; PMCID:PMC9283659.

Chapter 5:

Chansamouth V, Douangnouvong A, Thammavongsa P, Sombandith X, Keomany S, Rattana S, Newton PN, Day NP, Turner P, Mayxay M, van Doorn HR, Ashley EA. Understanding hospital antimicrobial prescribing decisions and determinants of uptake of new local antimicrobial prescribing guidelines in Laos. Wellcome Open Res. 2024 Sep 12;9:183. doi:10.12688/wellcomeopenres.20884.2. PMID: 39301442; PMCID:PMC11411237.

Chapter 6:

Chansamouth V, Inlorkham P, Keohavong B, Bellingham K, van Doorn HR, Mayxay M, Newton PN, Turner P, Day NPJ, Ashley EA. Implementing the WHO AWaRe antibiotic book guidance in lower-resource settings: the case of the Lao PDR. JAC Antimicrob Resist. 2024 Jan 22;6(1):dlae004. doi:10.1093/jacamr/dlae004. PMID: 38259905; PMCID:PMC10801825.

Outputs in relation to this thesis

1. Lao paediatric antimicrobial prescribing guidelines
2. Lao adult antimicrobial prescribing guidelines
3. Lao and English versions of AMR and AMU review report from 1994 to 2020 in Lao PDR
4. MicroGuide mobile phone application of Lao antimicrobial prescribing guidelines (both paediatric and adult versions)
5. National protocol for point prevalence survey on antimicrobial use in hospitals, 2021
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List of abbreviations

Abbreviation	Full names
ALMANACH	Algorithm for the Management of Childhood Illness
AMR	Antimicrobial Resistance
AMS	Antimicrobial Stewardship
AMU	Antimicrobial Use
aOR	adjusted Odds Ratio
App	Application
App-G	Mobile phone application-based antimicrobial prescribing guideline
AST	Antimicrobial Susceptibility Testing
AWaRe	Access, Watch, Reserve
BL/BLIs	Betalactam/Beta-lactamase Inhibitors
BSIs	Bloodstream Infections
CAI	Community-Acquired Infections
CI	Confidence Interval
CLSI	Clinical & Laboratory Standards Institute
CMPE	Centre for Malaria, Parasitology and Entomology
CNS	Central Nervous System
CRF	Case Record Form
CSF	Cerebrospinal Fluid
DDDs	Defined Daily Doses
DHR	Department of Healthcare and Rehabilitation
DLF	Department of Livestock and Fisheries
DTCs	Drug and Therapeutics Committees

ENT	Ear Nose and Throat
ENT-EYE	Ear Nose and Throat-Eyes
ESBL	Extended-Spectrum Beta-Lactamase
FAO	Food and Agriculture Organization of the United Nations
FDC	Fixed-Dose Combination
FDD	Food and Drug Department
GADSA	Gamified Antimicrobial Stewardship Decision Support App
GAP	Global Action Plan
GARP	Global Antimicrobial Resistance Partnership
GAS	Group A *Streptococcus*
GC	Generation Cephalosporins
GDP	Gross Domestic Product
GLASS	Global Antimicrobial Resistance and Use Surveillance System
HAI	Hospital Acquired Infections
HICs	High-Income Countries
IAPP	Imperial College Antibiotic Prescribing Policy Application
ICU	Intensive Care Unit
ICU-ER	Intensive Care Unit - Emergency Room
IFMT	Institut de la Francophonie pour la Médecine Tropicale
IPC	Infection Prevention and Control
IPD	Inpatients
IPL	Institût Pasteur du Laos
IQR	Interquartile Range
IV	Intravenous
LAK	Lao Kip

LAMPA	Lao Antimicrobial Prescribing Application
LMICs	Low- and Middle-Income Countries
LNT	Luang Namtha
LOMWRU	Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit
MDR	Multidrug Resistant
MoH	Ministry of Health
MP	Medical Prophylaxis
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MS	Mahosot
MTB	*Mycobacterium tuberculosis*
NA	Not Applicable
NCLE	National Centre for Laboratory and Epidemiology
NDM	New Delhi Metallo-betalactamase
NEML	National Essential Medicines
NTS	Non-typhoidal *Salmonella*
OBGY	Obstetrics and Gynaecology
ODK	Open Data Kit
OPD	Outpatients
OR	Odds Ratio
OxTREC	Oxford Tropical Research Ethics Committee
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PP-G	Paper-based antimicrobial prescribing guideline
PPS	Point Prevalence Survey
PTB	Pulmonary Tuberculosis

SAP	Surgical Antibiotic Prophylaxis
SCRIPT	Standardized Clinical Resource to Improve Pathway Targets
SEA	Southeast Asia
SST	Skin and Soft Tissue
ST	Sequence Type
STGs	Standard Treatment Guidelines
STIs	Sexually Transmitted Infections
SV	Salavan
SVK	Savannakhet
SW-CRCT	Stepped Wedge Cluster Randomized Controlled Trial
TB	Tuberculosis
TMP-SMX	Trimethoprim- Sulphamethoxazole
UHS	University of Health Sciences
UTI	Urinary Tract Infection
VTP	Vientiane Province
WHO	World Health Organization
XK	Xiengkhuang

General introduction about Lao PDR (Laos) and the healthcare system in Laos

Country profile of Laos

Laos is a land-linked country, situated in the WHO Western Pacific Region. It is bordered by China, Myanmar, Thailand, Cambodia and Vietnam. In 2023, it had a population of approximately 7.63 million people, with an estimated life expectancy of 68 years in 2022 (1). Officially, Laos consists of 49 ethnic groups, with 65% of the population residing in rural areas. The Lao social indicator survey in 2023 reported that the literacy rate among adolescents aged 15-24 was 82.1% for males and 86.3% for females. Immunisation coverage (all vaccines based on national program for children under two years) was as low as 47% (2). Seventy-five percent of the workforce in Laos are engaged in agriculture or related activities and agriculture accounted for 34.7% of the Gross Domestic Product (GDP) in Laos in 2009 (3). The country's economic growth has been driven by the hydropower energy and mining sectors. In 2023, the GDP per capita was USD 2,075.4, and in 2022, 70% of the workforce was employed in the agriculture sector. The World Bank classified Laos as a lower middle-income country (LMIC) in 2023 (1).

Healthcare system in Laos

Healthcare structure

The governmental healthcare system in Laos comprises three main administrative levels, including the Ministry of Health (MoH), Provincial Health Offices and District Health Offices. Based on data from the Department of Healthcare and Rehabilitation (DHR) of MoH in 2017, there are five central hospitals in the capital Vientiane, four regional hospitals, 13 provincial hospitals, 135 district hospitals (29 with the ability to perform surgery) and 1,020 health centres (866 with the ability to perform normal vaginal delivery), country-wide [DHR, unpublished data].

In 2010 there were 8,662 villages in Laos with ~ 14,800 village health volunteers (VHVs) (1.7 VHVs/village); approximately 5,239 villages (60%) had drug kits for the provision of primary healthcare and 222 had authorized private outpatient clinics. There were 0.8 hospital beds per 1,000 population in 2010-2011. The most common issues found in the service delivery system are overcrowding of patients at central and provincial levels and underuse of district and community-level facilities (4). There are also a number of private international medical facilities in Vientiane, with links to Vietnam, China, France and the United Nations. In nearby Thailand, there are Thai government and private hospitals within easy reach of Vientiane and other towns in the Mekong Valley.

In 2016, there were 20,484 health workers for the whole country (6,758,000 population) or 3/1,000 population. There were 2,716 physicians (0.4/1,000 population) and 913 pharmacists (0.13/1,000 population), one medical school and one-degree level pharmacy programme within the University of Health Sciences in Vientiane [Ministry of Health, unpublished data]. In 2020, Department of Health

Personnel, MoH of Laos reported data showing the huge disparity between the number of health workers in urban (6.16/1,000 population) versus rural (1.94/1,000 population) areas.

Health financing and national health insurance in Laos

From 2005 to 2015 Laos had one of the fastest growing economies in the world, with an average GDP growth rate of 7.8% per annum (5). Total health expenditure per capita increased from 29 USD in 2010-2011 to 59 USD in 2015-2016 but total health expenditure as a proportion of GDP fluctuated between 2.4% and 3% from 2010-2016 (6). In 2021, it was 2.74%. This was one of the lowest globally and below neighbouring countries, such as Thailand (5.16%), Cambodia (7.53%), Vietnam (4.59%), and Myanmar (5.63%) (7).

The main sources of revenue and financial flows within the healthcare system are 45.1% from out-of-pocket expenditure, 30.6% from the government, 17.7% from donors, 3.6% from health insurance and 3.1% from Non-Governmental Organisations (6). Though out-of-pocket expenditure decreased slightly, from 48.6% in 2010-2011 to 45% in 2015-2016, it remained the major component of health expenditure in Laos. In 2016, hospitals accounted for 46.8% of health expenses, with pharmaceuticals comprising 44.7%, the highest at all facility levels. However, detailed antimicrobial spending is unavailable, except for specific infectious diseases: 5% for respiratory infections, 1.3% for HIV/AIDS and sexually transmitted infections (STIs), 0.3% for tuberculosis, 2.5% for malaria, 1.6% for diarrhoeal diseases, and smaller amounts for leprosy, dengue fever, and other diseases (6).

In 2016, the government allocated LAK 72,351 million (~8,865,457 USD) for Social Health Insurance or 4.4% of general government health expenditure (5). In 2019, MoH declared that 22.5% of health expenditure in Laos still relied on the external funding. An economic downturn after the Covid-19 pandemic and the reduction of external financial support, makes Laos challenged in sustaining essential health services (8).

National Laboratory network in Laos

The national laboratory network structure in Laos is in line with the overall five-tiered organization of the national health system. The network structure includes the National Centre for Laboratory and Epidemiology (NCLE), Centre for Malaria, Parasitology and Entomology (CMPE), National Tuberculosis Centre (NTB), the Dermatology Centre, the Mahosot Hospital Microbiology Laboratory/Lao-Oxford-Mahosot Hospital Wellcome Trust Research Unit (LOMWRU), Institut Pasteur du Laos (IPL), Centre d'Infectiologie Christophe Mérieux du Laos (CICML), central, regional, provincial and district health centre laboratories.

Antimicrobial stewardship programme

Laos lacks a national antimicrobial stewardship program. Drug and Therapeutics Committees (DTCs) exist in all hospitals to oversee medication use, but face challenges due to limited resources, heavy workloads, and inadequate training. Though antimicrobial stewardship has been discussed, no formal plans exist. In 2008, the MoH established an Infection Prevention and Control (IPC) committee, with guidance for central and provincial hospitals. The 2013-2016 IPC strategy expanded this to all healthcare facilities, and IPC committees now operate in central, provincial, and some district hospitals.

Chapter 1: Data on antimicrobial use and resistance in human, animal health, and the environment in Lao PDR

Abstract

Objectives: To review the scientific evidence base on antimicrobial use (AMU) and antimicrobial resistance (AMR) in human and animal sectors in Laos.

Methods: We reviewed all publications from July 1994 (the first article describing AMR in Laos) to December 2020. Electronic searches were conducted using Google Scholar and PubMed with specific terms relating to AMR and AMU in Lao, French and English languages.

Findings: We screened 1,357 peer-reviewed and grey literature reports by title and abstract and then full articles/reports. Of 80 included, 66 (83%) related to human health, nine (11%) to animal health, four (5%) to both animal and human health and one (1%) to the environment. Sixty-two (78%) were on AMR and 18 (22%) on AMU. Extended spectrum beta lactamase (ESBL)-producing *Escherichia coli* was the greatest concern identified; the proportion of isolates increased fivefold from 2004 to 2016 (2/28 (7%) to 27/78 (35%)) from blood cultures submitted to the Microbiology Laboratory, Mahosot Hospital, Vientiane. Carbapenem-resistant *Escherichia coli* was first identified in 2015. Methicillin-resistant *Staphylococcus aureus* (MRSA) was uncommon, with 15 cases of MRSA from blood cultures between its first identification in 2017 and December 2020. AMR patterns of global antimicrobial resistance and use surveillance system (GLASS) target pathogens from livestock were less well documented. There were few data on AMU in human health and none on AMU in livestock. The first hospital AMU survey in Laos showed

that 70% (1,386/1,981) of in-patients in five hospitals from 2017 to 2018 received antimicrobial(s). Antibiotic self-medication was common.

Conclusion: AMR in Laos is occurring at relatively low proportions for some GLASS pathogens, except ESBL-producing *E. coli*, giving the country a window of opportunity to act quickly to implement strategies to protect the population from a worsening situation. Urgent interventions to roll out new guidelines with enhanced one-health antibiotic stewardship, reduce antibiotic use without prescriptions, enhance surveillance and improve understanding of AMU and AMR are needed.

Background

1. Antimicrobial resistance: global situation

Antimicrobial resistance (AMR) is the ability of microorganisms, including bacteria, fungi, viruses and parasites, to withstand exposure to antimicrobial medicines, such as anti-bacterials, antifungals, antivirals, anti-protozoals and anti-helminthics, so that the treatment becomes ineffective (9). Resistance can be acquired or intrinsic. Intrinsic resistance is the innate ability of bacteria to withstand the activity of some antimicrobial compounds which are found only in some strains or some particular bacterial species (e.g., *Klebsiella pneumoniae* is intrinsically resistant to ampicillin). Acquired resistance is the ability of bacteria to resist a particular antimicrobial compound to which it was previously susceptible. Therefore, in clinical settings, laboratory methods focus on detection of acquired resistance to quantify the burden of AMR (10).

AMR is a major global public health concern and is increasing in frequency for key pathogens and key antimicrobials. The evidence suggests that this increase is accelerated by misuse of antimicrobials. AMR results in both direct consequences, such as longer duration of illness, increased mortality and prolonged stay in hospital, and indirect consequences such as reduced productivity caused by sickness and increased family, community and health system economic burden (11, 12). In 2021, Global Burden of Diseases (GDB) Antimicrobial Resistance Collaborators estimated that bacterial AMR was linked to 4.71 million deaths (95% UI: 4.23-5.19). Of these, 1.14 million deaths (95% UI: 1.00-1.28 million) were directly caused by bacterial AMR based on data from 204 countries from 1990-2021 (13). Since 2000, the number of antibiotics in development has fallen sharply. Many

pharmaceutical companies have left the antibiotics market, stopping production and engagement in research and development (R&D), as antibiotic treatment courses are relatively short and inexpensive, and resistance can occur soon after they are introduced. This is in contrast to higher-priced drugs like antihypertensives or cholesterol-lowering agents that are used lifelong (14). By 2050, if AMR continues to increase with no appropriate action being taken, this could contribute 10 million excess deaths (15). AMR infections could globally lead to economic collapse similar to the 2008 financial crisis. The GDP in low-income countries (LMICs) might drop by more than 5%. AMR could push up to 28.3 million people into poverty, mostly (26.2 million) in developing countries. Healthcare costs could reach 1.2 trillion US dollars per year in high-AMR scenarios and it could be 0.3 trillion US dollars in low-AMR scenarios (16).

In order to address this major threat to global public health, there have been a number of international initiatives. The Global Action Plan on AMR (GAP-AMR) to combat AMR was established by WHO in 2015. In the same year, the Global Antimicrobial Resistance and Use Surveillance System (GLASS) was established. GLASS focuses on specific microorganisms in specific sample types (Table 1) (17). In 2023, five new pathogens were included (*Pseudomonas aeruginosa*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Salmonella* enterica serovar Typhi, and *Salmonella* enterica serovar Paratyphi A) (18). The AWaRe (access, watch, reserve) classification database was first developed in 2017 and updated by a WHO Expert Committee every two years with the latest update in 2023. It aims to enhance antimicrobial stewardship with a target of using at least 60% from the Access group (19).

Table 1: GLASS priority specimens and pathogens for surveillance of AMR (2023)

Target pathogens*	**Specimens**					
	Blood	CSF	Urine	Stool	**LRT**	Urethral, cervical, **rectal**, **pharyngeal** swabs
Acinetobacter spp.	•	o			•	
Escherichia coli	•	o	•		o	
Klebsiella pneumoniae	•	o	•		•	
Pseudomonas aeruginosa	•	o			•	
Staphylococcus aureus	•	o			•	
Streptococcus pneumoniae	•	•			•	
Neisseria meningitidis	•	•				
Haemophilus influenzae	o	•			•	
Salmonella spp. (non-typhoidal)	•	o		•		
***Salmonella* enterica serovar Typhi**	•			o		
***Salmonella* enterica serovar Paratyphi A**	•			o		
Shigella spp.				•		
Neisseria gonorrhoeae						•

Note: **LRT** = Lower Respiratory Tract, **CSF**= cerebrospinal fluid, • Data collected and included in the official GLASS report when are available, o Included in the GLASS database to accommodate data when submitted, but not necessarily included in the annual GLASS report, * New target pathogens and specimens (added in 2023) are marked in bold font.

2. Regional situation

Member States in the Western Pacific Region of the WHO approved the Action Agenda for Antimicrobial Resistance in 2014 at the WHO Regional Committee. The committee agreed with the three priority actions of the agenda, which were to: 1) strengthen development and implementation of comprehensive national plans to contain AMR and raise awareness in multiple sectors; 2) improve surveillance of AMR and monitoring of antimicrobial use; and 3) strengthen health systems capacity to contain AMR (9). Most LMICs in these regions, such as Vietnam, Cambodia, Philippines, Indonesia and Laos, already have national action plans in place to combat AMR. Although at least 22 AMR surveillance networks for bacteria

and fungi in LMICs are currently contributing to global surveillance, relatively few data are available from Laos (20-22).

In Laos, as is common elsewhere, different sectors tend to work on their own strategies with little interaction between them. In 2015, the first AMR Surveillance and Control Committee was established in Laos under the leadership of the Ministry of Health. This committee, in collaboration with WHO, World Organisation for Animal Health (WOAH) and Food and Agriculture Organization of the United Nation (FAO), released the first National Strategic Plan on Antimicrobial Resistance in Laos 2019-2023 in October 2019. In October 2016, the Global Antibiotic Resistance Partnership-Laos (GARP-Laos) committee was established as a Ministry of Health technical working group to review the scientific evidence-base to inform efforts to combat antimicrobial resistance in Laos, to provide evidence to the AMR Surveillance and Control Committee, and to inform the national action plan. This review results from this committee's work.

This review focuses on bacterial pathogens, particularly GLASS pathogen-antimicrobial combinations and *Mycobacterium tuberculosis* in humans, animals and environment. We did not include antimalarial, antiprotozoal, helminthic, fungal and antiviral resistance. We have presented the evidence on the use of antimicrobials in both human, animals and environment; and antimicrobial susceptibility and resistance in Laos and discuss the implications for health policy in the country. By reviewing these data, we also aimed to highlight gaps in research that raise fundamental issues for the development of policies to control antibiotic resistance and its consequences in Laos.

Methods

1. Information sources and search criteria

This narrative review of peer reviewed and grey literature focuses on bacterial pathogens, particularly GLASS target pathogens, *Mycobacterium tuberculosis* and available antimicrobial resistance data on other bacteria in humans, animals and the environment and antimicrobial use (AMU). We included all publications from 1994 (the year of the first article describing antimicrobial resistance in Laos) to 31 December 2020. We included articles in Lao, French and English languages.

1.1. Published literature

Electronic searches were conducted using Google Scholar and PubMed. The search terms used were “Laos, Lao, antimicrobial susceptibility, antimicrobial resistance, antimicrobial use, animals, pharmacy, prescription, prevention, self-medication, environment, *Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Staphylococcus aureus, Streptococcus pneumoniae, Salmonella* spp., *Shigella* spp., *Neisseria gonorrhoeae, Salmonella* Typhi*, Salmonella* Paratyphi, *Vibrio cholerae, Mycobacterium tuberculosis,* Extended Spectrum Beta Lactamase (ESBL) and methicillin resistant *Staphylococcus aureus* (MRSA)”. Eligible articles were included after scanning the abstracts. Full articles were then reviewed to obtain relevant data for inclusion.

1.2. Grey literature

Relevant Lao Government departments were contacted and visited and data and reports requested. Unpublished data including annual reports, student project theses, results of projects on antibiotic use and resistance in Laos were requested from the Food and Drug Department, Department of Healthcare and Rehabilitation, National Tuberculosis Centre, Microbiology Laboratory of Mahosot Hospital, Livestock and Fisheries Department of Ministry of Agriculture & Forestry, Faculty of Agriculture of Lao National University and Institut de la Francophonie pour la Médecine Tropicale (IFMT).

2. Data categorisation

Data were categorised into two groups: antimicrobial resistance and antimicrobial use. Each group included data from reviewed sources relating to humans, animals and environment.

3. Data display

In this literature review, extracted data from peer-reviewed and grey literature sources were descriptively displayed in different categories as mentioned above. The quality of evidence was not graded. Authors of related articles were not contacted for more information. There was no further analysis of extracted data.

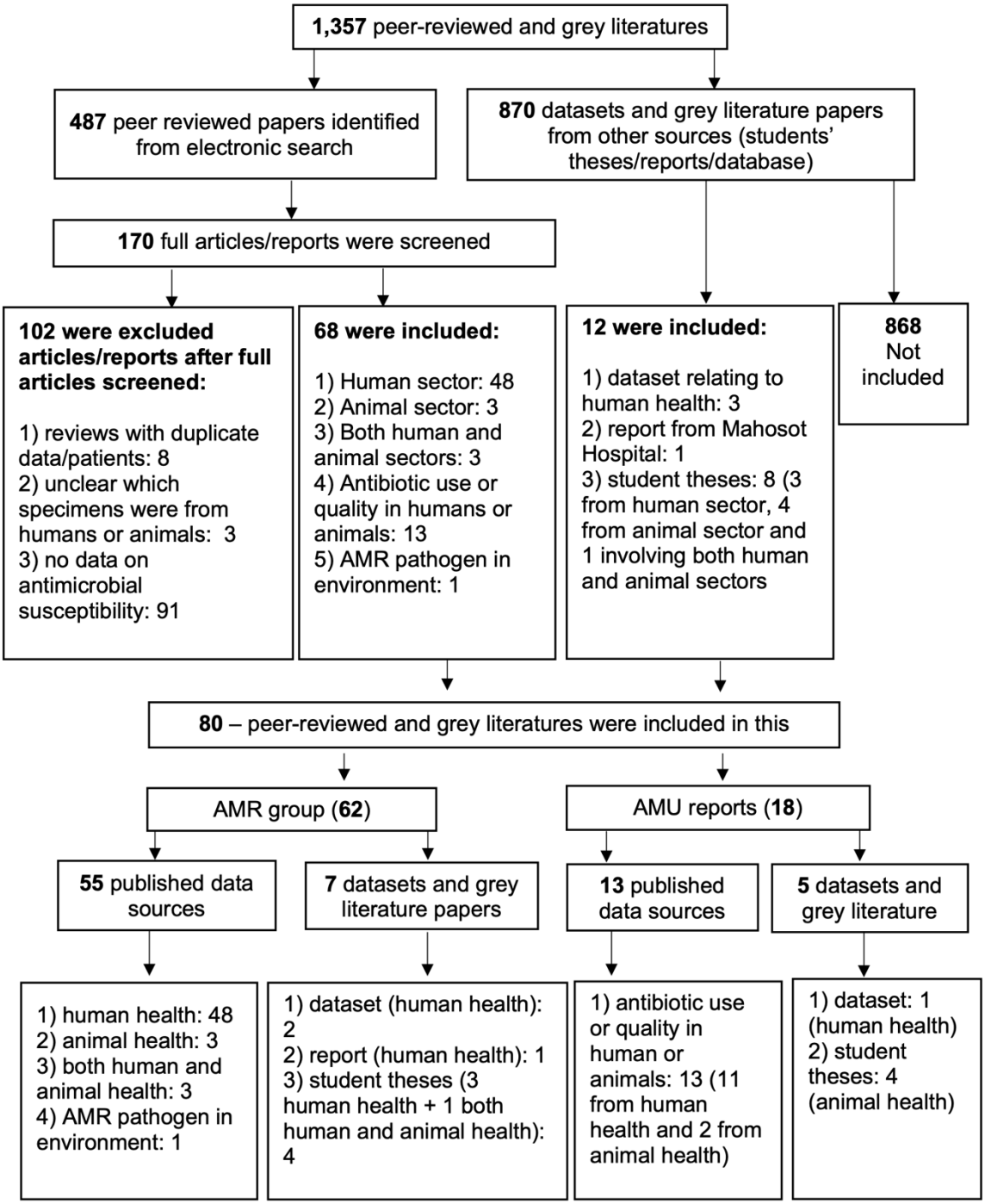
Results

From 28 July 1994 to 31 December 2020, 1,357 data sources, including 487 (36%) peer-reviewed papers from electronic searches and 870 (64%) grey literatures were identified and then screened by titles and abstracts. Finally, 80 were included (Figure 1), including 66 (83%) data sources related to human health only, nine (11%) related to animal health, four (5%) covered both human and animal health and one (1%) related to environmental antimicrobial resistant pathogens. Of 80 data sources, 62 (78%) were related to AMR and 18 (22%) were related to AMU in Laos; 41/80 (51%) were from, or related to, work done by the Microbiology Laboratory/LOMWRU, Mahosot Hospital, Vientiane, Laos (Figure 2). In total, 73 were in English, two in French, and five were in Lao language.

1. Evidence for AMR in bacteria infecting humans in Laos

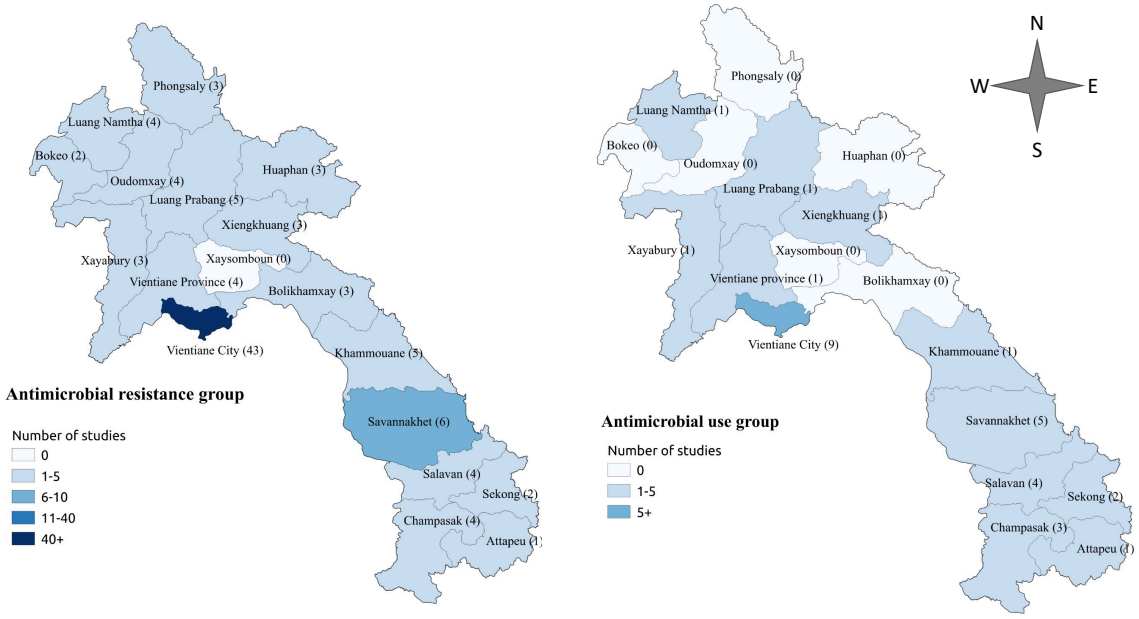
The majority (54/62 (87%)) of data sources on AMR described data in the human sectors alone, whilst four (6%) data sources described AMR in both human and animal sectors. Community-acquired infections (CAI) versus hospital acquired infections (HAI) are not discussed in this review as most available data sources did not include this information. The largest available dataset in this review was microbiology data from Mahosot Hospital from 2000-2016; this dataset did not include information to be able to identify HAI. However, among 41,907 patients with blood cultures submitted to this laboratory during this period, 86% of them had CAI (23, 24).

Figure 1: Search strategy and selection of studies for the review



AMR reports: included peer-reviewed and grey literatures with antimicrobial susceptibility data in either human, animal or environment sectors
AMU reports: included peer-reviewed and grey literatures with data of antimicrobial use in either human, animal or environment sectors

Figure 2: Geographical distribution of antimicrobial resistant (AMR) and antimicrobial use (AMU) data sources



Note: Numbers after each province name (in parentheses) refer to the number of studies relating to either AMR or AMU in Laos, regardless of whether in human, animal or environmental sectors. Thirteen and two data sources were not included in the AMR and AMU maps, respectively, because their study sites were not clearly specified.

In the next section, data on WHO GLASS pathogens are presented first, followed by *M. tuberculosis* and then other pathogens of local (and regional) importance. Clinically significant isolates from normally sterile sites are also presented first, followed by non-sterile sites followed by data from colonisation studies.

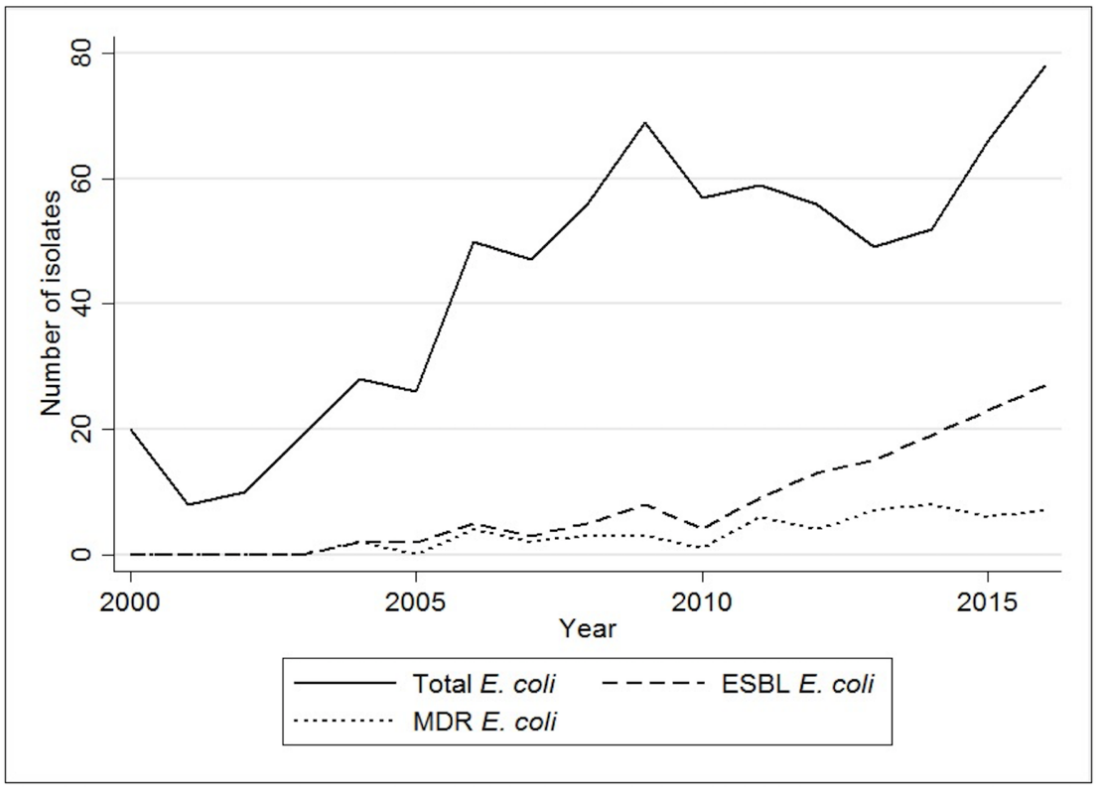
WHO GLASS pathogens

1. *Escherichia coli*

E. coli are diverse Gram-negative bacteria found in the intestines of humans, animals and in the environment. Between 1994 and 2020, there were 17 data sources (Appendix 1) that referred to *E. coli* and its antimicrobial susceptibility patterns. AMR is rising in *E. coli* globally with two resistance mechanisms of particular concern: production of ESBL and carbapenemases. A group of students from the University of Health Sciences (UHS), Vientiane described bacteria cultured from urine from adult in- and outpatients with UTI at Mahosot Hospital from January 2010 to November 2011 (23 months). Of 1,837 midstream urine specimens analyzed, 280 (15%, 95% CI: 13.6-17) yielded significant growth and the most common pathogen was *E. coli* (194/280 – 69%, 95% CI: 63.5-74.6). ESBL-producing *E. coli* was reported at 28/194 (14%, 95% CI: 9.8-20.2), 130/186 (70%, 95% CI: 62.7-76.4) were resistant to trimethoprim-sulfamethoxazole, 61/192 (32%, 95% CI: 25.2-38.9) to ofloxacin, 49/190 (26%, 95% CI: 19.7-32.6) to ciprofloxacin, 51/185 (18%, 95% CI: 21.3-34.6) to gentamicin and 22/151 (15%, 95% CI: 9.4-21.2) were resistant to nitrofurantoin (25). Between 2000 and 2016, of 750 *E. coli* isolated from the blood of patients admitted to Mahosot Hospital, 59% were resistant to ampicillin, 61% to trimethoprim-sulfamethoxazole, 32% to ciprofloxacin, 18% to gentamicin and 26% to chloramphenicol with a continuous increase of ESBL positive isolates and sporadic cases of carbapenem resistance (23, 26).

ESBL are enzymes produced by some bacteria that can hydrolyse third generation cephalosporins (27). ESBL-producing *E. coli* were first identified from the Mahosot Hospital Microbiology Laboratory in clinical samples in 2004 (28). The frequency of ESBL-producing *E. coli* bacteraemia during 2004-2016 was 135/693 (19%, 95% CI: 16.6-22.6), but the proportion of isolates producing ESBL increased 5-fold from 2004, 2/28 (7%, 95% CI: 0.9-23.5) to 2016 with 27/78 (35%, 95% CI: 24.2-46.2) from blood cultures from 2000 to 2016 at Mahosot Hospital (Figure 3) (23). More recent (2017-2018) data on urine cultures from patients with urinary tract infection (UTI) from Mahosot Hospital included 169 *E. coli* isolates, of which 90 (53%, 95% CI: 45-61) were ESBL-producers, and 43 (25%, 95% CI:19-33) were multidrug resistant (MDR – non-susceptible to ≥1 agent in ≥3 antimicrobial categories (24).

Figure 3: Trends of *E. coli* isolates from blood cultures from 2000 to 2016 at Mahosot Hospital, Vientiane



Two studies involving molecular characterisation of ESBLs in Laos were included in this review. The first looked at 54 ESBL *E. coli* isolates from blood, urine and pus samples of patients at Mahosot Hospital between 2004 and 2009 (28). All isolates harboured the $bla_{CTX\text{-}M}$ gene, similar to isolates in other Asian countries. CTX-M-14-like genes were the most common with CTX-M-15-like, CTX-M-27-like and CTX-M-55-like variants also identified. There were 15 different sequence types (ST) identified with the pandemic global lineage ST-131 being the most frequent (29). Another study, which included samples from the above two studies in a worldwide comparison of ST131 ESBL *E. coli* isolates, also highlighted that the CTX-M gene appears to have emerged as the predominant resistance gene in *E. coli* compared to the previous bla_{TEM} and bla_{SHV} variants from the 1990s and early 2000s (30).

Outside Vientiane City, of 2,270 febrile patients with available blood culture results from three northern (Luang Namtha, Oudomxay and Huaphanh) and one southern province (Salavan) during 2002 and 2010, *E. coli* was only found in the blood of 8 patients (0.4%, 95% CI: 0.15-0.7) patients, of which only one was ESBL positive (31-33).

1.1. Carbapenem resistance in *E. coli* in Laos

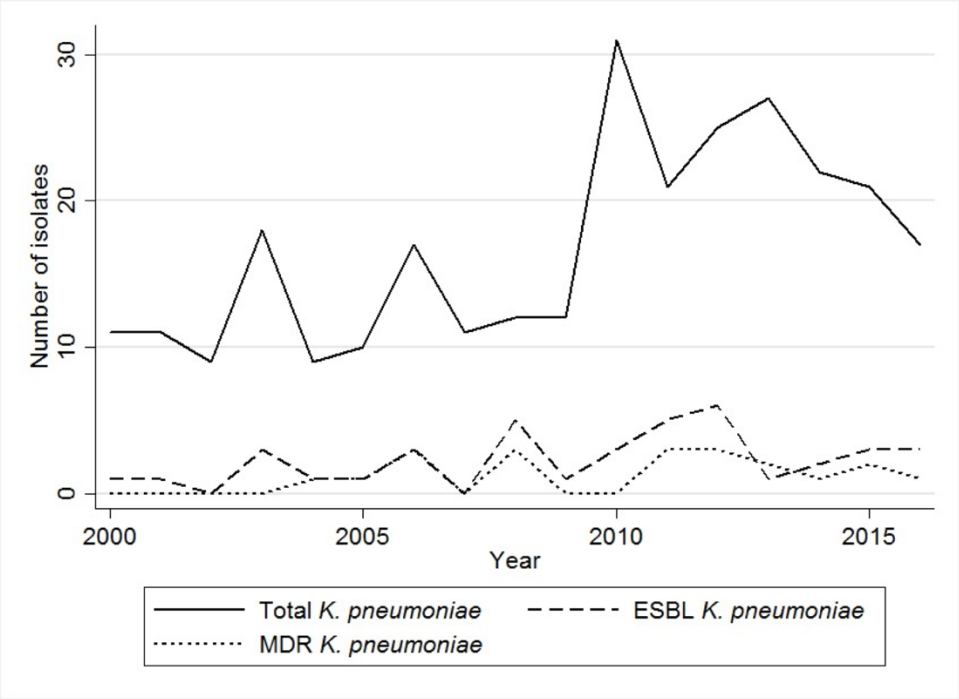
Carbapenem resistance in *E. coli* was first identified in Laos in 2015 from a pus specimen from a patient admitted to Mahosot Hospital. Since then up to December 2020, nine more isolates from hospitalized patients were identified by the Microbiology Laboratory at Mahosot Hospital (two from blood). Molecular characterisation was conducted for four isolates and all four carried New Delhi Metallo-betalactamase (NDM) genes (34, 35).

2. *Klebsiella pneumoniae*

Klebsiella pneumoniae are Gram-negative bacteria normally found in the human intestine. They are an important cause of neonatal sepsis, liver abscesses and healthcare-associated infections. All *K. pneumoniae* are regarded as naturally resistant to ampicillin/amoxicillin. Between 2000 and 2016, there were 284 *K. pneumoniae* isolates from blood cultures of patients in Mahosot Hospital. Of these, 69/272 (25%, 95% CI: 20.3-31) were resistant to trimethoprim-sulfamethoxazole, 44/217 (20%, 95% CI:15-26) to chloramphenicol, 33/245 (13%, 95% CI: 9-18) to gentamicin, 6% to ciprofloxacin and 19/231 (8%, 95% CI: 5-12.5) to amoxicillin-clavulanic acid (23).

ESBL-producing *K. pneumoniae* were first identified from the Mahosot Hospital Microbiology Laboratory in clinical samples in 2000. Of 284 *K. pneumoniae* isolates from blood cultures during 2000-2016 in Mahosot Hospital, 39 (14%, 95% CI: 10-18) were ESBL producers and 20/39 (51%, 95% CI: 35-68) were also MDR. However, ESBL-producing *K. pneumoniae* showed no clear trend over this period and the proportion varied from 3% to 41% (Figure 4) (23). *K. pneumoniae* from other hospitals in Vientiane also showed high levels of antimicrobial resistance. In 2017, of 30 *K. pneumoniae* isolates from the other three Ministry of Health hospitals in Vientiane (including a *K. pneumoniae* nosocomial outbreak in one hospital), 9/30 (30%, 95% CI: 15-49) were ESBL positive and 5/9 (56%, 95% CI: 21-86) were also MDR (24). Molecular characterization testing was performed for 32 *K. pneumoniae* isolates from blood from hospitalized patients at Mahosot Hospital during 2015 and 2016; 18 (56%, 95% CI: 38-74) carried the CTX-M-15 gene (36).

Figure 4: Trends in *K. pneumoniae* isolates from blood cultures from 2000 to 2016 at Mahosot Hospital, Vientiane



K. pneumoniae carbapenem susceptibility has been tested since 2010. Of 164 *K. pneumoniae* isolated from blood cultures from 2010 to 2016 (23). Five *K. pneumoniae* carbapenem resistant isolates were reported from non-blood specimens and one from blood during January-2018 and December-2020. Of these six, three isolates were tested for carbapenemase and all of them carried NDM genes (24).

2.1. ESBL- producing Enterobacterales carriage/colonization studies

2.1.1. ESBL-producing *E. coli* carriage/colonisation

Between March and June 2011, Stoesser et al. (2015) investigated ESBL carriage, by collecting stools from 397 healthy children from 12 pre-school childcare facilities in the capital city and wider province of Vientiane (80 km north of the capital city). Of 397 children, 100 specimens from 92 (23%, 95% CI: 19-28) children carried ESBL-producing Enterobacterales. The prevalence of ESBL-producing Enterobacterales colonisation in Vientiane capital was significantly higher than Vientiane Province (30% vs 16%; p=0.002) but no carbapenem resistance was found (29). Of the 100 ESBL-producing Enterobacterales isolates, 78 (78%, 95% CI: 69-86) were *E. coli.* Approximately 20% (100/397, 95% CI: 21-30) of the children were colonised with ESBL-producing *E. coli* in this population. These isolates were also resistant to trimethoprim-sulfamethoxazole (58/78, 74%, 95% CI: 63-83), 36/78 (46%, 95% CI: 35-58) resistant to chloramphenicol, 33/78 (42%, 95% CI: 31-54) resistant to gentamicin, 15/78 (19%, 95% CI: 11-30) resistant to ofloxacin and 1/78 (1%) resistant to nitrofurantoin. The most common ESBL gene was $bla_{\text{CTX-M-14}}$ (36/77, 47%, 95% CI: 35-58), followed by $bla_{\text{CTX-M-55}}$ 13/77 (17%, 95% CI: 32-55) and then $bla_{\text{CTX-M-14}}$ 10/77 (13%, 95% CI: 6-23) (29).

In Savannakhet Province (~462km south of Vientiane), Nakayama et al. (2015) described ESBL-producing *E. coli* colonization in 41/57 (72%, 95% CI: 58-83) stool specimens from healthy adults. The most common *E. coli* ESBL genes were $bla_{\text{CTX-M-1}}$ and $bla_{\text{CTX-M-9}}$ with 19/40 (48%, 95% CI: 31-64) each (37). In Xiengkhuang Province (~430 km northeast of Vientiane), Chang (2016) collected stool specimens from 268 asymptomatic villagers in a very remote area, inaccessible by car; there

was no toilet in the village and 98% (95% CI: 95-99) of villagers used organic fertilizers (e.g., animal excreta or vegetable matter). Of 268 asymptomatic villagers, 14 (5%, 95% CI: 3-9) carried ESBL producing Enterobacterales. Of these 14 isolates, 11 (79%, 95% CI: 49-95) were ESBL-producing *E. coli*. All 11 isolates were fully susceptible to meropenem and amikacin and susceptible to gentamicin (82%), ciprofloxacin (82%), co-trimoxazole (82%) and chloramphenicol (82%) (38).

A recent study published in 2021 showed that 174/236 (74%, 95% CI: 68-79) faecal specimens collected from 20 healthy European visitors to Laos, contained ESBL-producing Gram-negative bacteria during their stay in Laos. Of 292 isolates were available for whole-genome sequencing, 219 (75%, 95% CI: 70-80) were *E. coli.* ST101 was commonly identified (39).

2.1.2. ESBL-producing *K. pneumoniae* carriage/colonisation

ESBL-producing *K. pneumoniae* carriage/colonisation was also described by Stoesser et al. (29) and Chang et al. (38). Stoesser et al. (2015) described 18/100 ESBL-producing *K. pneumoniae* isolated from healthy pre-school children in Vientiane City and Vientiane Province (29). Of 18 isolates, all were resistant to trimethoprim-sulfamethoxazole, 14 (78%, 95% CI: 52-94) resistant to chloramphenicol, eight (44%, 95% CI: 21-69) resistant to ceftriaxone, four (22%, 95% CI: 6-48) resistant to gentamicin, two (11%, 95% CI: 1-35) resistant to nitrofurantoin and one (6%, 95% CI: 0.1-27) resistant to ofloxacin (29). Three ESBL-producing *K. pneumoniae* described by Chang et al. were resistant to gentamicin, trimethoprim-sulfamethoxazole and chloramphenicol, with 67% ciprofloxacin intermediate. However, all three were still susceptible to meropenem and amikacin (38).

2.1.3. Colistin-resistant *K. pneumoniae* in healthy Lao individuals

Colistin is not available for human use in Laos, but it is used for livestock(40, 41). Susceptibility to colistin amongst Enterobacterales is not routinely tested for in either human or animal microbiology laboratories. Olaitan et al. (2014) collected stool samples from 190 healthy Lao individuals for culture to test for colistin-resistant Enterobacterales carriage in Laos. From 190 stool samples, 11 colistin-resistant *K. pneumoniae* (5.8%) were isolated. All isolates were susceptible to ceftriaxone, cefotaxime, aztreonam, cefoxitin, ticarcillin/clavulanic, imipenem, tobramycin, gentamicin, amikacin, kanamycin and ofloxacin, 90% were susceptible to amoxicillin-clavulanic acid, 64% to ciprofloxacin and 55% to trimethoprim-sulfamethoxazole. Of 11 isolates, nine different STs were reported and seven (64%) had *mgr*B gene with no mutation (42). Rolain et al. (2016) found that four of these 11 (36%) isolates harboured the *mcr*-1 gene sequence and 2/4 (50%) also had either a stop codon or a mutation in the *mgrB* gene sequence (43).

3. Staphylococcus aureus

3.1. *Staphylococcus aureus* bacteraemia

Staphylococcus aureus is a Gram-positive bacterium that is found as a normal commensal of the healthy population, especially in the nose (44). *S. aureus* is a common cause of bacteraemia in Laos, especially in infants (45, 46). Phetsouvanh et al. (2006) showed that 69% of bacteraemias in infants aged<1 year admitted to Mahosot Hospital from 2000 to 2004 were caused by *S. aureus* (46). A review of 200 *S. aureus* isolates from blood cultures at Mahosot Hospital from 2000 to 2011 showed that *S. aureus* isolates were highly resistant to penicillin (93%), erythromycin (39%) and tetracycline (48%), but susceptible to methicillin (or

cloxacillin) (100%), gentamicin (99%), trimethoprim-sulfamethoxazole (89%) and vancomycin (100%) (47). One methicillin resistant *S. aureus* described in Elliot et al. (2012) (47) was retested in 2019 and found to be susceptible (23). Subsequently, Anderson et al. (2014) demonstrated that *S. aureus* was the cause in 39/85 (46%) of blood culture positive infants (0-60 days) in the same hospital from 2000 to 2011 (45). Of these 39 isolates, all were susceptible to cloxacillin, gentamicin, co-amoxiclav, ceftriaxone and vancomycin with 97% susceptible to trimethoprim-sulfamethoxazole, 72% to chloramphenicol but highly resistant to penicillin (95%), ampicillin (95%) and erythromycin (41%) (45).

Data describing *S. aureus* bacteraemia outside Vientiane City are limited. Bounsavath (2008) (n=204 from 2003 to 2006) and Mayxay et al. (2013) (n=1,938 from 2008 to 2010) described causes of fever among inpatients in Huaphanh Provincial Hospital and in- and outpatients from Luang Namtha and Salavan Provincial Hospitals, respectively. Of 2,142 febrile patients with blood culture results, *S. aureus* was isolated in 8/2,142 (0.4%). Of these eight isolates, all were susceptible to cloxacillin, 5/7 (71%) were susceptible to trimethoprim-sulfamethoxazole, 5/7 (71%) to chloramphenicol, 2/2 (100%) to gentamicin and 2/2 (100%) to vancomycin (32, 33).

3.2. Methicillin-resistant *S. aureus* (MRSA)

MRSA is increasing worldwide and may be community or hospital acquired. Antibiotics recommended to treat invasive infections with MRSA such as vancomycin are not widely available in LMICs, including in Laos. Monitoring of MRSA in Laos started in 1994 (48). The first isolation of MRSA (*mecA* positive) in Laos was reported by Iwanaga et al. (1997). The specimen was from the nose of an inpatient without signs of infection (49). In 2002 the first two MRSA isolates from

clinical specimens submitted to the National Centre for Laboratory and Epidemiology, Vientiane, were reported (50).

MRSA has been continuously monitored in the Microbiology Laboratory of Mahosot Hospital since 2000. The first MRSA case was identified by Mahosot Hospital from clinical specimens in 2008; the first MRSA in blood was identified in this laboratory in 2017. Since 2017, 14 subsequent cases were confirmed by blood culture until December 2020. Of concern, from 2017 to 2018, 95/619 (15%) *S. aureus* from non-blood culture specimens submitted to the Microbiology Laboratory at Mahosot Hospital were MRSA. Of the MRSA isolates from these patients, 10/90 (11%) were resistant to ciprofloxacin, 15/91 (16%) resistant to chloramphenicol, 80/94 (85%) resistant to tetracycline, 19/95 (20%) resistant to gentamicin and 7/93 (8%) resistant to trimethoprim-sulfamethoxazole, which are the main treatments for MRSA used in Laos, where glycopeptides are not currently readily available (24).

A study of the molecular epidemiology of *S. aureus* isolated from 2012 to 2014 from skin and soft tissue infections at Mahosot Hospital found 7/96 (7%) isolates to be MRSA, all of which were *mecA* positive (51). Amongst the 96 *S. aureus* isolates, 94 were penicillin resistant and *blaZ* (beta-lactamase gene) positive, 43 were tetracycline resistant, mainly associated with *tetK* (tetracycline efflux protein gene) and *tetM* (ribosomal protection protein gene associated with tetracycline resistance), and 12 were erythromycin resistant, associated with *ermA*, *ermB* and *ermC* (rRNA methyltransferase genes associated with macrolide/lincosamide resistance). There were 12 chloramphenicol resistant isolates associated with *cat* (chloramphenicol acetyltransferase gene), and four isolates were resistant to gentamicin, with *aacA-aphD* (aminoglycoside adenyl-/phosphotransferase gene associated with resistance to gentamicin and tobramycin) detected in all. There

were no genes conferring resistance to glycopeptides, linezolid, mupirocin, fusidic acid or macrolides (apart from *erm)* found (51).

4. *Salmonella* Typhi and non-typhoidal *Salmonella*

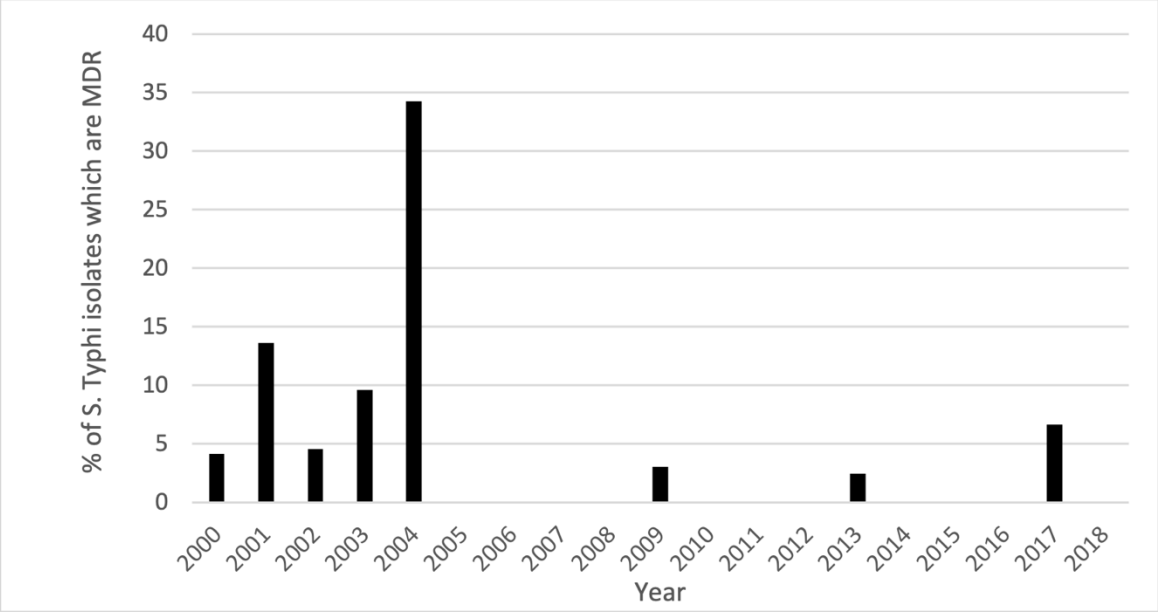
4.1. *Salmonella* enterica serovar Typhi

Salmonella Typhi is the cause of enteric fever and an important Gram-negative pathogen in Laos. Elsewhere in south and southeast Asia multidrug resistance in *S.* Typhi is a major problem. In 2006, Phetsouvanh et al*.* published the first report of the aetiology of community-acquired septicaemia and antibiotic susceptibility patterns in patients admitted to Mahosot Hospital. This included data from 2000-2004, based on blood cultures from 4,460 inpatients. The frequency of bacteraemia amongst these patients was 483 (10.7%). *S.* Typhi was isolated most frequently 246/483 (51%) (46).

Roberts et al*.* reported a large case series of 913 *S.* Typhi bacteraemias from the Mahosot Hospital Microbiology Laboratory (2000-2018), which covered data from Hongsakhone (2004) (31), Phongmany et al*.* (2005) (52), Phetsouvanh et al. (2006) (46), Bounsavath (2008) (32), Mayxay et al. (2013) (33), Chansamouth et al. (2016) (53) and the unpublished Mahosot Microbiology/LOMWRU dataset (23) (Figure 5). The results of this case series demonstrated that 12/854 isolates (1.4%) were resistant to quinolones (either ciprofloxacin or nalidixic acid or both), 76/815 (9%) to ceftriaxone, 71/893 (8%) to ampicillin, 70/865 (8%) to chloramphenicol, 67/885 (7.6%) to trimethoprim-sulfamethoxazole and 59/848 (7%) were MDR (resistant to first-line antibiotics ampicillin, chloramphenicol, and trimethoprim–sulfamethoxazole (co-trimoxazole)) (54). A study of the H58 lineage of MDR *S.* Typhi from 15 countries included 15 *S.* Typhi isolates from Laos that had the

Tn*2670*-like composite transposon located on the IncHI1- PST6 plasmid, which is known to carry antimicrobial resistance genes (55).

Figure 5: Trends of MDR *Salmonella* Typhi isolates from blood cultures from 2000-2018



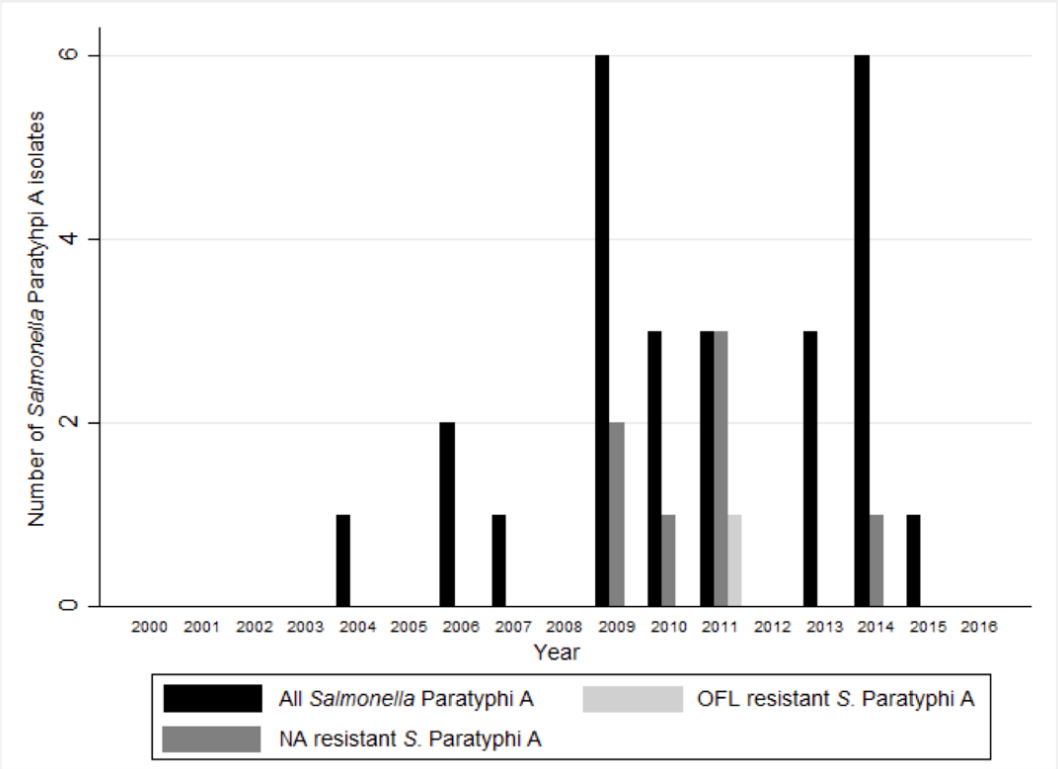
Note: Data from Mahosot Hospital and Huaphan, Xiengkhuang, Oudomxay, Luang Namtha and Salavan Provincial Hospitals, Laos. The Majority of MDR cases were from 2000 to 2004, especially related to a typhoid outbreak in Oudomxay in 2004.

4.2. *Salmonella* enterica serovar Paratyphi

Paratyphoid fever has not been described commonly in Laos (56). The majority of data on paratyphoid infections described in this review were from the bacteraemia database from Mahosot Hospital/LOMWRU. Of 26 patients with *Salmonella enterica* serovar Paratyphi bacteraemia between 2000 and 2016 (Figure 6) identified in the Microbiology Laboratory, Mahosot Hospital, 1/23 (4%) was resistant to ampicillin, 1/23 (4%) to chloramphenicol and none of them was resistant to trimethoprim-sulfamethoxazole, with no MDR *S.* Paratyphi A isolated from blood cultures during this period. Until recently, reduced quinolone susceptibility was assessed using nalidixic acid as a screen and there have been 7/26 (27%) nalidixic

acid resistant *S.* Paratyphi A isolates recorded. However, only 1/26 (4%) *S.* Paratyphi A was reported as resistant to ofloxacin or ciprofloxacin over this 16-year period. *Salmonella* Paratyphi B and C have not yet been detected in Laos (23).

Figure 6: Trends of *Salmonella* Paratyphi A isolates from blood cultures from 2000-2016 at Mahosot Hospital, Vientiane



Note: NA= nalidixic acid, **OFL**=Ofloxacin

4.3. Non-Typhoidal *Salmonella*

The epidemiology of non-typhoidal *Salmonella* (NTS) has not been well documented in Laos. Twelve data sources describing NTS were found in this review. The first report described 24 (3%) *Salmonella enterica* serovar Stanley isolates from stool cultures of 910 children, and nurses at the paediatric ward in Mahosot Hospital in 1970 but antimicrobial susceptibility testing (AST) was not reported (57). Yamashiro et al. (1998) investigated causes of diarrhoea in 880

patients during 1996 and 1997 in public hospitals and private clinics in Vientiane City; NTS was isolated from 5/880 (0.6%); no further investigation on AST on these isolates was reported (58). NTS bacteraemia was first described in Laos in the blood culture study of Phetsouvanh et al. (2006) (46).

During 2000 to 2012, 168 *Salmonella* spp. (63 from blood and 105 from faecal specimens) were isolated at Microbiology/LOMWRU, Mahosot Hospital. Phuong et al. (2017) reported that NTS isolated from faecal samples were more frequently resistant to ampicillin and trimethoprim-sulfamethoxazole than those isolated from blood ($p<0.05$). In contrast, NTS resistant to ciprofloxacin were found more frequently in blood than in stool ($p<0.001$). Of these 168 cases, 62 (37%) were classified as invasive-NTS and 6/50 (12%) patients with invasive-NTS were known to be HIV seropositive (59).

In 2017, of 519 stool cultures reported from the Microbiology Laboratory, Mahosot Hospital, 35 grew NTS. The reported rates of resistance were: ampicillin (9%), azithromycin (29%), chloramphenicol (20%), ciprofloxacin (23%), ceftriaxone (23%), nalidixic acid (6%), trimethoprim-sulfamethoxazole (26%) and 3% were MDR (24).

5. *Shigella* spp.

Shigella spp. are Gram-negative bacteria spread by the faecal-oral route which cause diarrhoea. The first report on antimicrobial susceptibility of diarrhoeal pathogens in Laos included 880 diarrhoeal specimens collected during 1996 and 1997 from three general hospitals and a private clinic in Vientiane. From these, 148 *Shigella* spp. were isolated, but only 128 underwent AST: almost all isolates were resistant to ampicillin and tetracycline but were susceptible to ofloxacin (58). In 2018, Darton et al. described 45 *Shigella* spp. (35 *S. flexneri*, nine *S. sonnei* and

one *S. boydii*). Of these 45, 14 (31%) of *Shigella* spp. isolated from stools in Lao patients were resistant to nalidixic acid and 34/45 (76%) were MDR. All isolates were susceptible to ceftriaxone and azithromycin (60). Unpublished data of culture of stools from patients with diarrhoea at Mahosot Hospital in 2017 showed that *Shigella* spp. were isolated from only 3/519 (0.6%) patients. Of these three isolates, one was *Shigella flexneri* (0.2%) which was resistant to trimethoprim-sulfamethoxazole, two (0.4%) isolates were *Shigella sonnei* and both were resistant to ampicillin while one was also resistant to nalidixic acid and ciprofloxacin (24).

6. *Neisseria gonorrhoeae*

There have been several reports of the susceptibility of *N. gonorrhoeae* in Laos at different time points. The first study was conducted by NCLE between 2000 and 2002, and reported the isolation of *N. gonorrhoeae* from 131/1,937 (7%) male urethral swabs and vaginal or cervical specimens. A very high proportion of the isolates were resistant to penicillin and tetracycline (98% and 96%, respectively). The proportion of isolates that were ciprofloxacin resistant increased from 12% (5/45) to 70% (41/59) from 2000 to 2002. The first clinical isolate of *N. gonorrhoeae* resistant to ceftriaxone was described in this study (0.8%). They also reported one further (0.8%) isolate with decreased spectinomycin susceptibility (61). According to subsequent publications, *N. gonorrhoeae* in Laos have remained susceptible to ceftriaxone and spectinomycin but have retained a high frequency of resistance to tetracycline, penicillin and ciprofloxacin (62-64).

During 2001 and 2002, Thammalangsy et al. (2006) isolated *N. gonorrhoeae* from endocervical specimens in 4/500 (0.8%) pregnant Lao women. All isolates were susceptible to ceftriaxone and spectinomycin but two were resistant to ciprofloxacin,

three to penicillin and all to tetracycline (62). Sihavong et al. (2007) reported that 3.7% (41/1,125) of women seen at the Obstetrics and Gynaecology outpatient clinic of Setthathirath Hospital in Vientiane were infected with *N. gonorrhoeae*. Although all 41 isolates were susceptible to ceftriaxone and spectinomycin, all were resistant to tetracycline, 98% resistant to penicillin and 20% resistant to ciprofloxacin (63). Data on the susceptibility of *N. gonorrhoeae* isolated in the Microbiology Laboratory, Mahosot Hospital from 2011-2015 were reported by Phuangsouvanh et al. (2017), which showed similar antimicrobial susceptibility patterns. Of 12,281 genital samples (99.8% patients were female), *N. gonorrhoeae* was found in 158 (1.3%) patients (64). All isolates were susceptible to ceftriaxone and spectinomycin. However, 99%, 90% and 85% were resistant to tetracycline, penicillin and ciprofloxacin, respectively. Azithromycin susceptibility has not been tested for in *N. gonorrhoeae* in Laos. Other sexually transmitted pathogens have been described rarely in Laos. *Chlamydia trachomatis* was described by Thammalangsy et al. (2006) and Sihavong et al. (2007) with frequencies of 10% of 500 pregnant and 4% of 846 outpatient women by a nucleic acid hybridization test, respectively. No antimicrobial susceptibility data were reported (62, 63).

7. *Streptococcus pneumoniae*

Streptococcus pneumoniae is the leading cause of bacterial community-acquired pneumonia and an important cause of meningitis. Globally, increasing penicillin resistance of *S. pneumoniae* is of concern. In 2010, Moore et al. described 35 patients with invasive pneumococcal disease in Mahosot Hospital from 2003 to 2009 diagnosed by either PCR or conventional culture (65). Of these 35 patients, seven were positive in both blood and CSF, 12 were positive in CSF alone and 16 were positive in blood alone. Among invasive pneumococcal disease cases, 23

isolates (either from blood or CSF or both) were available for AST; all 23 isolates were fully susceptible to ceftriaxone and ofloxacin, 14/23 (61%) were resistant to trimethoprim-sulfamethoxazole, 3/23 (13%) to erythromycin, 3/23 (13%) to chloramphenicol and 2/23 (9%) had reduced susceptibility to penicillin (minimum inhibitory concentrations were 0.39 μg/mL and 0.125 μg/mL, respectively-based on CLSI guidelines) (65).

Dubot-Pérès et al. (2019) reported a large study of the aetiology of central nervous system infections in Mahosot Hospital from 2003 to 2011, which included isolates from the earlier study by Moore et al. (2010) from CSF specimens. Of 1,065 inpatients with CNS infection tested for a wide range of pathogens, 12 were CSF and/or blood culture positive for *S. pneumoniae* and had AST results; three (25%) had reduced susceptibility to penicillin (minimum inhibitory concentrations>0.06 μg/mL, based on CLSI guidelines), two (17%) were resistant to chloramphenicol and five (42%) were resistant to trimethoprim-sulfamethoxazole (66).

Rudge et al. (2019) studied *S. pneumoniae* as a cause of respiratory infections in Laos. The research team collected nasopharyngeal swabs, throat swabs and sputum from patients with influenza-like illness (ILI) for 548 episodes of ILI/4,885 participants from 25 villages in Vientiane during 2015 and 2016. Quantitative polymerase chain reaction (qPCR) and bacteriological culture were performed from samples for these 548 ILI episodes. *S. pneumoniae* was the most common organism detected at 93/548 (17%). The clinical significance is unclear as *S. pneumoniae* is commonly found colonising the upper respiratory tract. Of 47 *S. pneumoniae* isolates with AST results, all were fully susceptible to ofloxacin but 72%

of them were resistant to tetracycline. *S. pneumoniae* penicillin susceptibility data were not given (44).

8. *Acinetobacter baumannii*

Infections with *Acinetobacter baumannii* are typically nosocomial although community-acquired *Acinetobacter* pneumonia is well-described in a few geographical areas (67). From 2000 to 2016 there were 120 *A. baumannii* isolates grown from blood cultures from the Microbiology Laboratory, Mahosot Hospital; the first imipenem resistant *A. baumannii* isolated from blood culture was identified in 2009. There were a further four (3%) imipenem resistant *A. baumannii* isolates from blood up to the end of 2016. During the same period, 15/79 (19%) were resistant to gentamicin, 14/70 (20%) resistant to ceftazidime, 13/69 (19%) resistant to ciprofloxacin and 17/79 (22%) resistant to trimethoprim-sulfamethoxazole (23).

A. baumannii is an important cause of ventilator-associated pneumonia; however, the significance of this bacterium as a pathogen when cultured from respiratory samples is often unclear, with the possibility of isolates colonising the respiratory tract or ventilator. During 2018, 57 specimens from endotracheal tubes of intensive care unit (ICU) patients were submitted to the Microbiology Laboratory at Mahosot Hospital for bacterial culture. Of these, *Acinetobacter* spp. was found in 29 (51%) patients and one (2%) was *A. baumannii*. Of all isolated *Acinetobacter*, 17 (57%) were categorised as being of uncertain clinical significance and 13 (43%) isolates were available for AST. Of these 13, 6/13 (46%) were resistant to gentamicin, 5/13 (38%) resistant to ceftazidime, 3/13 (23%) resistant to ciprofloxacin and 6/13 (46%) resistant to trimethoprim-sulfamethoxazole. Only six were tested for meropenem susceptibility and 3/6 (50%) were resistant (24).

In 2017, 22 carbapenem-resistant *A. baumannii* isolates from all specimens from the same hospital were described. Of these, 18 (82%) were susceptible to amikacin but all were resistant to ceftazidime, ciprofloxacin and tetracycline (24, 34, 68).

9. *Mycobacterium tuberculosis*

In 2010, Iem *et al.* (2013), conducted the first multi-centre study of resistance in *Mycobacterium tuberculosis* in Laos in a cross-sectional study in Mahosot Hospital (Vientiane) and two provincial hospitals (Khammuane and Luang Prabang). *M. tuberculosis* was confirmed in 87 (84%) of 104 sputum samples that were culture positive on Löwenstein-Jensen medium, with the other 17 (12%) being non-tuberculous mycobacteria. Eight of 87 (9.2%) isolates of *M. tuberculosis* were resistant to one or more anti-tuberculous agents, of which seven were mono-resistant to isoniazid (INH) and one was MDR (defined as resistant to both INH and rifampicin (RIF), and was subsequently found to be extensively drug resistant (XDR) TB (defined as MDR and resistant to fluoroquinolones and injectable antituberculous drugs i.e., amikacin, kanamycin and/or capreomycin). The frequency of resistant TB did not significantly differ between the three sites (69). Genetic characterisation of these *M. tuberculosis* isolates from this national survey (July-2010 to December-2011) was conducted for 202 *M. tuberculosis* isolates; the East African-Indian (EAI) was the most common identified in all provinces, except Xiengkhuang. Beijing strains were found mostly in the north and centre (70).

During 2016 and 2017, 1,006 sputum samples were submitted to 42 TB laboratories throughout the country as a part of the Lao National anti-tuberculosis drug resistance survey; 946 (94%) were GeneXpert MTB/RIF positive (897 (95%) new cases and 49 (5%) previously treated cases). Of these, 820 (87%) samples were

available for AST. Resistance to first line drug treatment was found in 70 (8.5%). Of these 70, 40 (57%) were resistant to INH. Five (0.6% of 820 cases) were multi-drug resistant. No second line TB drug (kanamycin, capreomycin and ofloxacin) resistance was reported (71).

AMR of other bacteria of local and regional importance

Diverse infectious diseases are common in Laos, including melioidosis, rickettsial disease and leptospirosis, but in terms of AMR, there are very limited data available (Appendix 2).

1. Burkholderia pseudomallei

Burkholderia pseudomallei is a Gram-negative bacterium found mostly in the soil and the cause of melioidosis. Melioidosis was first diagnosed in Laos in 1999 from a patient at Mahosot Hospital, Vientiane (72). Melioidosis is becoming a leading cause of bacteraemia in Mahosot Hospital (35, 73). Between 1999 and 2017 the Microbiology Laboratory/LOMWRU, Mahosot Hospital, diagnosed 1,359 patients with melioidosis for the whole country (73). Acquired resistance is not a major problem in *Burkholderia pseudomallei*, although it is intrinsically resistant to many antimicrobials. Treatment usually relies on ceftazidime or meropenem in the acute phase followed by trimethoprim-sulfamethoxazole. Only 5/620 (0.8%) Lao isolates were resistant to trimethoprim-sulfamethoxazole between 2003 and 2012 (74). *Burkholderia pseudomallei* resistant to ceftazidime was first reported in 2017 from a culture of throat swab submitted to the Microbiology Laboratory, Mahosot Hospital (24).

2. *Orientia tsutsugamushi*

Scrub typhus is a rickettsial disease caused by the Gram-negative intracellular bacterium, *O. tsutsugamushi* and is well described in Laos as a cause of fever in patients with negative blood culture and as a cause of central nervous system infections (33, 75, 76). Although, fluoroquinolones have been used in some countries, Tantibhedhyangkul et al. (2010) described ciprofloxacin and ofloxacin resistance *in vitro* in *O. tsutsugamushi* isolates from Laos, probably representing innate resistance. This suggests that fluoroquinolones should not be used to treat scrub typhus (77). There have been no reports of *O. tsutsugamushi* resistance to doxycycline in Laos. Watt et al. (1996) demonstrated laboratory and clinical evidence of doxycycline and chloramphenicol resistance in scrub typhus infected mice which was the first evidence of natural occurring antimicrobial resistance in *O. tsutsugamushi* (78).

Recently, Phuklia et al. (2019) reported *in vitro* AST data to investigate the antimicrobial susceptibility of *O. tsutsugamushi*. The team performed AST against doxycycline, azithromycin, chloramphenicol and ofloxacin in seven laboratory strains of *O. tsutsugamushi* (from Thailand, Myanmar, Japan and New Guinea) and 51 *O. tsutsugamushi* clinical isolates from Laos (n=45) and Thailand, (n=six). No resistance to doxycycline, azithromycin and chloramphenicol was detected, but ofloxacin-resistance was confirmed (79). These data call into question the occurrence of *O. tsutsugamushi* doxycycline and chloramphenicol resistance. The results of a clinical trial of seven days' doxycycline versus three days' doxycycline versus three days' azithromycin in uncomplicated scrub typhus in Vientiane are currently being analysed.

3. *Leptospira* spp.

The antimicrobial susceptibility of *Leptospira* spp. was first studied in Laos by Boss et al. (2019). Eighty-three *Leptospira* spp. isolates cultured, between 2006 and 2016, from patient samples submitted to the Microbiology Laboratory, Mahosot Hospital, were tested against six antimicrobial agents (azithromycin, ceftriaxone, ciprofloxacin, doxycycline, gentamicin and penicillin G) by a novel disk diffusion method. As there are no published susceptibility interpretation guidelines for *Leptospira* spp., the authors only reported the zone of inhibition produced by *Leptospira* spp. isolates. Azithromycin had the highest median zone diameter (85 mm) followed by ciprofloxacin, penicillin G, ceftriaxone, doxycycline and gentamicin at 70, 70, 69, 56 and 35 mm, respectively. The large zone sizes likely reflect a high level of antimicrobial susceptibility suggesting that drug resistance to these six antimicrobials has not yet occurred in Lao *Leptospira* spp. (80). However, this method has not been validated yet.

4. *Vibrio cholerae*

Antimicrobial susceptibility of Lao *V. cholerae* was first described in 1995 with strains fully susceptible to all tested antimicrobials (ampicillin, tetracycline, erythromycin, ofloxacin and polymyxin) (81). Iwanaga et al. (2000) described 99 *Vibrio cholerae* isolates from an outbreak in Laos in 1998; 95/99 (96%) were resistant to tetracycline (82). Phantouamath et al. (2001) reported broader *V. cholerae* O1 antimicrobial susceptibility data from Laos (1993-1999); 209 *V. cholerae* O1 isolates were tested for susceptibility to ampicillin, erythromycin, ofloxacin, nalidixic acid, chloramphenicol, tetracycline, sulfamethoxazole-trimethoprim and polymyxin B. Over these 7 years, the overall susceptibility patterns for ampicillin, erythromycin, ofloxacin and nalidixic acid changed little. Isolates were

highly resistant to sulfamethoxazole-trimethoprim and moderately resistant to tetracycline in 1998 (83).

V. cholerae resistance genes in isolates from outbreaks in 1993 and 2000 were studied by Iwanaga et al. 2004: 24/26 (92%) isolates before 1997 carried a class I integron harbouring the *aadA1* gene cassette and were resistant to streptomycin. Twenty-four isolates carried an SXT (sulfamethoxazole-trimethoprim) constin (a conjugative, self-transmissible integrating element) and 20 of them were resistant to chloramphenicol, tetracycline, streptomycin, and trimethoprim-sulfamethoxazole, while four were susceptible to all the antimicrobials tested (84).

5. *Streptococcus pyogenes* (Group A *Streptococcus*)

Streptococcus pyogenes is a Gram-positive organism which causes a range of infections including pharyngitis, scarlet fever, rheumatic fever, cellulitis and necrotising fasciitis. Rattanavong et al. (2016) described 124 GAS isolates cultured between 2004 and 2013 from the Microbiology Laboratory, Mahosot Hospital. As is found globally, all isolates were fully susceptible to penicillin. Antimicrobial resistant GAS frequency was low with 7% resistant to chloramphenicol, 8% resistant to erythromycin and <1% resistant to ofloxacin. Of those isolates resistant to erythromycin, 70% were also resistant to chloramphenicol (85). Anderson et al. (2014) also described two infant GAS bacteraemias between 2000 and 2011 but no antimicrobial susceptibility data were reported (45).

6. *Neisseria meningitidis*

Neisseria meningitidis is a Gram-negative diplococcus causing bacterial meningitis. Chloramphenicol-resistant *N. meningitidis* has been detected at Mahosot Hospital (35). Over 11 years in three laboratories in Southeast Asia (Thailand, Laos and Cambodia), 8/23 (44%) of *N. meningitidis* isolated from blood or CSF were resistant to chloramphenicol, 11/23 (48%) had reduced susceptibility to penicillin, whilst all were susceptible to ceftriaxone (86).

7. *Helicobacter pylori*

Helicobacter pylori is common in Southeast Asia (SEA). *H. pylori* was first described in Laos by Rasachak et al. (2000) with this pathogen detected in 68% of endoscopic biopsy specimens of 171 patients during 1996 and 1997 in Mahosot Hospital using the CLO (Campylobacter-Like Organism) test (87). Standard triple therapy (proton pump inhibitor (PPI), amoxicillin and clarithromycin) remains the first line *H. pylori* infection eradication therapy in Laos. Antimicrobial resistant *H. pylori* was reported in Laos in 2016 by Vanarath et al. (2016). During 2010 and 2012, 119 dyspeptic patients with *H. pylori* infection were tested for clarithromycin and fluoroquinolone resistance using a GenoType®HelicoDR test. Of 119 *H. pylori* strains, 15 (12.6%) were resistant to clarithromycin and 16/119 (13%) resistant to fluoroquinolones (88).

8. *Clostridioides difficile*

Clostridioides difficile is a spore-forming, toxin-producing Gram-positive anaerobe. Infection is typically healthcare associated and follows prior antimicrobial therapy. It presents as diarrhoea but may cause life-threatening pseudomembranous colitis. It is usually treated with oral metronidazole or oral vancomycin. *C. difficile* was first described in Laos in 2017 by Cheong et al. (2017). Of all stool specimens submitted

to the Microbiology Laboratory, Mahosot Hospital, during September and October 2013, five (7%) of 70 samples grew *C. difficile*. All isolates were susceptible to moxifloxacin, metronidazole and vancomycin, whereas 4/5 (80%) were intermediately susceptible to clindamycin and 1/5 (20%) was resistant (89).

2. Evidence of antimicrobial resistance in animals

Even though data on antibiotic use in domestic animals in Laos is very limited, some studies have shown that the percentage of antibiotic-resistant *Salmonella* spp. in pork/pig carcasses at slaughterhouses and retail markets, in central and southern Laos, ranged from 39%-93% (Appendix 3) (90-93).

2.1. *Salmonella* spp.

In 2008, a high percentage of pigs, 37/47 (76%), carried *Salmonella* spp. at a slaughterhouse in Vientiane. Of these 37 *Salmonella* spp. isolates, 2% were resistant to nalidixic acid and 12% were MDR (defined as resistant to three or more of ampicillin, tetracycline, chloramphenicol, streptomycin and trimethoprim-sulfamethoxazole) (90). Boonmar et al., (2013) described *Salmonella* spp. contamination in 4/17 (82%), 25/27 (93%) and 4/5 (80%) of beef, pork and buffalo meat samples, respectively, in retail markets in Pakse District, Champasak. All available isolates (60/80-75%) were susceptible to ciprofloxacin and norfloxacin, cefotaxime (94-100%) and nalidixic acid (86-100%) but many were resistant to ampicillin (60-70%), tetracycline (60-75%) and streptomycin (57-80%) (91).

A larger study in Savannakhet and Vientiane City found *Salmonella* spp. in 72% (81/112) pork meat samples in fresh markets, 53% (73/137) pig carcasses and 39% (50/129) rectal swabs of pig carcasses. Of 237 *Salmonella* spp. isolates from 378 specimens, 10% (24/237) were resistant to nalidixic acid (92). A study in

Champasak showed a smaller proportion of *Salmonella* spp. contamination at 7% (16/225) of buffalo carcasses and 5% (2/44) of cattle carcasses but AST was not performed (94).

Sunn (2018) conducted his PhD (Doctor of Philosophy) project to determine the characteristics of ESBL-producing *Salmonella* spp. and *E. coli* isolated from pigs and their meat products in Thailand, Laos, Cambodia and Myanmar (93); 86 *Salmonella* spp. isolates from 140 pig rectal swabs and pork carcasses from Laos were tested for antimicrobial susceptibility. Of 86 isolates, one (1%) was resistant to colistin, two (2%) to ceftazidime, two (2%) to cefotaxime and two (2%) to cefpodoxime (his thesis did not state whether these two resistant isolates were the same isolates and both were resistant to all three cephalosporins). Of these two cefpodoxime resistant isolates, one isolate was confirmed as ESBL producing (93).

2.2. Escherichia coli

E. coli antibiotic resistance patterns were also described in two research projects, one by a Master's student from Chulalongkorn University and one in a Lao infectious diseases fellowship project. Chang (2016) collected 252 swabs from healthy domestic animals (chickens, dogs, cats, cows, goats, pigs and horses) from a remote rural village in Xiengkhuang Province (430km Northeast from Vientiane City); 21/252 (8%) grew ESBL-producing *E. coli*. Of these 21, one animal sample grew *E. coli* and *K. pneumoniae* that were both ESBL producing. Among 21 ESBL-producing *E. coli*, all were fully susceptible to amoxicillin-clavulanic acid, meropenem and amikacin, with a spectrum of resistance to gentamicin (48%), tetracycline (67%), ciprofloxacin (43%), chloramphenicol (14%) and trimethoprim-sulfamethoxazole (43%). These domestic animals were mostly born in the village

and were fed with local products (38).

In 2012, stools from 190 healthy humans, 44 goats and 18 pigs were collected from rural Laos. Of these, six colistin-resistant *E. coli* were isolated from humans and four from pigs; all of them belonged to novel STs. All ten colistin-resistant *E. coli* isolates contained the *mcr-1* gene. Olaitan et al. (2015) suggested pathogen horizontal transmission from pig to human; a boy carried colistin-resistant *E. coli* with the same novel ST as his family's pig and the boy had had no exposure to colistin but fed the pig with no personal protection (95). Colistin is available in Laos in the form of water-soluble powder (Spira-Tylocol) for infectious disease treatment and prevention in livestock. However, there are no records on the frequency of use of this medication in Laos. Sunn (2018) described *E. coli* contamination of pig and pork carcasses in Vientiane City. Of 140 swabs collected, 133 (95%) grew *E. coli* and resistance to colistin was found in 38 (28%), to ceftazidime in four (3%), to cefotaxime in nine (7%) and ESBL-producing *E. coli* were found in six (4%) (93).

2.3. Other pathogens

Boonmar et al. detected *Campylobacter* spp. in 3/184 (1.6%) of faecal samples from cattle and 1/100 (1%) in buffalo bile but no antimicrobial susceptibility data were reported (96). Thu et al. (2019) described *Enterococcus faecalis* and *Enterococcus faecium* antimicrobial resistance molecular characteristics from livestock samples on the Thai-Lao border during 2013 and 2014. They demonstrated that 171/232 (74%) specimens contained *E. faecalis* (30 isolates) and *E. faecium* (143 isolates) from rectal swabs of pigs, swabs of pork carcasses and meat swabs, being sold by pork retailers in Savannakhet Province and Vientiane City. Of 30 *E. faecalis* isolates, 28 (93%) were resistant to tetracycline, 28 (93%) to streptomycin, 26 (87%)

to erythromycin (clinical breakpoint: 8μg/mL), 19 (63%) to gentamicin, and 13 (43%) to chloramphenicol but all were susceptible to ampicillin and vancomycin. In contrast, antibiotic resistance patterns of *E. faecium* were less striking with 79/143 (55%) resistant to tetracycline, 61/143 (43%) to erythromycin, 34/143 (24%) to streptomycin and only 13/143 (9 %) to ampicillin, 11/143 (8%) to chloramphenicol, 1/143 (1%) to gentamicin and no vancomycin resistance was detected (97).

3. Antimicrobial Use in Laos

This section includes the accessibility and quality of antimicrobials for use in human health, followed by AMU in human and then AMU in animals (Appendix 4).

3.1. Accessibility and quality of antimicrobials for use in human health

3.1.1. Accessibility of antimicrobials

The number of private pharmacies in Laos dramatically increased from ~300 in 1988 to 1,800 in 1996 (98). In 2004, there were 1,896 private pharmacies and this has increased slightly year on year. By 2013, there were 2,093 pharmacies in Laos (99), which are subdivided into three classes; Class one pharmacies are large, can act as wholesalers and are staffed by licensed pharmacists, Class two pharmacies are smaller, can still act as wholesalers and have at least a licensed assistant pharmacist staff member; and Class three pharmacies are small, and their owner is neither a licensed pharmacist nor a licensed assistant pharmacist but rents a pharmacy license from a pharmacist [FDD unpublished data]. The majority of private pharmacies in Laos are Class three and the FDD, MoH wishes to reduce the number of these pharmacies [FDD unpublished data]. Between 2003 and 2013, Class three pharmacies reduced from 1,805/2,014 (89.6%) to 1,055/2,093 (50.4%) (99).

In 2016, there were approximately 86 private drug and medical equipment companies and 13 pharmaceutical factories in Laos. The government part-owns two of these factories, along with their three branches (99). The Lao Food and Drug Department (FDD) is responsible for drug registration, licensing of pharmacies/drug companies/drug industries, and oversees their distribution, import, drug quality control, domestic manufacture and also monitors the supply chain. A list of registered antimicrobials in Laos is available on the Lao Ministry of Health official website (http://www.fdd.gov.la/index.php).The main sources of packaged antibiotics are neighbouring countries such as Thailand and China (99).

3.1.2. Quality of antimicrobials

There are more data on the quality of antimalarial medicines in Laos compared to other antimicrobial agents (100, 101). Although there are few recent data, the majority of doctors, drug sellers and customers in Laos seem unaware of the potential risks of poor-quality medicines. Lack of knowledge and information on medicine use have been described as common in Laos, especially in more remote areas (102-105).

Between 1997 and 1999, the quality of ampicillin, tetracycline, chloroquine and aspirin were tested in 366 private pharmacies in Savannakhet Province. The proportion of substandard medicines decreased from 169/366 (46%) to 66/300 (22%) between 1997 and 1999. In 1999, of 240 antibiotics, 33 (14%) were of unknown origin, whilst the majority of them came from Laos 94/240 (39%), Thailand 89/240 (37%), Vietnam 23/240 (10%) and France 1/240 (0.4%). The proportion of substandard antibiotics decreased during this period of time, including ampicillin from 66/98 (67%) to 7/77 (9%) and tetracycline from 38/100 (38%) to 10/81 (12%).

However, the fact that 9-12% of ampicillin and tetracycline were poor quality remains unacceptable. In addition, in the 1999 survey 10/98 (10%) of pills sold as ampicillin contained no detectable ampicillin, and hence were probably falsified (106).

In 2015 ~56% and ~39% of people living in rural and urban areas of Vientiane, respectively, had not heard about the issue of poor-quality medicines (105). More than one third of doctors from 25 selected public hospitals in four provinces in Laos thought that the antibiotics available in their hospitals were of poor quality. On the other hand, for consumers the cost of medications was of greater concern than their quality (103, 104). A large random survey of the quality of antibiotics in five southern provinces of Laos, conducted in 2012, did not demonstrate any falsified antibiotics but there was a high frequency of substandard antibiotics (107).

3.2. Antimicrobial use in humans

3.2.1. Antimicrobial use in healthcare facilities

A large survey of use of medicines in Laos in 2004 showed that nearly half (47%) of Lao outpatients visiting 30 health facilities investigated throughout the entire country were prescribed antibiotics for mild diseases such as simple diarrhoea or common colds (108). In addition, a quarter of outpatients were given prescriptions using non-generic names of antibiotics. Nearly 70% of Lao doctors prescribed antibiotics at least once daily and stated that they had not received much information on appropriate antibiotic use during their careers. The doctors stated that they mainly prescribed antibiotics according to the National Standard Treatment Guidelines, advice from their peers, more experienced colleagues, pharmaceutical companies or the Internet. Doctors indicated a preference for local antibiotic

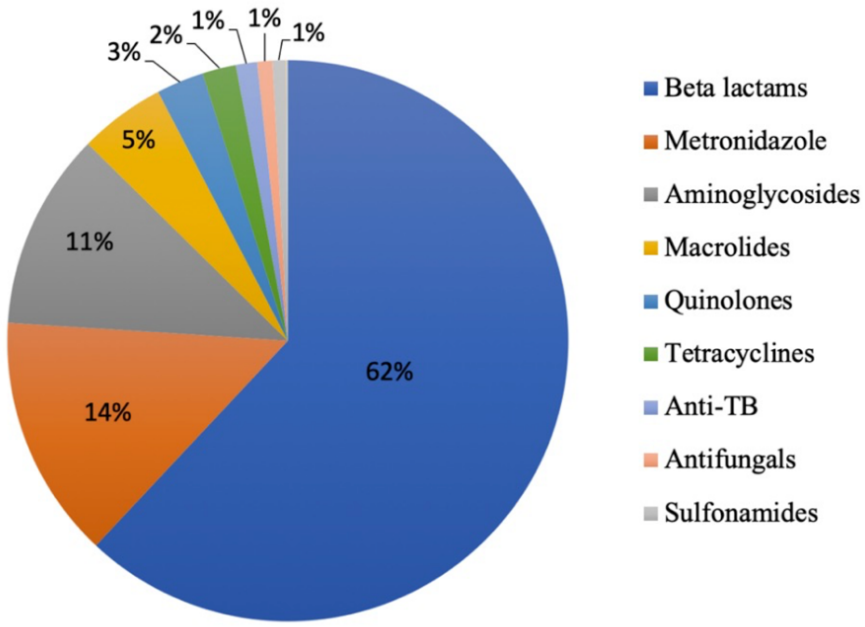
guidelines written in Lao language to international ones in other languages (104). In addition, Keohavong et al. (2019) interviewed 54 healthcare providers in health facilities in southern Laos, finding that 98% prescribed antibiotics based on patients' symptoms. The majority of them (90.7%) had heard about antimicrobial resistance but only 44.4% had heard about World Antibiotic Awareness Week and only 46.3% had ever been trained in the rational use of drugs (109). In Laos, antibiotics can be easily accessed without prescription from physicians. Mayxay et al. described the prescription of antibiotics for inpatients and outpatients in Luang Namtha Provincial Hospital (north of Laos) between 2008 and 2010; 560/1,095 (51%) patients received antibiotics but only 39/560 (7%) of these received antibiotics considered appropriate to their condition. Amoxicillin and doxycycline were the most frequently prescribed agents (33).

The first hospital antibiotic use survey in Laos was conducted in 2017 according to the Global Point Prevalence Survey system (http://www.global-pps.com) and was organised by the Microbiology Laboratory/LOMWRU at Mahosot Hospital. During 2017 and 2018, five general hospitals (Mahosot Hospital and Xiengkhuang, Luang Namtha, Vientiane and Salavan Provincial Hospitals) across Laos participated in this survey. Of 1,981 hospital charts screened during these two years, 1,386 (70%) patients received antimicrobial(s); the proportion of antimicrobial prescription was higher in provincial hospitals than in central hospitals at 72% *versus* 66% (p=0.003). Of 1,386 patients prescribed antimicrobial(s), 596 (43%) were prescribed more than one antimicrobial. Of all prescriptions, 2,011/2,052 (98%) were empiric and 882/2,052 (43%) were prescribed for either medical or surgical prophylaxis. Beta lactams accounted for 1,272/2,052 (62%) (67% were cephalosporins, 30% penicillins, 2% beta-lactam/beta lactamase inhibitors and 1% carbapenems),

followed by metronidazole 287/2,052 (14%) and aminoglycosides 226/2,052 (11%) (Figure 7 and 8) (110). This was higher than the proportion (47%) mentioned in 2006 by Keohavong et al. (108).

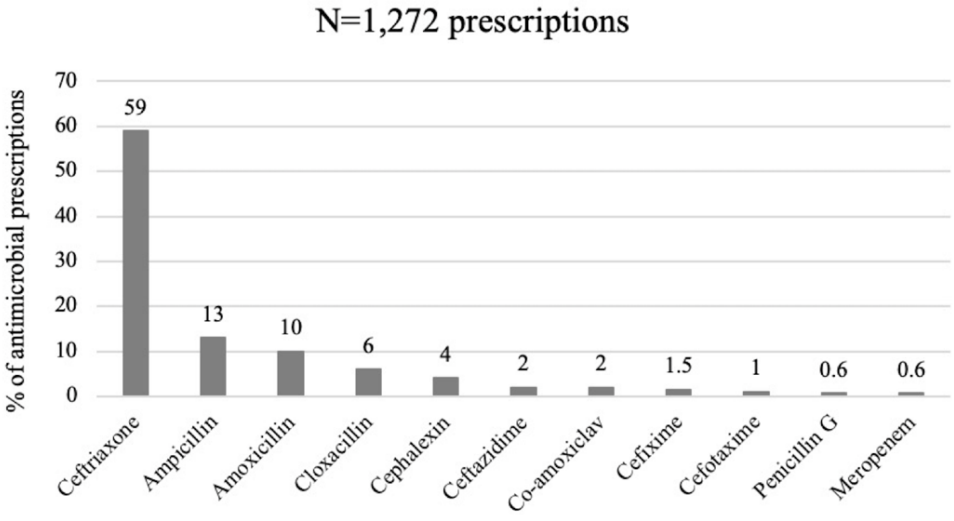
In 2019, Keohavong and colleagues also described the use of antibiotics in the treatment of common colds or upper respiratory infections in the provincial and district hospitals of Savannakhet Province. Of 154 outpatients at Savannakhet Provincial Hospital, 106 (61%) received antibiotics; whilst 299/422 (71%) outpatients from district hospitals received antibiotics. Of 405 patients given antibiotics, 395 (97.5%) received first line antibiotics (amoxicillin, ampicillin, erythromycin and penicillin V) based on Lao National Standard Treatment Guidelines. However, few of them used correct doses and durations as described in these guidelines. Of patients receiving antibiotics, 397/413 (94.4%) were prescribed for upper respiratory infection and 8/164 (4.9%) were for the common cold (109).

Figure 7: Overall hospital antimicrobial prescriptions in six general hospitals in Laos from 2017 to 2018



Note: Six general hospitals=Mahosot Hospital, Xiengkhuang, Luang Namtha, Vientiane and Salavan Provincial Hospitals

Figure 8: Commonly prescribed beta lactams in six general hospitals in Laos from 2017 to 2018



Note: Six general hospitals=Mahosot Hospital, Xiengkhuang, Luang Namtha, Vientiane and Salavan Provincial Hospitals

3.2.2. Antimicrobial use in humans in the community

A study of antimicrobial self-medication for reproductive tract infections in Vientiane and Champasak Province (southern Laos), showed that the main source (~58%) of advice on antibiotic use was from pharmacy staff. Approximately 18% chose their antibiotics by following a previous doctor's prescription. Family/relatives or friends (~13%) were also key information sources first consulted by an ill person for their choice of antibiotics. Only 9% of patients knew the correct dose of treatment and the majority used the wrong duration of treatment (111).

Phonlavong and Kitikannakorn (2018) conducted a self-administered questionnaire survey among 384 individuals from 3 districts of Vientiane City in 2017, showing that the majority of survey participants (326/384 (85%)) self-medicated by purchasing antibiotics from pharmacies. Moreover, 69/384 (18%) purchased antibiotics from grocery shops. 164/384 (42.7%) claimed they complete a prescribed course of antibiotic treatment and 247/384 (64.3%) had never kept leftover antibiotics for their future use. 199/384 (51.8%) were aware that self-medication was potentially harmful (112). The use of antibiotics prior to hospital consultation was significantly higher in children (60%) than in adults (47%) ($p<0.0001$) (113).

Before medical consultation, patients with fever tended to use more antibiotics than those without fever (42% and 20% ($p<0.001$), respectively) (113). 39% of 796 participants in a large survey on healthcare-seeking behaviour in Salavan Province between 2017 and 2018 stated that they used an antibiotic during their previous illness and 22% claimed that they used antibiotics without indication or from informal sources(114). Similar research described that ampicillin was mentioned the most

when asking about antibiotics with 76% of 775 respondents. The common purpose (44%) of using an antibiotic was to heal skin wounds (115). Ampicillin, amoxicillin, penicillin and tetracycline were frequently chosen for self-medication before deciding to go to hospital (53, 111, 113). Khennavong et al. (2011) presented results of a prospective study of urinary antibiotic activity in 1,153 patients in Vientiane. There was surprisingly little concordance between antibiotic activity in urine (36%) and whether patients stated that they had taken antibiotics during the previous 48 hours (24%). Evidence of antibiotics in urine was more frequently found in patients with suspected central nervous system infections or suspected septicaemia than suspected typhus patients (57% and 37% ($p>0.0001$), respectively) (113).

3.3. Antimicrobial use in animals

The use of antibiotics in Lao agriculture is thought to be common but is not adequately supervised and there are few available data (40, 41, 116). The purposes of antibiotic use in livestock are to prevent and treat livestock infections and to increase productivity, as growth promoters (41). No antimicrobial agents for animals have been registered with the Department of Livestock and Fisheries (DLF) in Laos. However, some antibiotics and vaccines are available at the DLF pharmacy and at private animal clinics [DLF, unpublished data]. Information and advice regarding the appropriate use of antibiotics in Lao agriculture is frequently requested by farmers (117). However, there are no technical guidelines for antibiotic use in animals in Laos and no available data on their use for different domestic animals in different farming systems.

A search of 826 available student theses at the Department of Veterinary Medicine and Department of Livestock and Fisheries, University of Agriculture, Vientiane, Laos completed between 2002 and 2017, found no thesis focusing on bacterial

antibiotic susceptibility in the animal sector nor antimicrobial use in agriculture in Laos. Four theses focused on antibiotic use in pet dogs, finding use of cephalexin, amoxicillin, clavulanate, oxytetracycline, sulphonamides, enrofloxacin and gentamicin (118-121). Labatut and Suter (2010) also described the use of antibiotics in domestic elephants in Xayabury Province, Laos for treatment of, for example, abscesses, superficial wounds and eye problems. Oxyblue spray or penicillin-streptomycin were commonly used for abscesses and enrofloxacin for urinary tract infection. As the country lacks provincial veterinary diagnostic laboratories, most infectious diseases treatment in animals is empirical (122).

Poupaud et al. (2021) published findings of a study of the antibiotic supply chain in the animal sector in Laos; the research team showed that the owners of 49% of 96 chicken farms and 60% of 96 pig farms stated that they used antibiotics on their farms. Tetracycline was the most commonly used antibiotic, used in 10/29 (34%) chicken farms. On the other hand, amoxicillin (17/73 (23%)) was the most given in pig farms (40).

4. Antimicrobial resistant pathogens in the environment

There is very little information on contamination with drug-resistant micro-organisms in the Lao environment. In 2003, NCLE investigated drug-resistant *V. cholerae* from surface water samples from 13 branches of the Mekong River in cholera-epidemic areas in Laos after the outbreak in 2000. Twenty-two non-O1 and non-O139 *V. cholerae* isolates were tested against polymyxin B, tetracycline, ampicillin, amoxicillin-clavulanic acid, erythromycin, nalidixic acid, chloramphenicol, trimethoprim-sulfamethoxazole and streptomycin. Polymyxin B resistance was found in 2/22 (9%) and ampicillin-resistance in 15/22 (68%) of isolates but the *V. cholerae* were susceptible to other tested antibiotics (123).

Discussion

Data on antimicrobial use and resistance in Laos are scattered and limited to some geographical areas of Laos. The majority of publications on antimicrobial susceptibility are from one laboratory at Mahosot Hospital. Even though the number of publications on infectious diseases in Laos has been increasing since 2000 (124), there are few articles that specifically describe the situation regarding antimicrobial use or resistance in Laos and nearly all the publications are in English. This review gathered data on antimicrobial resistance and use in humans, animals and the environment in Laos between 1994 and 2020. Fifteen percent of the data on antimicrobial susceptibility or antimicrobial use in this review are unpublished and are mostly not yet publicly available. In addition, most peer-reviewed data sources were descriptive studies. Some peer-reviewed data sources had overlapping study periods.

Antimicrobial resistance awareness in Laos

Until 2020, there was little evidence of antimicrobial resistance awareness in Laos (104, 105, 108). A large multi-centre study of public awareness of antibiotic resistance across 12 WHO member states (two from each region, not including Laos) around the world showed that the level of knowledge and awareness around appropriate antibiotic use varies from country to country (17). Many participants (32-62%) thought that they should stop taking antibiotics when they felt better. Nearly half (43%) thought that they could buy the same antibiotics again if they had made them feel better during a previous illness and 44% believed that antibiotic resistance is only a problem in people who take antibiotics regularly (17).

Antimicrobial misuse in animal husbandry is thought to be one of the most important

drivers of antimicrobial resistance. However, in this review, apart from four veterinary student theses on antibiotic use in dogs, and one publication on antimicrobial use in elephants, we could not find any other data on antibiotic use in animal husbandry during this review period in Laos. There is an urgent need in Laos to collect and analyse data on antibiotic use, consumption and resistance in humans, animals and the environment. Between 2010 and 2030, total antimicrobial use in food animals globally is expected to increase to 67% (https://cddep.org/publications/_global_trends_antimicrobial_use__food_animals/), so it is likely that the amount of antibiotics used in Laos, where a large percentage of GDP comes from agriculture, will be high. Work to improve our understanding of the use and impact of antibiotics in the Lao context is urgently needed. In addition, further qualitative studies on antibiotic awareness would help policy makers to clearly understand the issues. They could then apply appropriate public education or other interventions to be able to influence behaviour.

Antimicrobial resistance data compared to adjacent countries

Laos started to participate in GLASS in 2018. Data on antibiotic resistance amongst the priority pathogens for GLASS are not well documented in Laos compared to neighbouring countries. There are sporadic published articles on GLASS pathogens but most publications investigated causes of fever rather than specific pathogens and their susceptibility patterns. Laos does, however, have some antibiotic resistance data for all GLASS priority pathogens.

The main concern is an increase in ESBL-producing *E. coli*. The frequency of ESBL-producing *E. coli* from clinical samples increased five times between 2004 and 2016 (23). This shows a similar trend to community-acquired ESBL *E. coli* bacteraemia in Northeast Thailand during 2004 and 2010 with a ~fivefold increase (5%-23%),

38% of which were also MDR. However, the proportion of MDR *E. coli* in hospital-acquired bacteraemia (63%) was much higher than in community-acquired bacteraemia (125). In Lao data, data on hospital-acquired bacteraemia have not been well described, further research focused on this area is crucial. In this review, there is evidence that carbapenems are still highly active against ESBL-producing *E. coli* and ESBL-producing *K. pneumoniae* in Laos with only ten cases of carbapenem resistant *E. coli* detected in all types of clinical specimen and six cases in *K. pneumoniae*. Recent data from Vietnam reporting antimicrobial resistance data in 13 hospitals across the country, showed 961/8,830 (11%) of *E. coli* from all specimens from 2016 to 2017 were resistant to imipenem (126). There is evidence of emergence of colistin-resistant *K. pneumoniae* in Laos. It would be of great concern if combined carbapenem and colistin-resistance were to emerge (colistin is not currently available in Laos for human use) as this would lead to infections that are untreatable in Laos (Table 2 and 3).

Carriage of ESBL-producing Enterobacterales is well described in Laos, with data showing higher carriage in Savannakhet Province than in comparable rural sites in Thailand (51%) (29, 37) and Vietnam (88% in 199 healthy individuals in Bavi district, Hanoi) (127). The high proportion of ESBL-producing Enterobacterales in both hospital patients and healthy individuals in the community reveals that Laos needs urgent strategies to control their spread.

Table 2: *E. coli* antimicrobial resistance data compared to adjacent countries

Antimi-crobials	Laosϕ	Vietnam** (126)		Cambodia (128)	Thailand (125)
	Blood; n=750 [2000-2016]	All specimens; n=9092 [2016-2017]	Blood & CSF; n=1535 [2016-2017]	Blood; n=130 [2007-2010]	Blood; n=4278 [2004-2010]
ESBL	135/693 (19%)*	4085/6953 (59%)	655/1107 (59%)	62 (47.7%)	-
AK	2/135 (1%)	4188/8785 (48%)	637/1471 (43%)	5 (3.8%)	130/3408 (4%)
CN	120/675 (18%)			73 (56.2%)	903/4228 (21%)
CFT	-	5441/8195 (66%)	931/1402 (66%)	67 (51.5%)	885/3892 (23%)
CAZ	69/180 (38%)			47 (36.2%)	721/3817 (19%)
C	148/579 (26%)	-	-	-	18/72 (25%)
CIP	74/231 (32%)	5813/8682 (67%)	953/1475 (65%)	85 (65.4%)	1120/3836 (29%)
AMC	94/673 (14%)	1476/3251 (45%)	180/577 (31%)	64 (49.2%)	1139/3910 (29%)
IPM	-	961/8830 (11%)	116/1483 (8%)	-	6/3179 (0.6%)
MEM	0/144 (0)			0	2/2546 (0.08%)
TMP-SMX	429/704 (61%)	5704/7843 (73%)	935/1377 (68%)	214 (95.4%)	2257/3799 (59%)

Note: ϕ LOMWRU, unpublished data, *****Duration: 2004-2016; ESBL-producing *E. coli* in 2016 only was 27/78 (35%) in blood. However, ESBL-producing *E.* coli in urine (2017-2018) was 90/169 (53%) amongst *E. coli* culture positive, ****** Antimicrobial testing data from Vu et al. 2021 (126) shown by class of antibiotic rather than antibiotic agent. **AK**= Amikacin, **CN**= Gentamicin, **CFT**=Cefotaxime, **CAZ**=Ceftazidime, **C**=Chloramphenicol, **CIP**=Ciprofloxacin, **AMC**=Co-amoxiclav, **IPM**=Imipenem, **MEM**=Meropenem, **TMP-SMX**=Trimethoprim-sulphamethoxazole.

Table 3: *K. pneumoniae* antimicrobial resistance data compared to adjacent countries

Antimi-crobials	Laosϕ	Vietnam** (126)		Cambodia (128)	Thailand (125)
	Blood; n=284 [2000-2016]	All specimen; n=3870 [2016-2017]	Blood; n=482 [2016-2017]	Blood; n=32 [2007-2010]	Blood; n=1661 [2004-2010]
ESBL	39/284 (14%)	1186/2958 (40%)	128/365 (35%)	14 (43.8%)	-
AK	0/26 (0)	1756/3780 (46%)	195/470 (41%)	0	138/1370 (10%)
CN	-			9 (28.1%)	412/1636 (25%)
CFT	-	1995/3732 (53%)	221/471 (47%)	15 (46.9%)	515/1499 (34%)
CAZ	13/44 (30%)	-	-	8 (24%)	482/1533 (31%)
C	44/217 (20%)	-	-	-	4/24 (17%)
CIP	3/47 (6%)	1593/3619 (44%)	177/459 (39%)	7 (21.9%)	396/1500 (26%)
AMC	69/272 (25%)	1080/1999 (54%)	112/285 (38%)	9 (28.1%)	490/1571 (31%)
IPM	-	1049/3816 (27)	109/476 (23%)	-	4/1350 (0.3%)
MEM	0/26 (0)	-	-	-	3/1013 (0.3%)
TMP-SMX	272	1753/3348 (52%)	215/454 (47%)	24 (75%)	486/1454 (33%)

Note: # *Klebsiella* spp., ϕ LOMWRU, unpublished data, ****** Antimicrobial testing data from Vu et al. 2021 (126) shown by class of antibiotic rather than antibiotic agent, **AK**= Amikacin, **CN**= Gentamicin, **CFT**= Cefotaxime, **CAZ**= Ceftazidime, **C**=Chloramphenicol, **CIP**= Ciprofloxacin, **AMC**= Co-amoxiclav, **IPM**= Imipenem, **MEM**= Meropenem, **TMP-SMX**= Trimethoprim- sulphamethoxazole.

Typhoid fever is well documented as a leading cause of community acquired bacteraemia in Laos (33, 46, 54). Studies conducted between 2000 and 2018 suggest that MDR and quinolone resistance are rare in *S.* Typhi: only 4.6% were resistant to quinolones and 7% were multi drug resistant (54). This contrasts with the position in neighbouring countries such as Vietnam, where 80% of *S.* Typhi are nalidixic acid resistant and Cambodia, where 90% exhibit decreased ciprofloxacin susceptibility (128, 129).

MRSA is a universal public health concern, and well documented in countries neighbouring Laos. In 2021, Vu et al. reported 3,302/4,515 (73%) of MRSA in all specimen types and 476/674 (71%) in blood and CSF from 13 hospitals in Vietnam (126). In Thailand, the proportion of MRSA bacteraemia was high among hospital-acquired bacteraemia patients (48%, n=441) and 7% (n=1,145) among community-acquired bacteraemia patients. The proportion of MRSA not susceptible to vancomycin (VRSA) was 0.4% (6/1,380) (125). MRSA bacteraemia was also common in a large bacteraemia study (n=4,833 adult patients) in Phnom Penh, Cambodia; 22% (10/46) of *S. aureus* were MRSA and all were susceptible to vancomycin (128). In contrast, in Laos only six MRSA were isolated from blood between 2000 and 2020; MRSA in non-blood specimens was higher (15%). Vancomycin resistant *S. aureus* has not been reported in Laos (Table 4).

Table 4: *S. aureus* antimicrobial resistance data compared to adjacent countries

Antimi-crobials	Laos (47)	Vietnam** (126)		Cambodia (128)	Thailand (125)
	Blood; n=200 [2000-2011]	All specimens; n=4833 [2016-2017]	Blood & CSF; n=715 [2016-2017]	Blood; n=46 [2007-2010]	Blood; n=1881 [2004-2010]
MRSA	0*ϕ	3302/4515 (73%)	476/674 (71%)	10/46 (22%)	357/389 (92%)
CIP	-	1720/4619 (37%)	297/689 (43%)	-	7/63 (11%)
ERY	70/180 (39%)	3861/4661 (83%)	545/639 (79%)	24/46 (52%)	436/1785 (24%)
CN	2/166 (1%)	1674/4090 (41%)	294/637 (46%)	-	106/719 (15%)
P	158/170 (93%)	2347/2400 (98%)	490/504 (97%)	45/46 (98%)	-
TET	39/81 (48%)	-	-	24/46 (52%)	-
TMP-SMX	16/151 (11%)	1021/4158 (25%)	233/661 (35%)	11/46 (24%)	341/1828 (19%)
VAN	0/52 (0)	45/2680 (2%)#	7/565 (1%)#	-	6/1380 (0.4%)

Note: # Resistant and Intermediate, ***** the first MRSA bacteraemia in Laos was identified in 2017. ϕ LOMWRU, unpublished data, ****** Antimicrobial testing data from Vu et al. 2021 (126) showed as a class of antibiotic rather than antibiotic agent, **CIP**= Ciprofloxacin, **ERY**= Erythromycin, **CN**= Gentamicin, **P**= Penicillin, **TET**= Tetracycline, **TMP-SMX**= Trimethoprim- sulphamethoxazole, **VAN**= Vancomycin.

N. gonorrhoeae resistant to ceftriaxone was reported in Laos in 2003 (1/131–0.8%) (61). However, continued surveillance since 2003 has not yielded any further reports of ceftriaxone or spectinomycin resistance in this species. The proportion of *N. gonorrhoeae* resistant to ciprofloxacin, penicillin and tetracycline is approximately 75-100% (62-64). A study from Thailand from 2008-2014 in a central hospital in Bangkok showed that *N. gonorrhoeae* was fully susceptible to ceftriaxone and spectinomycin (n=340) but had similar resistance patterns to Laos for ciprofloxacin, penicillin and tetracycline (130). Olsen et al. (2013) reported 5% resistance to ceftriaxone among 108 *N. gonorrhoeae* infections in Hanoi in 2011, which were all susceptible to spectinomycin (131) (Table 5).

Table 5: *N. gonorrhoeae* antimicrobial resistance data compared to adjacent countries

Antimi-crobials	Laos (64)	Vietnam (131)	Cambodia (132)	Thailand (130)
	Genital specimens; n=158 [2011-2015]	Isolates; n=108 [2011]	Isolates; n=15 [2006]	Isolates; n=370 [2008-2014]
AZ	-	12/108 (11%)	-	0/281 (0)
CFX	-	1/108 (1%)	-	0/289 (0)
CRO	0/158 (0)	5/108 (5%)	-	0/350 (0)
CIP	134/158 (85%)	106/108 (98%)	14/15 (93%)	307/349 (88%)
PG	142/158 (90%)	52/108 (48%)	11/15 (73%)	300/350 (85.7%)
SPEC	0/158 (0)	0/108 (0)	-	0/30 (0)
TET	157/158 (99%)	88/108 (82%)	-	312/350 (89%)

Note: AZ=Azithromycin, **CFX**=Cefixime, **CRO**=Ceftriaxone, **CIP**=Ciprofloxacin, **PG**=Penicillin G, **SPEC**=Spectinomycin, **TET**=Tetracycline.

Laos is surrounded by countries with a high frequency of antibiotic resistant pathogens. Lack of antibiotic susceptibility and antibiotic use data puts Laos at a disadvantage in terms of understanding and controlling antibiotic resistance. However, the Lao data suggest that key bacterial pathogens within the country generally have a lower frequency of antibacterial resistance than adjoining countries but Laos has a severe and growing problem with ESBL production in *E. coli* and *K. pneumoniae*.

Regulations related to antimicrobial use and resistance in Laos

There is no antimicrobial use regulation in both human and animal health sectors. Drug and Therapeutics Committees (DTCs) and Standard Treatment Guidelines (STGs) are essential tools to help improve the quality of treatment. DTCs have been established in all central and provincial hospitals since 1999 (133) but they are not fully functional and there is a lack of systematically collected local data to inform treatment guidelines. Lao National Standard Treatment Guidelines were first available in 1998 and the latest edition (edition 4) was released in 2012. The

guidelines cover a variety of diseases for both adults and children but do not include antimicrobial stewardship. Lao antimicrobial prescribing guidelines (both adult and paediatric) in Lao language were just released in 2020 (134, 135). These guidelines were approved by the Department of Healthcare and Rehabilitation, MoH. The guidelines focus on antimicrobial prescriptions and will support the rational use of antimicrobials by Lao doctors. However, there is some evidence that guidelines alone might not guarantee the rational use of antibiotics and engagement; training and feedback from health workers will be crucial (33, 104, 106). There are other treatment guidelines available in Laos, e.g., malaria treatment guidelines for provincial and district hospitals, Lao PDR National Guidelines for the Use of Antiretroviral Therapy in Adults and Children, National Tuberculosis control program-National technical guidelines, National Guidelines for the Treatment of Sexually Transmitted Infections (Table 9).

Data on AMU and AMR in Laos are mostly from Vientiane City. The majority (49%) of data sources on AMR and AMU were from one site, LOMWRU/ Mahosot Hospital. Though the number of publications on infectious diseases in Laos has greatly increased since 2000 (124, 136), there are few articles that specifically describe the AMU and AMR situations in Laos. Fifteen percent of the data sources on AMR and AMU in this review were not peer-reviewed. The majority of data were from epidemiological studies, cross-sectional studies and three large microbiology datasets from LOMWRU/Mahosot Hospital from 2000 to 2020.

Conclusion and suggestions

Based on the findings from this review, antimicrobial resistance in Laos seems to be lower than in adjoining countries, except for ESBL-producing *E. coli*. This may partly reflect the paucity of representative data resulting from a lack of systematic surveillance and research. Although there are not enough data to inform this objectively, Laos may have had historically lower antibiotic use due to being relatively isolated and relatively impoverished, with a lack of access to antimicrobials as a result of there being only a small accessible commercial market. This gives the country a window of opportunity to act quickly to implement strategies to protect the population from a worsening situation – prevention is better than cure. Enhanced coordinated and systematic AMU and AMR surveillance across the country is needed. Laos needs enhanced regulation of antibiotic availability, without compromising appropriate access, and strengthened antibiotic stewardship in health facilities and the community for systematic control and rationalisation of AMU, in order to prevent resistance before it spreads and becomes harder to manage. Strategies should also be put in place to control the use of colistin in livestock, as colistin is currently a last resort for treating key drug resistant pathogens. Based on this review, some suggested strategies which could be considered as priorities to combat AMR in Laos include:

- Provide accessible, evidence-based antimicrobial use and stewardship guidelines in Lao language, regularly updated based on the most up to date AMR situation in Laos
- Enforce regulations to reduce the use of third generation cephalosporins
- Enforce regulations to stop the use of colistin in the animal sector

- Strengthen the Drug and Therapeutics Committees (DTCs); and Infection Prevention and Control (IPC)
- Enforce regulations to stop over-the-counter sales of broad-spectrum antimicrobials without prescription from doctors
- Ensure the country has access to appropriate antibiotics when needed based on the current AMR situation in Laos (e.g., nitrofurantoin or vancomycin)
- Empower Lao pharmacists, in hospitals and in the community, to ensure appropriate antimicrobial use
- Extend research on antimicrobial use and resistance in humans, animals and the environment

Updated AMR and AMU data after 2020

From 2020 to April 2024, all peer-reviewed articles were re-reviewed using PubMed and Google Scholar during the review period of 18th to 20th May 2024, with similar search terms. During these three years and four months, 19 published articles (excluding review articles and four AMR articles in humans because it was unclear which data were from Laos (137-141)) relating to AMR and AMU in human, animal and the environment in Laos were available. Of these, seven were related to AMU (five in human health and two in animal health) and 12 were related to AMR (four in human health, five in animal health, two in both human and animal health and one in humans, animals and the environment) (Table 6). The proportion of available AMU data in Laos was 58% higher over the three-year period in contrast to the original review (1994-2020). In addition, only three publications addressed AMR in animal health, three in human and animal health combined and one focusing on the

environment aspects during 1994-2020. These figures were similar to available data from 2021 to April 2024.

Recent data on AMR colonisation in humans and animals have become available, with *E. coli* being a key focus in several One-Health studies. Up to 70% of healthy individuals were found to carry ESBL-producing *E. coli*, while colistin-resistant *E. coli* was detected in 15–46% of cases (142, 143). In the animal sector, *E. coli* colonisation in pigs (pork or pig carcass) and poultry was described. Colistin-resistant *E. coli* has been identified in 5–29% of pigs or pork, and in 8–23% of chickens (meat or feces) across the country (142-146). AMR in the environment in Laos is still rarely documented. Few publications have described *E. coli* contaminating the Mekong river basin, or on vegetables in the fresh markets in Laos but with no further information on their AST (147, 148). Zhou Y. et al. described *mcr*-positive- *E. coli* in the environment (wastewater) in Laos (143). With the increased availability of microbiological facilities, collecting AMR data related to the environment in Laos could become more feasible.

Table 6: Peer-reviewed articles relating to antimicrobial use and resistance in human, animal and the environment in Laos between 2021 and 2024

Author/date	AMU/ AMR	Focus	Objective	Sample size/settings	Study duration	Main findings
Sychareun V. et al. (2021) (149)	AMU	Human	To assess knowledge, attitudes and reported practice of healthcare providers (HCPs) and explore their perceptions regarding antibiotic use and antibiotic resistance relating to pregnancy, childbirth and children under two in Laos	Paper CRF from: 217 HCPs and interview: 30HCPs/ two district hospitals	2019	85% of participants were aware that AMR was a big problem in their practices. Only 36% thought that AMR could spread from animals to humans. Of HCPs, 85% said that they prescribed antibiotics during the previous week, 27% normally gave antibiotics to a child with a common cold and 67% prescribed antibiotic for normal vaginal delivery prophylaxis.
Kounnavong S. et al. (2022) (150)	AMU	Human	To assess knowledge, attitudes, and reported practice of pregnant women regarding antibiotic use and antibiotic resistance as well as their approach towards antibiotic use for their newborn babies	539 women/two districts, Vientiane Province	2019-2020	Around 23% of women believed that antibiotics worked against viral infections, 30% thought that antibiotics were antipyretic and nearly half decided by themselves when they wanted to stop antibiotics. Only 32% said that inappropriate use of antibiotic could cause problem in long-tern. The use of antibiotic was reported more frequent in children than pregnant women
Yan W. et al. (2022) (151)	AMU	Human	To investigate the antibiotic prescribing pattern to women during and after delivery in two districts in Laos	1,777 medical records/ district hospitals and health centres	2019-2020	All women from these medical records received antibiotics during their hospital admission and at discharge with oral antibiotics for extra 4-5 days. The most common use of antibiotics was ampicillin or amoxicillin, C-section and women with episiotomy received ampicillin and

						gentamicin, while uncomplicated vaginal delivery received amoxicillin.
Chansamouth V. et al. (2022) (152)	AMU	Human	To describe the patterns of hospital antimicrobial use in six general hospitals in Laos from 2017 to 2020	4,377 medical records with antimicrobial prescribed/six general hospitals	2017-2020	The prevalence of AMU in Lao hospitals was 71%. Pneumonia was the most common prescribing indication. Most frequent prescribed antibiotics were ceftriaxone (40%), Metronidazole (17%) and gentamicin (10%). The percentage of prescription adherent to the local treatment guidelines was only 26%.
Tebernero P. et al. (2022)* (153)	AMU	Human	To investigate the availability and quality of selected antimalarials and antibiotics sold to patients in the private sector in five southern Lao provinces	1,173 medicine samples/Ten districts from five southern provinces	2012	Among 1,025 active pharmaceutical ingredients (APIs) analyzed, 19.6% of antibiotics were found to be substandard, with no evidence of falsification. Trimethoprim, ceftriaxone, and sulfamethoxazole frequently fell below the standard range, while doxycycline, ofloxacin, and ciprofloxacin were often found with higher-than-acceptable API content.
Poupaud M. et al. (2021) (40)	AMU	Animal	To explore how the implementation of the new regulations might effectively reduce and adapt the sale, distribution and use of veterinary antibiotics in Lao	36 antibiotic suppliers, 96 chicken farms and 96 pig farms/Vientiane Capital and Vientiane Province	2018	23 stakeholders were identified (four international, eight public and 12 private sectors). Of 96 chicken and 96 pig farms, 49% and 60% claimed that they used antibiotics within their farms, respectively. They usually sought advice before starting antibiotics with 81% and 89%, respectively. The most commonly used antibiotics for chicken were oxytetracycline, ampicillin and amoxicillin. While amoxicillin, penamecillin-streptomycin and oxytetracycline were frequently used in pig farms

Poupaud M. et al. (2022) (154)	AMU	Animal	To explore the views and practices of commercial pig, poultry and fish farmers regarding antibiotics in Laos	454 farms (364 farmers)/ Vientiane Capital and Vientiane Province	2018	Of 454 farms, 57% admitted that antibiotics were used in their farms. Antibiotic was found to be used in fish farm (7.5%) less than pig (92%; OR: 29 (11.4-73.4; 95%CI) and poultry (86%; OR: 15 (7-31; 95%CI) farms. Of these antibiotics, 65% were in the WHO list of critically important antibiotics for humans.
Kantele A. et al. (2021) (39)	AMR	Human	To characterize the colonization dynamics using fine-scale genomic analysis of daily stool samples from volunteers	Faecal samples of 20 healthy European visitors/ Vientiane Capital	2015	ESBL-producing Gram-negative bacteria was identified in 70% of all participants by the end of the study. Of all participants, 95% were acquired two to seven strains and the colonization altered each day. The most common isolated organisms were *E. coli*, *K. pneumoniae* and other Gram-negative bacteria)
Vihta KD et al. (2021) (155)	AMR	Human	To investigate the annual prevalence of and associations between AMR in commensal opportunistic pathogens isolated from BSIs and other body-sites for multiple pathogen-drug combinations in Oxfordshire and LMICs	Data on *E. coli* and *S. aureus* BSIs and non-sterile specimens/ Oxfordshire and LMICs	2004-2017 (Oxford-shire) and 2008-2019 (LMICs)	The prevalence of resistance was similar across drug-years for each species, with 276/312 (88%) species-drug-years with prevalence within ± 10% between blood/ other isolates. These findings were consistent across various countries, regardless of their income level.
Sewunet T. et al. (2022) (156)	AMR	Human	To determine colonization rate of ESBL-E and CRE and characterize molecular features of carbapenemase-producing isolates and the plasmids carrying the	Rectal swabs of 137 hospitalised patients/intensive care units at five hospitals	2019	Of 47 Enterobacterales isolates, the most common organisms were *K. pneumoniae* which accounted for 25 isolates and 12 isolates for *E. coli*. ESBL-*E. coli* was found by 83%, while ESBL-*Klebsiella* spp. was 41%. Of 25 *K. pneumoniae* isolates, 5 (20%) isolates were carbapenem-resistant.

			gene among patients admitted to intensive care units of five selected hospitals in Laos			
Snaith et al. (2023) # (157)	AMR	Human	To investigate the diversity of mobile genetic elements involved with AMR gene carriage in ESBL-producing *E. coli* that colonized travellers to Laos	Faecal samples of 23 healthy European visitors/ Vientiane Capital	2015	105 distinct plasmids were revealed, of these, 40 (38%) carried AMR gene. These plasmids varied and not documented before. Thirty-eight replicon types of plasmids with F-type plasmids were the most common amongst those carrying AMR genes.
Lay KK. et al. (2021) (145)	AMR	Animal	To examine the prevalence and genetic characteristics of ESBL-production and colistin-resistance in *Salmonella* and *Escherichia coli* from pigs and pork in the border area among Thailand, Cambodia, Laos, and Myanmar	82 rectal swabs and 58 carcass swabs of pigs/slaughterhouse and market, Vientiane	2017-2018	*E. coli* and Salmonella spp. were found in pig rectal swabs and pork carcass by 96% *vs.* 88%, and 34% *vs.* 76%, respectively. The percentage of ESBL-producing *Salmonella* spp. was 1/86 (1.2%) and colistin resistance was also 1/86 (1.2%). The percentage of ESBL-producing *E. coli* was much higher with 6/133 (4.5%) and colistin resistance was 38/133 (29%).
Meunsene D. et al. (2021) (158)	AMR	Animal	To investigate the prevalence of *Salmonella* in meat sold at retail markets in the middle Mekong Basin area along the border of Thailand and Laos, surrounding the Thai-Lao Friendship Bridge I	235 raw meat samples (pork, chicken and beef, respectively)/five retail markets in Vientiane Capital	2019	The prevalence of *Salmonella* spp. isolated from pork, chicken and beef was 75%, 64% and 69% from five retail markets in Vientiane Capital. Of 165 antimicrobial susceptibility tested isolates, 58% were resistant to tetracycline, 35% to ampicillin and 32% to sulfamethoxazole-trimethoprim.
Pungpian C. et al. (2021) (146)	AMR	Animal	To examine the prevalence and genetics underlying the resistance	351 *E. coli* isolates and 237 S*almonella* spp. from pig rectal	2014-2018	The percentage of colistin-resistant *E. coli* was 5% (19/351) and 0.5% (1/218) in *Salmonella* spp.. The percentage of *mcr-*

			to carbapenems and colistin in *E. coli* and *Salmonella* isolated from pigs, pig carcasses, and pork in Thailand, Laos, and Cambodia border provinces	swabs and pig carcass swabs/ slaughterhouse in Vientiane and Savannakhet		carrying *E. coli* was 6%. All isolates were fully susceptible to meropenem.
Inthavong P. et al. (2022) (144)	AMR	Animal	To determine the levels of resistance to antimicrobials in *E. coli* and *Salmonella* spp. in chicken and pigs in Laos	3,638 caecal samples from healthy pigs and chicken/five provinces across Laos	2018-2021	The percentage of *E. coli* isolates was 87% (3,150/3,638) and 58% (2,098/3,638) *Salmonella* spp. The percentage of colistin resistance *E. coli* was 18% in pigs and 8% in chickens. Ciprofloxacin resistance was found 21% in pigs and 18% in chickens, no meropenem resistance was detected in chickens and <1% was found in pigs.
Xaymountry S. et al. (2022) (159)	AMR	Animal	To investigate the prevalence, seasonal variation and antimicrobial resistance of *Salmonella* isolated from pork, beef and chicken meat at retail markets in Vientiane capital, Laos	Raw meat swabs (258 pork, 81 beef, 106 poultry)/ three retail big markets in Vientiane capital	2018-2019	The prevalence of *Salmonella* spp. found in pork, beef and chicken meat was 49%, 62% and 61%, respectively. *S.* Rissen (37.0%), *S*. Derby (10.8%) and *S.* Corvallis (38.0%) were the most common found in each specimen type, respectively. 72% of isolates were resistant to tetracycline, followed by 62% of ampicillin, 52% of sulfamethoxazole-trimethoprim and 26% of chloramphenicol.
Moser AI. et al. (2021) (142)	AMR	Human & Animal	To compare extended-spectrum cephalosporin resistance (ESC-R) and/or colistin-resistant *E. coli* (CST-R-*Ec*) found in local people, poultry, and chicken meat in Vientiane, Laos	60 healthy local people (12 hotels), 60 faecal samples from poultry (7 different farm), 60 raw chicken meat swabs (24 markets),	2018	Local people (70% and 15%), poultry (20% and 23%), and chicken meat (22% and 13%) colonized ESC-R-*Ec* and CST-R-*Ec*, respectively. ESC- R-*Ec* mainly harboured *bla*CTX-M- 15 and *bla*CTX-M-55 genes, mostly associated with IS*Ecp1* or IS*26* elements. Most CST-R-*Ec* carried *mcr-1* on IncX4, IncI2, IncP1, and IncHI1 plasmids similar or identical to those

						reported globally. Additionally, strains with chromosomal *mcr-1* or possessing plasmid-mediated *mcr-3* were also identified.
Pungpian C. et al. (2021) (160)	AMR	Human & Animal	To examine the prevalence and genetics underlying AMR in *E. coli* isolated from pigs, pig carcasses, pork, and humans in Thailand and Laos border provinces	431 *E. coli* isolates from pig carcasses, pork and human/four border provinces with crossing points between Thailand and Laos (Nong Khai-Vientiane and Mukdahan-Savannakhet t)	2013-2018	The overall MDR- *E. coli* was identified by 63% from Lao isolates, including 77%, 66%, 57% an 49% from pig, pig carcasses, pork and human, respectively. Of all isolates, 44% harboured *intI1*. The percentage of *intI1*-positive *E. coli* from pigs was more predominant than that from pork and humans ($p = 0.017$ and $p=0.002$, respectively).
Zhou Y. et al. (2022) (143)	AMR	Human, Animal & Environ-ment	To investigate the molecular epidemiology of *mcr* using a ‘‘One-Health” approach in Laos and to predict whether any dominant plasmid backbone and/or strain type influences the dissemination of *mcr*	673 samples (rectal swabs from healthy human, poultry and the environment (water, flies, bird etc.)/Vientiane, Laos	2018	The overall prevalence of *mcr*-positive-*E. coli* (MCRPEC) was 14.6% (98/673). The prevalence in human samples was (46% (45/98), 14.3% (2/14) in dog feces, 12% (24/200) in flies, 11% (11/100) in chicken meat, 9% (8/90) in chicken cloacal, 8% (4/50) in chicken caeca, and 7.5% (4/53) in wastewater. No MCRPEC were found in bird feces or water from canals, rivers, and reservoirs. More resistant to co-amoxiclav, sulfamethoxazole-trimethoprim, levofloxacin, ciprofloxacin, and gentamicin was found in MCRPEC than *mcr*-Negative-*E. coli* ($p < 0.05$). Genomic analysis revealed the presence of MCRPEC across various clonal types.

Note: * Corrected version of Tabernero P. et al. (2019) (107), **#** Included specimens from Kantele A. et al. (2021) (39).

Chapter 2: Trends in hospital antimicrobial use in six hospitals across Lao PDR from 2017 to 2020

Abstract

Background: AMU is one of the key drivers of AMR. Data on the use of antimicrobials in hospitals in Laos, which could be used to inform antimicrobial stewardship approaches, are limited.

Objectives: This study aimed to describe the patterns of hospital antimicrobial use in six general hospitals in Laos over a four-year period, from 2017 to 2020, as a basis for informing AMR action in Laos.

Methods: Point prevalence surveys (PPS) of AMU were conducted at four-month intervals in six general hospitals across Laos from 2017 to 2020. Modified Global-PPS data collection tools were used to collect demographic and antimicrobial prescribing data. The surveys solely focused on hospitalized inpatients. Antimicrobial prescriptions were described based on the prescribing indications, WHO AWaRe classification (Access, Watch, Reserve or Not recommended) and whether the prescriptions adhered to the local treatment guidelines.

Findings: The overall prevalence of AMU among inpatients was 71% (4,377/6,188; 95% CI: 70-73), varying by hospital and survey round from 50.4% (135/268; 95% CI: 44-56) to 88.4% (61/69; 95% CI: 78-95). The majority of patients were adults (3,421 patients) aged ≥15 years (78%; 95% CI: 77-79). Among the 4,377 patients prescribed antimicrobials, 44% received more than one agent. The total number of prescriptions assessed was 6,555. Ceftriaxone was the most commonly used

(39.6%) antimicrobial, followed by metronidazole (17%) and gentamicin (10%). Pneumonia was the most common diagnosis among those prescribed antimicrobials in both children aged ≤5 years (29% among those aged ≤1 year and 27% among those aged >1 to ≤5years) and adults aged ≥15 years at 9%. The percentage of antimicrobial use adherence to the local guidelines was 26%; inappropriate use was mainly found for surgical prophylaxis (99%). Adult patients received Access group antimicrobials less commonly than children (47% *vs* 63%, p-value<0.0001). Most (99%) Watch group prescriptions were without a microbiological indication.

Conclusion: AMU among hospitalized patients in Laos is high with frequent inappropriate use of antimicrobials, especially as surgical prophylaxis. Continued monitoring and enhanced antimicrobial stewardship interventions are needed in Lao hospitals.

Background

Acquired AMR emerges quickly in some pathogens soon after the deployment of many antimicrobials, reducing their efficacy (161, 162) and has become an urgent global health concern, causing increasing mortality and healthcare costs, especially in LMICs (140, 163, 164). There is demand for new classes of antibiotics, as well as to reconsider old antibiotics which are active against multidrug resistant bacteria (165). Although AMR may be intrinsic, antimicrobial use (either appropriate or inappropriate) is one of the key drivers of acquired AMR (12).

Data of inpatient antimicrobial prescriptions from the Global Point Prevalence Survey (Global-PPS) conducted in 53 countries worldwide in 2015 (64% of participating hospitals were from European countries) showed that the proportion of inpatients prescribed antimicrobials ranged from 27%-50%; which was highest in Africa (50%), followed by West and central Asia (43.8%) and Southern Europe (39%). Overall antimicrobial prescriptions adhered to the local guidelines for 77.4% of 36,792 prescriptions; ranging from 66.3% of 1,612 in West and central Asia to 85.8% of 2,139 in North America (166). A multicentre study of hospital antimicrobial use in 2019 in four African countries (Ghana, Uganda, Zambia and Tanzania) showed a similar pattern of hospital antimicrobial use which ranged from 30%-57%. Compliance to local guidelines was between 55% and 88% (167). Studies from WHO Western Pacific countries, such as Malaysia, Japan, China and Vietnam, have reported the use of antimicrobials in hospitals ranging from 28.5%-67.4% (168-171). Understanding hospital antimicrobial usage within countries may help to find effective tools to combat AMR tailored to the local context.

A situational analysis of AMR and AMU in humans, animals and the environment in Laos found that data on AMR and AMU in Laos were sparse. Use of antimicrobials

in inpatients ranged from 45-70% between 2004 and 2018. Appropriateness of use has not been properly assessed before (141). Few studies mentioned inappropriateness of antibiotic prescriptions in Lao, such as antibiotic prescription for the common cold (33, 109). Laos began participating in the Global-Point Prevalence Survey (Global-PPS) of antimicrobial consumption and resistance in 2017 to provide the first data on hospital antimicrobial prescribing in the country as a part of a project on surveillance of antimicrobial use and resistance in Laos.

The aim of this study was to describe the patterns of hospital antimicrobial use in six general hospitals across Laos over a 4-year period, from 2017 to 2020, as a basis for informing AMR action in Laos.

Methods

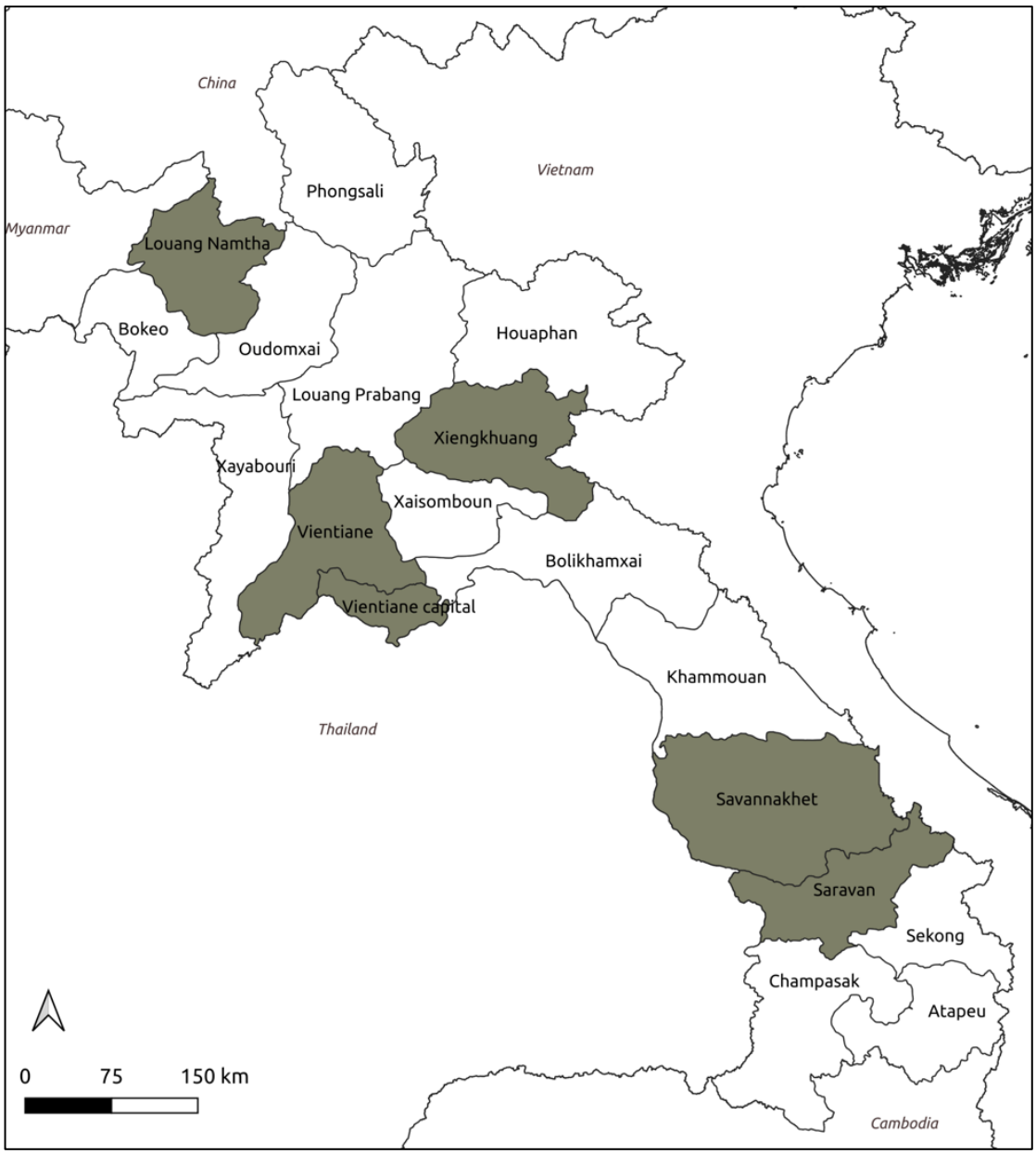
Study design and setting

Point prevalence surveys (PPS) of antimicrobial use were repeatedly conducted in inpatients in six hospitals: two referral (200-450 beds, including Mahosot Hospital in Vientiane Capital and Savannakhet Provincial Hospital) and four provincial hospitals (60-100 beds), including Luang Namtha, Xiengkhuang, Vientiane and Salavan Provincial Hospitals. Mahosot, Xiengkhuang, Luang Namtha and Salavan participated in the surveys from mid-2017 (one survey a year), with Vientiane Provincial Hospital joining in 2018 and Savannakhet in 2019. These six hospitals were included in the survey because they were geographically dispersed, with two hospitals located in the north, two in the centre, and two in the south of Laos (Figure 9). These six hospitals in one prefecture and five out of 17 provinces were considered representative of different regions in Laos.

Data collection and study procedure

Data collection was performed using an adapted version of the Global-PPS protocol (2019) (172), in which healthy newborn babies on maternity wards were not included in the denominator. Lao data were submitted to Global-PPS until the end of 2018. Inpatient records from all wards for patients recorded as present at 8:00 am on the survey day were screened for antimicrobial prescriptions; all screened patients were counted as the denominator. All patients documented with a prescription of any kind of antimicrobial agent(s) prescribed in the 24 hours before 8:00 am on the survey day were counted as the numerator. Survey days were a convenience sample of weekdays, one day per ward.

Figure 9: Hospital antimicrobial use point prevalence survey sites in Laos



Patients' demographic and clinical characteristics and treatment status, including age, body weight, ward, antimicrobial agent(s), route of administration, dosage, unit, diagnoses, and prescribing indication were recorded. Data on topical antimicrobials were not collected. Surveys were not conducted during public holidays or weekends.

Data were collected directly from hospital charts, without interviewing patients or ward staff, unless the number of charts and number of patients were inconsistent or handwriting was illegible. Each ward survey was completed within the survey day. If hospital charts were unavailable on the wards during the survey time (e.g., because being consulted on by other medical specialties), the survey team came back to the wards on the same day for those hospital charts, but ignored all information recorded after 8:00 am on the survey day.

The surveys were conducted three times per year. Survey rounds were based on Lao seasons with the wet season from May to October and dry season from November to April (173). The dry season consists of cool dry (November to February) and hot dry (March to April) seasons. The first survey round of the year was in the hot dry season (March-April ± one month), the second survey round was in the wet season (May-October ± one month) and the third survey round was in the cool dry season (November-February ± one month).

Spectrum (broad or narrow) of antibiotics was classified based on Hagedoorn *et al.* (174) (Table 7). Prescribing indications were classified into treatment of infection, medical prophylaxis (medical prophylaxis-general, medical prophylaxis-trauma and medical prophylaxis-vaginal delivery), surgical prophylaxis, unclear and unknown (Table 8). Treatment was classified as empiric or targeted (i.e., based on microbiology results).

Table 7: Broad spectrum and narrow spectrum definition (174)

Narrow		Broad	
Class	**Agent**	**Class**	**Agent**
Beta-lactamase sensitive penicillins	benzylpenicillin (pen G), pheneticillin, benzathine, phenoxymethylpenicillin, benzathine benzylpenicillin, phenoxymethylpenicillin (pen V)	Combinations of penicillins, including beta-lactamase inhibitors	ampicillin and beta-lactamase inhibitor, amoxicillin and beta-lactamase inhibitor, piperacillin and beta-lactamase inhibitor
Beta-lactamase resistant penicillins	cloxacillin, flucloxacillin, oxacillin	2nd generation cephalosporins	cefaclor, cefprozil, cefuroxime
Penicillins with extended spectrum	amoxicillin, ampicillin, piperacillin	3rd generation cephalosporins	cefotaxime, ceftazidime, cefixime, ceftriaxone, cefdinir, cefpodoxime
1st -generation cephalosporins	cefazolin, cefadroxil, cefalexin	Macrolides	erythromycin, azithromycin, clarithromycin, josamycin, midecamycin
Sulfonamides/trimethoprim	trimethoprim	Sulfonamides/ trimethoprim	sulfamethoxazole-trimethoprim
Nitrofurans	furazolidone, nitrofurantoin	Tetracyclines	doxycycline, tetramycine
Other	colistin (polymxin), tazobactam	Lincosamides	clindamycin
		Carbapenem	meropenem
		Quinolones	ciprofloxacin, ofloxacin, levofloxacin
		Aminoglyco-sides	gentamicin, tobramycin, amikacin, neomycin
		Glycopeptides	vancomycin, teicoplanin
		Imidazole derivates	metronidazole
		Other	rifampicin

Table 8: Prescribing indication classifications

Indications	Details
Treatment of infection	Treatment of infection
Medical prophylaxis	Medical prophylaxis-general: gastrointestinal bleeding, liver cancer, prophylaxis for opportunistic infections in HIV patients, malnutrition, neonatal infection prophylaxis (including preterm delivery, low birthweight or birth asphyxia without sign or symptoms of infections)
	Medical prophylaxis-trauma: e.g., head, eye, chest, abdomen, knee, leg, arm trauma (mostly from road traffic crashes)
	Medical prophylaxis-vaginal delivery: normal delivery via vaginal route with or without episiotomy
Surgical prophylaxis	Antimicrobial(s) given for prophylaxis purposes, e.g., elective surgery
Unclear	Not enough information to indicate why antimicrobials were prescribed (e.g., pleural effusion or diarrhoea (only) without further information of possible cause)
Unknown	Not known why antimicrobial(s) was given

Adherence to the guidelines was assessed using local treatment guidelines in place at the time of prescribing (Table 9, focusing on pre-2021 guidelines). The evaluation was based on the diagnosis in the patient's medical notes at the start of the antimicrobial treatment, and only for diagnoses covered by the local treatment guidelines. Adherence was not assessed when there were no local guidelines or the prescription indications were unknown or unclear. Adherence to the guidelines in this study was based solely on the choice of antimicrobial(s), without considering dosage, route of administration and duration of use. New local antimicrobial prescribing guidelines were available in January 2021 (134, 135). The adherence to these new guidelines is discussed in greater detail in Chapters 3 and 4.

Table 9: List of the most recent treatment guidelines relating to infectious diseases in Laos

Guidelines	Ed.	Year	Language	Publisher	Available at
Surgery Prophylaxis					
Protocoles D'Antibioprophylaxie en Chirurgie	-	1996	French	Mahosot Hospital	Mahosot Hospital
Infectious diseases					
Diagnosis and treatment in district hospitals	2	2004	Lao/English /French	IFMT	IFMT
Standard treatment guidelines	4	2012	Lao	MoH	MoH
Mahosot Microbiology Review	7	2013	Lao/English	LOMWRU	LOMWRU, UHS Library
Pocket book of hospital care for children	4	2017	Lao/English	WHO, MoH	WHO, MoH
Antimicrobial prescribing guidelines					
Lao Paediatric Antimicrobial Prescribing Guidelines	1	2020	Lao	DHR, MoH	DHR, MoH
Lao Adult Antimicrobial Prescribing Guidelines	1	2020	Lao	DHR, MoH	DHR, MoH
Specific infectious disease					
Malaria					
Malaria treatment guidelines for provincial and district hospitals	-	2011	English	CMPE, MoH	CMPE, MoH
Guidelines for diagnosis and treatment of uncomplicated malaria for Health centres and village health volunteers/workers, Lao PDR	1	2011	Lao/English	CMPE, MoH	CMPE, MoH
Lao National Malaria Treatment Guidelines	-	2022	Lao	CMPE	CMPE
Tuberculosis					
Guidelines for clinical management of HIV and Tuberculosis co-infection	-	2011	Lao	CMPE, MoH	MoH

National Tuberculosis control program-National technical guidelines	3	2014	Lao/English	MoH	MoH
National tuberculosis treatment guidelines	4	2018	Lao	MoH	MoH
Sexually transmitted infection and HIV/AIDs					
Lao PDR National Guidelines for the Use of Antiretroviral Therapy in Adults and Children	5	2017	English	MoH	MoH
National Guidelines for the Treatment of Sexually Transmitted Infections	4	2018	Lao	MoH	MoH
Kidney infection					
Nephritis treatment guidelines	-	2017	Lao/English	LPA	LPA
Nephrotic syndrome treatment guidelines	-	2018	Lao/English	LPA	LPA
Malignancy in children					
Supportive care guideline in childhood cancer	-	2018	Lao/English	LPA	LPA
Covid-19					
Covid-19 case management: Lao PDR	6	2023	Lao	DHR	DHR
Hepatitis B and C					
National Guidelines of diagnosis, treatment and prevention of hepatitis B and C	-	2021	Lao	DHR, MoH	DHR, MoH

Note: Ed. = Edition, **IFMT**= Institut de la Francophonie pour la Médicine Tropicale, **CMPE**= Center for Malariology, Parasitology, and Entomology, **MoH**= Ministry of Health, **LOMWRU**= Lao-Oxford-Mahosot Hospital Wellcome Trust Research Unit, **DHR**= Department of Healthcare and Rehabilitation. **UHS** (University of Health Sciences): http://uhs-elibrary.la/ Elibrary.php?&parentID= 0&CatID=11 . **LPA** (Lao Paediatric Association): https://laopediatricassociation.la/guidelines?lang=en.

Data analysis

Descriptive analysis was performed for patients' characteristics, the trend of antimicrobial prescriptions through seasons, survey round, and antimicrobial prescriptions by medical specialty and organ involved. Frequency, mean (95% confidence interval (CI)), and median with interquartile range (IQR) were used to describe data. Antimicrobial prescriptions were described based on the prescribing indications, WHO AWaRe classification (Access, Watch, Reserve or Not recommended) (175) and whether the prescription adhered to the local guidelines. Pearson's chi-squared test or Fisher's exact test were used to compare the proportions of categorical variables. Time series data analysis was used to assess the seasonality and trends of antimicrobial use over the survey period using Chi-squared goodness of fit test and binary regression.

Results

Between July 2017 and December 2020 (41 months), ten rounds of antimicrobial use PPS were conducted in six hospitals across Laos. Over these 41 months, records of 6,188 inpatients were screened for antimicrobial use; revealing that 4,377 (71% (95% CI: 69-72)) inpatients received antimicrobial treatment, with 6,555 antimicrobial prescriptions in total. The use of antimicrobials varied from the lowest prevalence of 50.4% (135/268; 95% CI: 44.2-56.5) in one survey round in Savannakhet Provincial Hospital to the highest of 88.4% (61/69; 95% CI: 78.4-94.9) in Salavan Provincial Hospital (Figure 10). The majority of patients included were adults (≥15 years), 3,421/4,377 (78.2%; 95% CI: 76.9-79.4). Infants (≤1 year) accounted for 435/4,377 (10%; 95% CI: 9-10.8). Among 435 infants, 217 (50%; 95% CI: 45.1-54.7) were neonates (≤28 days). Of the 4,377 patients, 1,336 (30.5%; 95% CI: 29.2-31.9) were admitted to surgical departments and 43.8%; 95% CI: 42.3-45.3) or 1,918 were prescribed more than one antimicrobial (Table 10).

Figure 10: Antimicrobial use in six survey hospitals in Laos, from 2017 to 2020, for the five most commonly used antimicrobial classes

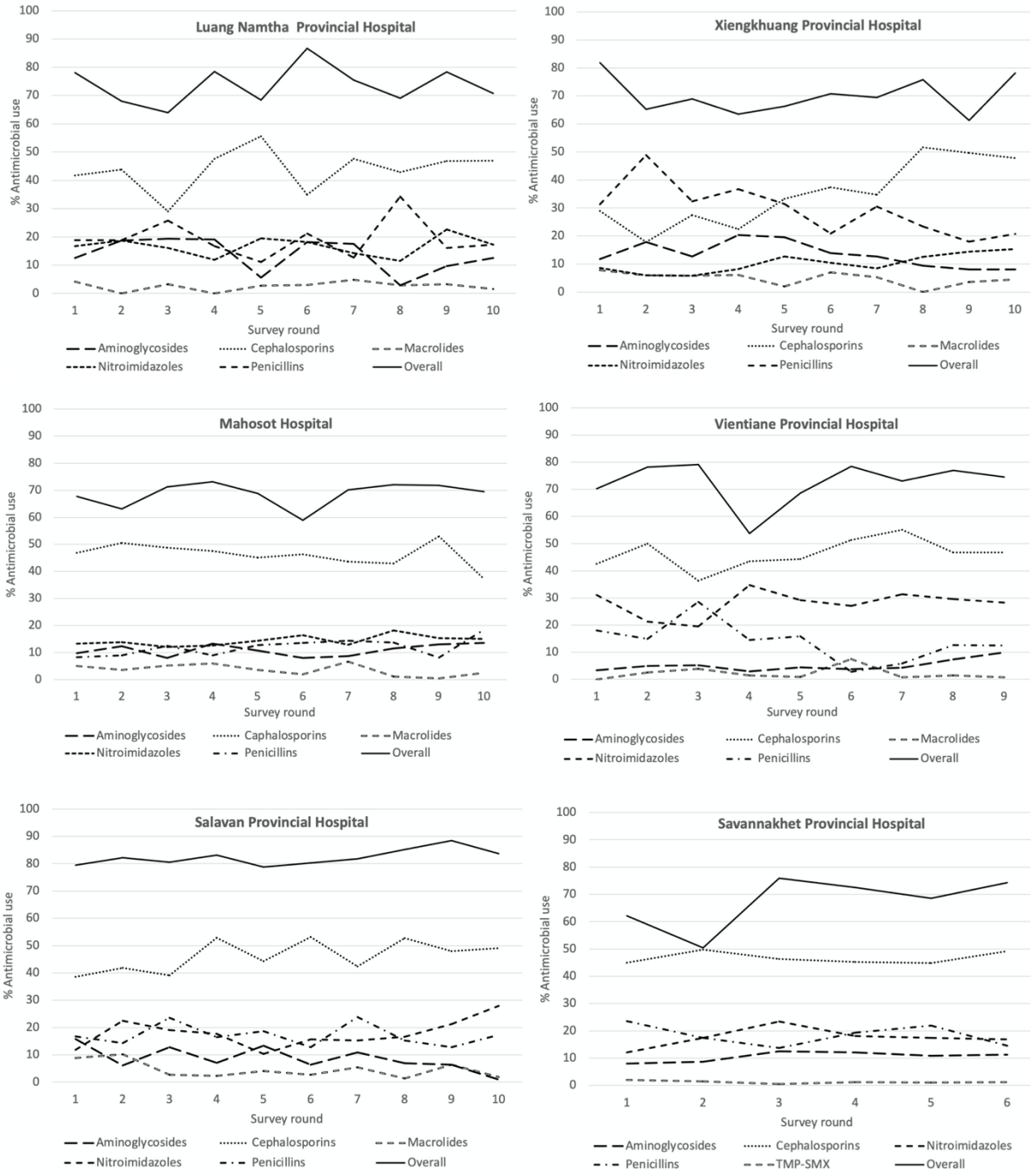


Table 10: Overall patient characteristics and prevalence of antimicrobial use in six survey hospitals across Laos from 2017 to 2020

Characteristic	2017	2018	2019	2020	Total
Number of survey rounds	1	3	3	3	10
Screened patient documents [a]	489	1,450	2,161	2,088	6,188
Patients with antimicrobial(s) prescribed (%)	360 (74)	1,036 (71)	1,449 (67)	1,532 (73)	4,377 (71)
Number of prescriptions	533	1,518	2,187	2,317	6,555
Antimicrobial use by hospital (%):					
Mahosot Hospital (MS)	176/260 (68)	426/618 (69)	412/631 (65)	401/564 (71)	1,415/2,073 (68)
Vientiane Provincial Hospital (VTP)	-	154/202 (76)	175/261 (67)	223/298 (75)	552/761 (72.5)
Luang Namtha Provincial Hospital (LNT)	32/41 (78)	72/102 (81)	102/132 (77)	124/169 (73)	330/444 (74)
Xiengkhuang Provincial Hospital (XK)	90/110 (81.8)	199/302 (66)	215/312 (69)	202/287 (70)	706/1,011 (70)
Salavan Provincial Hospital (SV)	62/78 (79.5)	185/226 (82)	198/247 (80)	179/209 (86)	624/760 (82)
Savannakhet Provincial Hospital (SVK)	-	-	347/578 (60)	403/561 (72)	750/1,139 (66)
Age, median (IQR) years	33 (17-57)	32 (18-54)	31 (17-54)	32 (18-52)	32 (18-54)
Age category (%) [a]: ≤1 year	31 (9)	104 (10)	138 (9)	162 (11)	435 (10)
>1 to ≤5 years	31 (9)	64 (6)	104 (7)	90 (6)	289 (7)
>5 to ≤14 years	19 (5)	51 (5)	80 (6)	81 (5)	232 (5)
≥15 years	279 (77)	816 (79)	1,127 (78)	1,199 (78)	3,421 (78)
Department (%) [a]: Intensive Care	16 (4)	79 (8)	104 (7)	136 (9)	335 (8)
Medicine	108 (30)	270 (26)	331 (23)	345 (22)	1,054 (24)
Paediatrics	49 (14)	122 (12)	221 (15)	201 (13)	593 (14)

Surgery	120 (33)	307 (30)	449 (31)	454 (30)	1,330 (30)
Obstetrics & Gynaecology	50 (14)	199 (19)	246 (17)	271 (18)	766 (17)
Other	17 (5)	59 (6)	98 (7)	125 (8)	299 (7)
Number of antimicrobial(s) (%) [a]: One	210 (58)	608 (59)	789 (54)	852 (56)	2,459 (56)
Two	127 (35)	377 (36)	586 (40)	578 (38)	1,668 (38)
≥Three	23 (6)	51 (5)	74 (5)	102 (7)	250 (6)
Route of administration (%) [b]: Oral	140 (26)	353 (23)	392 (18)	340 (15)	1,225 (19)
Parenteral	393 (74)	1,165 (77)	1,795 (82)	1,977 (85)	5,330 (81)
Indication (%) [b]					
Treatment of infection	295 (55)	798 (53)	1,173 (54)	1,198 (52)	3,464 (53)
Medical prophylaxis-general	36 (7)	81 (5)	120 (5)	136 (6)	373 (6)
Medical prophylaxis-trauma	6 (1)	21 (1)	51 (2)	78 (3)	156 (2)
Medical prophylaxis-vaginal delivery	22 (4)	97 (6)	114 (5)	124 (5)	357 (5)
Surgical prophylaxis	125 (23)	366 (24)	453 (21)	480 (21)	1,424 (22)
Unclear indication	12 (2)	34 (2)	56 (3)	82 (4)	184 (3)
Unknown	37 (7)	121 (8)	220 (10)	219 (9)	597 (9)
Indication documented in patient records (%)[b]	482 (90)	1,356 (89)	1,900 (87)	2,014 (87)	5,752 (88)
Treatment (%) [b]: Empirical	521 (98)	1,491 (98)	2,167 (99)	2,288 (99)	6,467 (99)
Targeted	12 (2)	27 (2)	20 (1)	29 (1)	88 (1)
Stop/review date documented (%) [b]	4 (0.7)	28 (1.8)	4 (0.2)	16 (0.7)	52 (0.8)
Targeted sites for prescriptions (%) [b]:					
Bone and Joint	8 (1)	44 (3)	67 (3)	61 (3)	180 (3)

Cardiovascular System	2 (0.4)	8 (0.5)	12 (0.6)	13 (0.6)	35 (0.5)
Central Nervous System	15 (3)	24 (2)	46 (2)	89 (4)	174 (3)
Ear-Nose-Throat	41 (8)	86 (6)	149 (7)	91 (4)	367 (6)
Gastrointestinal	133 (25)	362 (24)	583 (27)	556 (24)	1,634 (25)
Male genital tract	10 (2)	26 (2)	21 (1)	34 (1)	91 (1)
Obstetrics/Gynaecology	75 (14)	307 (20)	396 (18)	478 (21)	1,256 (19)
Ophthalmology	4 (0.7)	9 (0.6)	9 (0.4)	12 (0.5)	34 (0.5)
Respiratory tract	105 (20)	301 (20)	318 (15)	286 (12)	1,010 (15)
Sepsis	26 (5)	40 (3)	104 (5)	171 (7)	341 (5)
Skin and Soft Tissue	39 (7)	118 (8)	159 (7)	219 (9)	535 (8)
Urinary tract	45 (8)	101 (7)	175 (8)	132 (6)	453 (7)
Not defined	30 (6)	92 (6)	148 (7)	175 (7)	445 (7)
Compliance with pre-2021 guidelines (%) [b]:					
Adherence [c]	122 (32)	264 (26)	353 (24)	397 (26)	1,136 (26)
Non-adherence [c]	263 (68)	766 (74)	1,115 (76)	1,117 (74)	3,261 (74)
Not assessed	148 (28)	288 (32)	719 (33)	803 (35)	2,158 (33)

[a] denominator was number of patients with antimicrobial(s); [b] denominator was number of prescriptions; [c] denominator only included "Adherence" and "Non-adherence" categories, excluding "Not accessed" category.

Trends of antimicrobial use

Overall antimicrobial use varied between hospitals over ten survey rounds. The median (range) use at Salavan was at 82% (78.8-84.4), Luang Namtha at 73.1% (63.9-89.8), Vientiane Province at 74.5% (53.8-79.1), Xiengkhuang at 68.6% (61.3-81.8), Mahosot at 69.8% (58.9-73.2). There were significant differences in the proportion of patients prescribed antimicrobials in each survey round by individual hospital (Figure 11). Season had no discernible effect on antimicrobial use at Mahosot, Xiengkhuang and Salavan. However, the use of antimicrobials varied by seasons in Vientiane Province, Luang Namtha and Savannakhet. After controlling for seasonality, there was no trend in the proportion of patients prescribed antimicrobials over the survey period in each survey hospital (Figure 11).

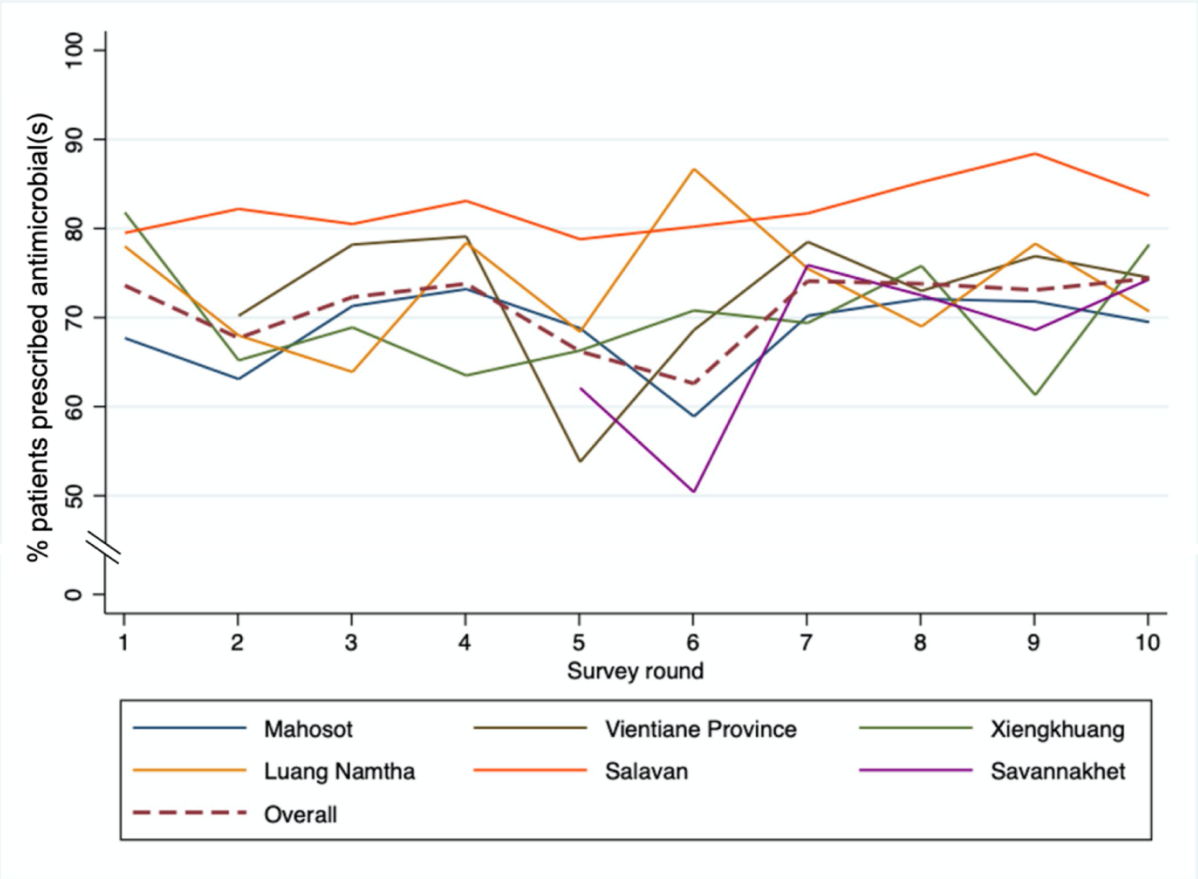
The overall proportions of the use of each antimicrobial class did not change by season over each survey year, apart from the use of macrolides in 2019 which was higher in the cool dry season (34 (4.7%; 95% CI: 3-6)) but with similar proportions for the hot dry (18 (2.5%; 95% CI: 1.6-4)) and wet seasons (19 (2.3%; 95% CI: 1.4-3.6)) with p=0.03 (Table 11).

Table 11: The use of antimicrobials by season in six survey hospitals from 2017 to 2020

Antimicrobial class	**2017**	**2018**				**2019**				**2020**			
	Wet (n=533)	Hot dry (n=477)	Wet (n=573)	Cool dry (n=468)	*p*	Hot dry (n=648)	Wet (n=812)	Cool dry (n=727)	*p*	Hot dry (n=637)	Wet (826)	Cool dry (n=854)	*p*
Aminoglycosides (n= 679)	62 (11.6)	54 (11)	57 (9.9)	60 (12.8)	0.34	70 (10.8)	74 (9.1)	76 (10.4)	0.52	58 (9.1)	82 (9.9)	86 (10)	0.81
Antifungals (n= 47)	7 (1.3)	2 (0.4)	8 (1.4)	1 (0.2)	0.07	5 (0.8)	6 (0.7)	6 (0.8)	1	6 (0.9)	3 (0.4)	3 (0.3)	0.23
Anti-helminthics (n= 12)	0	0	0	0	-	3 (0.5)	2 (0.2)	3 (0.4)	0.75	1 (0.2)	1 (0.1)	2 (0.2)	1
Antimalarials (n= 1)	0	0	1 (0.2)	0	-	0	0	0	-	0	0	0	-
Anti-tuberculosis (n= 49)	9 (1.7)	4 (0.8)	5 (0.9)	7 (1.5)	0.60	4 (0.6)	6 (0.7)	3 (0.4)	0.73	3 (0.5)	3 (0.4)	5 (0.6)	0.93
Antivirals (n= 13)	0	1 (0.2)	0	0	-	5 (0.8)	3 (0.4)	0	0.05	0	4 (0.5)	0	-
BL/BLIs (n= 78)	15 (2.8)	5 (1)	5 (0.9)	6 (1.3)	0.74	12 (1.8)	14 (1.7)	8 (1.1)	0.45	0	9 (1.1)	4 (0.5)	-
Carbapenems (n= 57)	1 (0.2)	2 (0.4)	1 (0.2)	4 (0.8)	0.27	4 (0.6)	9 (1.1)	11 (1.5)	0.28	8 (1.3)	7 (0.8)	10 (1.2)	0.72
Cephalosporins (n= 2,919)	216 (40.5)	198 (41.5)	243 (42.4)	194 (41.4)	0.94	282 (43.5)	370 (45.6)	323 (44.4)	0.73	304 (47.7)	400 (48.4)	389 (45.5)	0.47
Lincosamides (n= 2)	0	0	0	0	-	0	0	0	-	0	1 (0.1)	1 (0.1)	-
Macrolides (n= 213)	34 (6.4)	22 (4.6)	25 (4.4)	21 (4.5)	0.98	18 (2.8)	19 (2.3)	34 (4.7)	0.03	8 (1.3)	16 (1.9)	16 (1.9)	0.58
Nitroimidazoles (n= 1,103)	65 (12.2)	80 (16.8)	78 (13.6)	64 (13.7)	0.28	100 (15.4)	143 (17.6)	126 (17.3)	0.50	124 (19.5)	159 (19.2)	264 (19.2)	0.99
Penicillins (n= 1,116)	87 (16.3)	90 (18.9)	110 (19.2)	94 (20.1)	0.88	124 (19.1)	133 (16.4)	114 (15.7)	0.20	102 (16)	121 (14.6)	141 (16.5)	0.56
Quinolones (n= 121)	20 (3.7)	10 (2.1)	17 (3)	9 (1.9)	0.52	14 (2.2)	9 (1)	7 (1)	0.15	11 (1.7)	7 (0.8)	17 (2)	0.12
Trimethoprim-sulfamethoxazole (n= 51)	8 (1.5)	2 (0.4)	7 (1.2)	0	-	3 (0.5)	7 (0.9)	6 (0.8)	0.67	8 (1.3)	3 (0.4)	7 (0.8)	0.14
Tetracyclines (n= 94)	9 (1.7)	7 (1.5)	16 (2.8)	8 (1.7)	0.29	4 (0.6)	17 (2.1)	10 (1.4)	0.05	4 (0.6)	10 (1.2)	9 (1)	0.56

Note: Hot dry season: March to April; cool dry season: November to February; wet season: May-October, p-value: Chi-squared test or Fisher's exact test were used to test for differences in the proportion of antimicrobial use across different seasons; *p*= p-value.

Figure 11: Trends of antimicrobial use in six hospitals in Laos from 2017-2020



Choice of antimicrobials

Among 6,555 antimicrobial prescriptions from 2017 to 2020, antibiotics accounted for 6,433 (98%; 95% CI: 97.8-98.4), anti-tuberculosis drugs for 49 (0.75%; 95% CI: 0.5-0.9), antifungals for 47 (0.7%; 95% CI: 0.5-0.9), antivirals (aciclovir and antiretrovirals) for 13 (0.2%; 95% CI: 0.1-0.3), anti-helminthics for 12 (0.2%; 95% CI: 0.09-0.3) and an antimalarial for 1 (0.02%). Of all prescriptions, the cephalosporins class was the most prescribed at 2,919 (44.5%; 95% CI: 43-46), followed by penicillins at 1,116 (17%; 95% CI: 16-18), then nitroimidazoles at 1,104 (16.8%; 95% CI: 16-18), aminoglycosides at 679 (10.4%; 95% CI: 9.6-11) and macrolides at 213 (3.2%; 95% CI: 2.8-3.7) (Table 12).

Of the cephalosporins (n=2,919), ceftriaxone accounted for 2,595 (89%; 95% CI: 88-90) prescriptions. Cefalexin was the only first-generation cephalosporin (1stGC) used, accounting for 154 (5%; 95% CI: 4-6) prescriptions and 4 (0.1%; 95% CI: 0.04%-0.35%) patients were prescribed 2ndGC (cefuroxime). Ampicillin was the most prescribed of the penicillin class at 462/1,116 (41%; 95% CI: 38-44) prescriptions, followed by amoxicillin at 407/1,116 (35%; 95% CI: 34-39) and cloxacillin at 212/1,116 (19%; 95% CI: 17-21). The majority of beta lactam/beta-lactamase inhibitors (BL/BLIs) and carbapenem use was in Mahosot at 67/78 (86%; 95% CI: 76-93) and 56/57 (98%; 95% CI: 91-99.9) prescriptions, respectively. Of BL/BLIs, amoxicillin/clavulanic acid was the most prescribed at 45/78 (58%; 95% CI: 46-69), followed by ceftriaxone/sulbactam at 30/37 (38%; 95% CI: 65-92) and cefoperazone/sulbactam at 3/78 (4%; 95% CI: 0.8-11) (Table 12).

Prescribing indication

The majority of prescribed antibiotics were broad spectrum (174) making up 5,163/6,433 (80%; 95% CI: 79-81) prescriptions. The most common indication for prescribing antimicrobial(s) for patients of all ages (n= 6,555) was pneumonia in 804 (12%; 95% CI: 11-13), followed by appendicitis in 397 (6%; 95% CI: 5-7), sepsis in 304 (5%; 95% CI: 4-5), skin and soft tissue infection in 270 (4%; 95% CI: 3.6-5) and gastrointestinal tract infection in 238 (3.6%; 95% CI: 3-4). Pneumonia was also the most common indication for prescribing in adults aged ≥15 years and children aged >28 days to ≤5 years at 465/5,093 (9%; 95% CI: 8-10) and 287/730 (39%; 95% CI: 36-43), respectively. Antimicrobials were prescribed mostly for sepsis in neonates at 172/415 (41%; 95% CI: 37-46). Tonsillopharyngitis and abdominal infection were diagnosed more frequently in older children (aged >5 to ≤14 years).

The proportion of patients prescribed antimicrobials varied by age group. Penicillins tended to be used more frequently in infants (aged ≤1 year) at (306/754 (40%; 95% CI: 37-44)), compared to 109/391 (28%; 95% CI: 23-33) children aged >1 to ≤5 years and only 55/317 (17%; 95% CI: 13-22) children aged > to ≤14 years (p <0.0001). Overall, cephalosporins were prescribed more frequently in children aged >1 to ≤14 years at 344/708 (48%; 95% CI: 45-92), than children aged ≤1 years at 154/754 (20%; 95% CI: 18-23), p <0.0001. Cephalosporin prescriptions were predominantly used in adults aged ≥15 years, accounting for 2,590/5,410 (47%; 95% CI: 46-49) prescriptions, compared with 498/1,462 (34%; 95% CI: 32-36) prescriptions in children <15 years (p<0.0001). Antimalarials, antivirals and lincosamides were used in adults only (Figure 12).

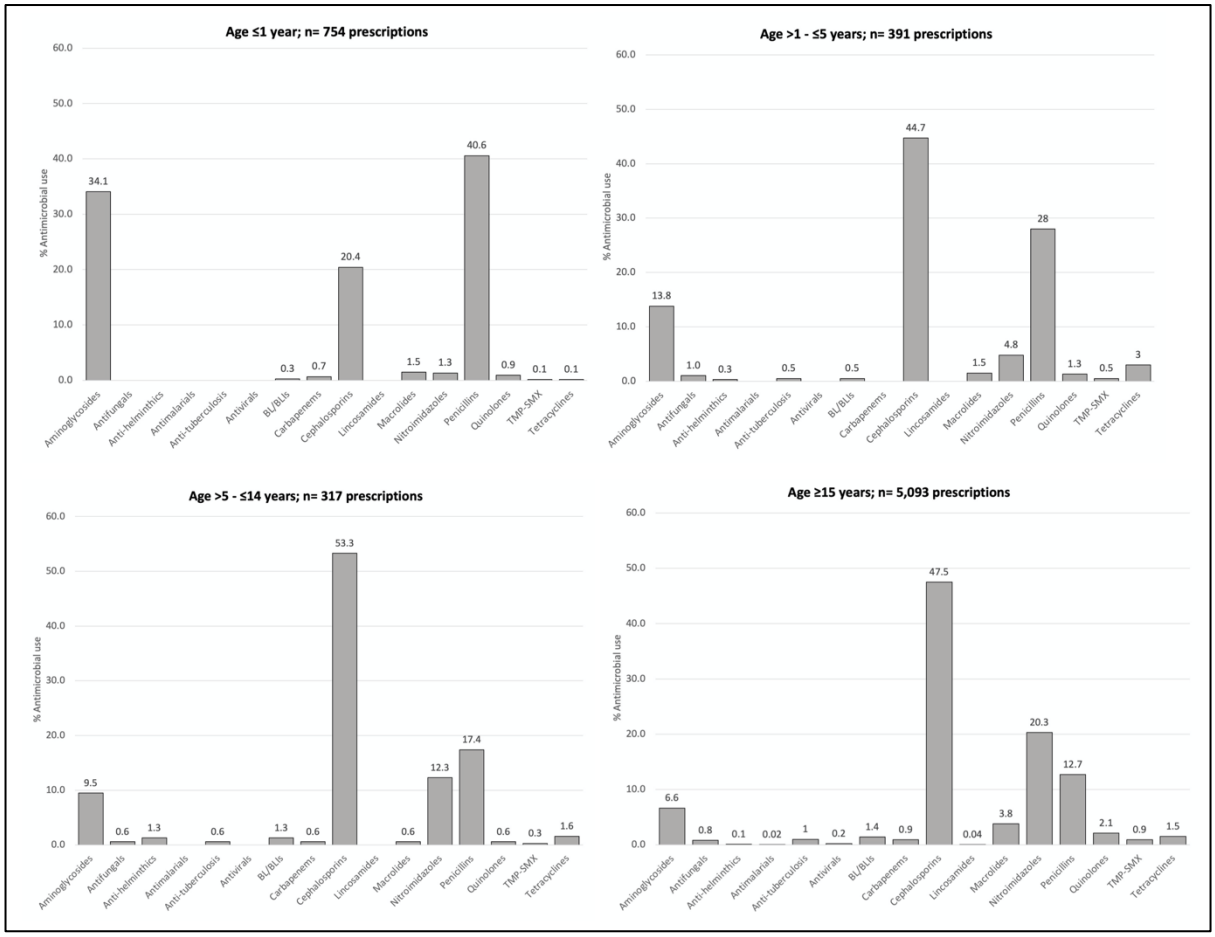
Table 12: Trends of antimicrobial use in six survey hospitals in Laos from 2017 to 2020

Class	Antimicrobial agents	Hospitals						
		MS	VTP	LNT	XK	SV	SVK	Overall
		n= 2,090 (%)	n= 880 (%)	n= 479 (%)	n= 1,010 (%)	n= 962 (%)	n= 1,134 (%)	n= 6,555(%)
Antifungals	Amphotericin B	8 (0.4)	-	1 (0.2)			3 (0.3)	12 (0.2)
	Fluconazole	15 (0.7)	-	1 (0.2)	-	1 (0.1)	11 (1)	28 (0.4)
	Nystatin	2 (0.1)	4 (0.5)	-	-	-	1 (0.09)	7 (0.1)
Anti-helminthics	Albendazole	6 (0.3)	3 (0.3)	-	-	-	-	9 (0.1)
	Mebendazole	-	-	1 (0.2)	-	-	-	1 (0.02)
	Praziquantel	-	2 (0.2)	-	-	-	-	2 (0.03)
Antimalarials	Chloroquine	1 (0.05)	-	-	-	-	-	1 (0.02)
Anti-TB	Rifampicin, isoniazid	1 (0.05)	-	-	-	-	4 (0.4)	5 (0.08)
	3FDC	1 (0.05)	-	-	3 (0.3)	1 (0.1)	-	2 (0.03)
	4FDC	22 (1.1)	1 (0.1)	4 (0.8)	-	9 (0.9)	3 (0.3)	42 (0.6)
Antivirals	Aciclovir	4 (0.2)	1 (0.1)	-	-	1 (0.1)	1 (0.09)	7 (0.1)
	Antiretrovirals	1 (0.05)	-	-	-	-	5 (0.4)	6 (0.09)
Aminoglycosides	Amikacin	7 (0.3)	-	-	-	-	-	7 (0.1)
	Gentamicin	218 (10.4)	48 (5.5)	66 (13.8)	135 (13.4)	84 (8.7)	121 (10.7)	672 (10.3)
BL/BLIs	Amoxicillin/ Clavulanic acid	34 (1.6)	1 (0.1)	2 (0.4)	7 (07)	1 (0.1)	3 (0.3)	45 (0.7)
	Cefoperazone/ Sulbactam	3 (0.1)	-	-	-	-	-	3 (0.05)
	Ceftriaxone/ Sulbactam	30 (1.4)	-	-	-	-	-	30 (0.5)
Carbapenems	Imipenem	6 (0.3)	-	-	-	-	-	6 (0.09)
	Meropenem	50 (2.4)	1 (0.1)	-	-	-	-	51 (0.8)
Cephalosporins								

1st GC	Cefalexin	40 (1.9)	5 (0.6)	14 (2.9)	23 (2.3)	23 (2.4)	49 (4.3)	154 (2.4)
2nd GC	Cefuroxime	4 (0.2)	-	-	-	-	-	4 (0.06)
3rd GC	Cefixime	19 (0.9)	-	-	2 (0.2)	1 (0.1)	1 (0.09)	23 (0.4)
	Cefotaxime	14 (0.7)	3 (0.3)	2 (0.4)	14 (1.4)	9 (1)	13 (1.2)	55 (0.8)
	Ceftazidime	41 (2)	7 (0.8)	194 (40.5)	2 (0.2)	22 (2.3)	16 (1.4)	88 (1.3)
	Ceftriaxone	850 (40.7)	398 (45.2)	-	312 (30.9)	388 (40.3)	453 (40)	2595 (39.6)
Lincosamides	Clindamycin	1 (0.05)	-	1 (0.2)	-	-	-	2 (0.03)
Macrolides	Azithromycin	59 (2.8)	18 (2.1)	11 (2.3)	24 (2.4)	42 (4.4)	9 (0.8)	163 (2.5)
	Clarithromycin	13 (0.6)	-	2 (0.4)	16 (1.6)	2 (0.2)	-	33 (0.5)
	Erythromycin	2 (0.1)	1 (0.1)	-	11 (1.1)	1 (0.1)	1 (0.09)	16 (0.2)
	Roxithromycin	1 (0.05)	-	-	-	-	-	1 (0.02)
Nitroimidazoles	Metronidazole	299 (14.3)	248 (28.2)	81 (17)	104 (10.3)	171 (17.8)	200 (17.6)	1103 (16.8)
Penicillins	Ampicillin	47(2.3)	83 (9.4)	45 (9.4)	109 (10.8)	102 (10.6)	76 (6.7)	462 (7.1)
	Amoxicillin	130 (6.2)	19 (2.2)	36 (7.5)	104 (10.3)	15 (1.6)	103 (9.1)	407 (6.2)
	Cloxacillin	59 (2.8)	10 (1·1)	7 (1.5)	70 (6.9)	49 (5.1)	17 (1.5)	212 (3.2)
	Penicillin G	9 (0.4)	3 (0.3)		7 (0.7)	-	8 (0.7)	27 (0.4)
	Penicillin V	3 (0.1)	-	1 (02)	3 (0.3)	-	1 (0.09)	8 (0.1)
Quinolones	Ciprofloxacin	24 (1.2)	1 (0.1)	1 (0.2)	18 (1.8)	11 (1.1)	1 (0.09)	56 (0.9)
	Levofloxacin	12 (0.6)	-	-	-	-	1 (0.09)	13 (0.2)
	Norfloxacin	5 (0.2)	-	-	8 (0.8)	3 (0.3)	1 (0.09)	17 (0.3)
	Ofloxacin	8 (0.4)	-	4 (0.8)	6 (0.6)	7 (0.7)	10 (0.9)	35 (0.5)
TMP-SMX	TMP-SMX	22 (1.1)	9 (1)	-	3 (0.3)	-	14 (1.2)	51 (0.8)
Tetracyclines	Doxycycline	19 (0.9)	14 (1.6)	5 (1)	29 (2.9)	19 (2)	8 (0.7)	94 (1.4)

Note: **MS**=Mahosot, **VTP**=Vientiane Province, **XK**=Xiengkhuang, **LNT**=Lunag Namtha, **SV**=Salavan, **SVK**=Savannakhet, **3FDC** (fixed-dose combination)= Rifampicin, pyrazinamide and isoniazid**, 4FDC**=Rifampicin, pyrazinamide, ethambutol and isoniazid, **GC**=Generation Cephalosporin, **TMP-SMX**= Trimethoprim-sulfamethoxazole; **BL/BLIs**=Beta-lactam/Beta-lactamase inhibitors

Figure 12: The use of antimicrobials by age group in six hospitals from 2017 to 2020



Note: **BL/BLIs**= Beta-lactam/Beta-lactamase inhibitors; **TMP-SMX**= Trimethoprim-sulfamethoxazole

Among patients who were diagnosed with pneumonia (n= 804), cephalosporins were commonly used in children aged >1 to ≤5 years at 51 (6%; 95% CI: 5-8), aged >5 to ≤15 at 10 (1%; 95% CI: 0.6-2) and adults (≥15 years) at 254 (32%; 95% CI: 28-35). While penicillins were frequently used in children aged ≤1 years at 85 (11%; 95% CI: 8-13). Aminoglycosides and penicillins were prescribed more in children than adults (p <0.0001) for pneumonia. A similar pattern was observed in patients with sepsis or skin and soft tissue infection (Table 13).

Table 13: Antimicrobial use for the top five treatment indications in patients of all ages from 2017-2020

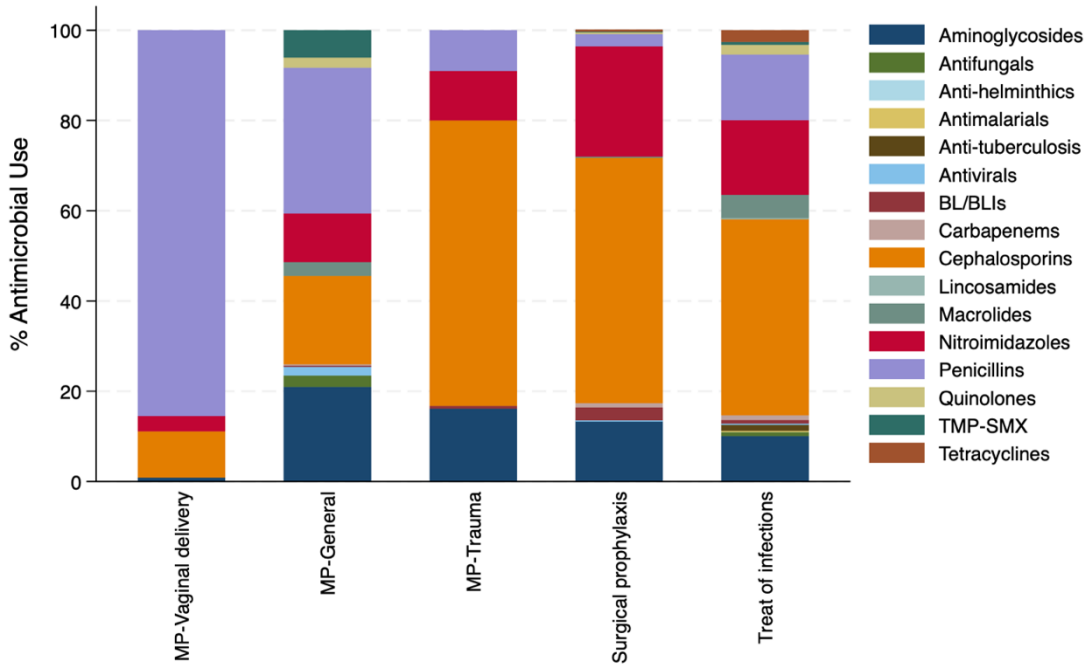
Indication	Patient age	Amino; n (%)	BL/BLI; n (%)	Car; n (%)	Ceph; n (%)	Linco; n (%)	Macro; n (%)	Nitro; n (%)	P; n (%)	Quino; n (%)	TMP-SMX; n (%)	TET; n (%)
Pneumo-nia (n=804)	≤28 days (n=34)	12 (35)	0	1 (3)	5 (15)	0	0	0	16 (47)	0	0	0
	>28 days to ≤1 year (n=182)	56 (31)	2 (1)	0	49 (27)	0	6 (3)	0	69 (38)	0	0	0
	>1 to ≤5 years (n=105)	21 (20)	0	0	51 (49)	0	4 (4)	0	29 (28)	0	0	0
	>5 to ≤14 years (n=18)	1 (6)	0	1 (6)	10 (56)	0	0	1 (6)	4 (22)	0	1 (6)	0
	≥15 years (n=465)	12 (3)	3 (1)	6 (1)	254 (55)	0	120 (26)	20 (4)	39 (8)	8 (2)	0	2 (0.4)
	p-value	*			*		*	0.002	*			
Appendi-citis (n=397)	≤28 days (n=0)	0	0	0	0	0	0	0	0	0	0	0
	>28 days to ≤1 year (n=0)	0	0	0	0	0	0	0	0	0	0	0
	>1 to ≤5 years (n=1)	0	0	0	1 (100)	0	0	0	0	0	0	0
	>5 to ≤14 years (n=48)	2 (4)	0	0	27 (56)	0	0	19 (40)	0	0	0	0
	≥15 years (n=348)	19 (5)	2 (0.6)	2 (0.6)	183 (53)	0	0	140 (40)	1 (0.3)	0	1 (0.3)	0
	p-value	1			0.81			1				
Sepsis (n=303)	≤28 days (n=172)	57 (33)	0	2 (1)	31 (18)	0	2 (1)	5 (3)	74 (43)	1 (0.6)	0	0
	>28 days to ≤1 year (n=13)	5 (38)	0	0	3 (23)	0	0	0	4 (31)	1 (8)	0	0
	>1 to ≤5 years (n=9)	3 (33)	0	0	3 (33)	0	0	0	3 (33)	0	0	0
	>5 to ≤14 years (n=14)	0	0	0	10 (71)	0	0	0	4 (29)	0	0	0

	≥15 years (n=96)	2 (2)	0	8 (8)	60 (63)	0	0	10 (10)	7 (7)	5 (5)	1(1)	2 (2)
	p-value	*			*				*			
SST infection (n=270)	≤28 days (n=15)	6 (40)	0	0	1 (7)	0	0	0	8 (53)	1	0	0
	>28 days to ≤1 year (n=13)	5 (38)	0	0	1 (8)	0	0	0	7 (54)	1	0	0
	>1 to ≤5 years (n=19)	1 (5)	1 (5)	0	3 (16)	0	0	2 (11)	12 (63)	1	0	0
	>5 to ≤14 years (n=18)	4 (22)	0	0	3 (17)	0	0	4 (22)	7 (39)	1	0	0
	≥15 years (n=205)	22 (11)	4 (2)	3 (1)	70 (34)	1 (0.5)	3 (1)	60 (29)	40 (20)	2 (1)	0	0
	p-value	0.001			0.02			0.004	*			
GI tract infection (excluded appendi-citis) (n=238)	≤28 days (n=0)	0	0	0	0	0	0	0	0	0	0	0
	>28 days to ≤1 year (n=2)	0	0	0	2 (100)	0	0	0	0	0	0	0
	>1 to ≤5 years (n=0)	0	0	0	0	0	0	0	0	0	0	0
	>5 to ≤14 years (n=6)	1 (17)	0	0	2 (33)	0	0	1 (17)	1 (17)	0	0	0
	≥15 years (n=230)	1 (0.4)	2 (1)	2 (1)	104 (45)	0	5 (2)	85 (37)	25 (11)	6 (3)	0	0
	p-value				0.31							

Note: **Amino**=Aminoglycosides, **BL/BLI**=Beta-lactam/Beta-lactamase inhibitors, **Car**=Carbapenems, **Ceph**=Cephalosporins, **Linco**=Lincosamides, **Macro**=Macrolides, **Nitro**=Nitroimidazoles, **P**=Penicillins, **Quino**=Quinolones, **TMP-SMX**=Trimethoprim-Sulfamethoxazole, **TET**=Tetracyclines, **SST**=Skin and Soft Tissue, **GI**=Gastrointestinal, * = p-value<0.0001.

Just over half (3,464/6,555 (53%; 95% CI: 52-54)) of all prescriptions were for treating infections, while 2,310/6,555 (35%; 95% CI: 34-36) were for either medical prophylaxis (886/6,555 (13%; 95% CI: 12.7-14)) or surgical prophylaxis (1,424/6,555 (22%; 95% CI: 21-23)). During the 4-year survey period, duration of all surgical prophylaxis was longer than one day. Among surgical prophylaxis prescriptions, 777/1,424 (55%; 95% CI: 52-57) were for cephalosporins (720/777 (93%; 95% CI: 91-94) were ceftriaxone), with metronidazole the next most frequent at 345/1,424 (24%; 95% CI: 22-26), and gentamicin at 192/1,424 (13%; 95% CI: 12-15). Penicillins (442/886 (50%; 95% CI: 46-53)) were the most frequently prescribed class for medical prophylaxis, of which 215/442 (49%; 95% CI: 44-53) were for ampicillin, 214/442 (48%; 95% CI: 44-53) amoxicillin, and 13/442 (3%; 95% CI: 2-5) cloxacillin (Figure 13).

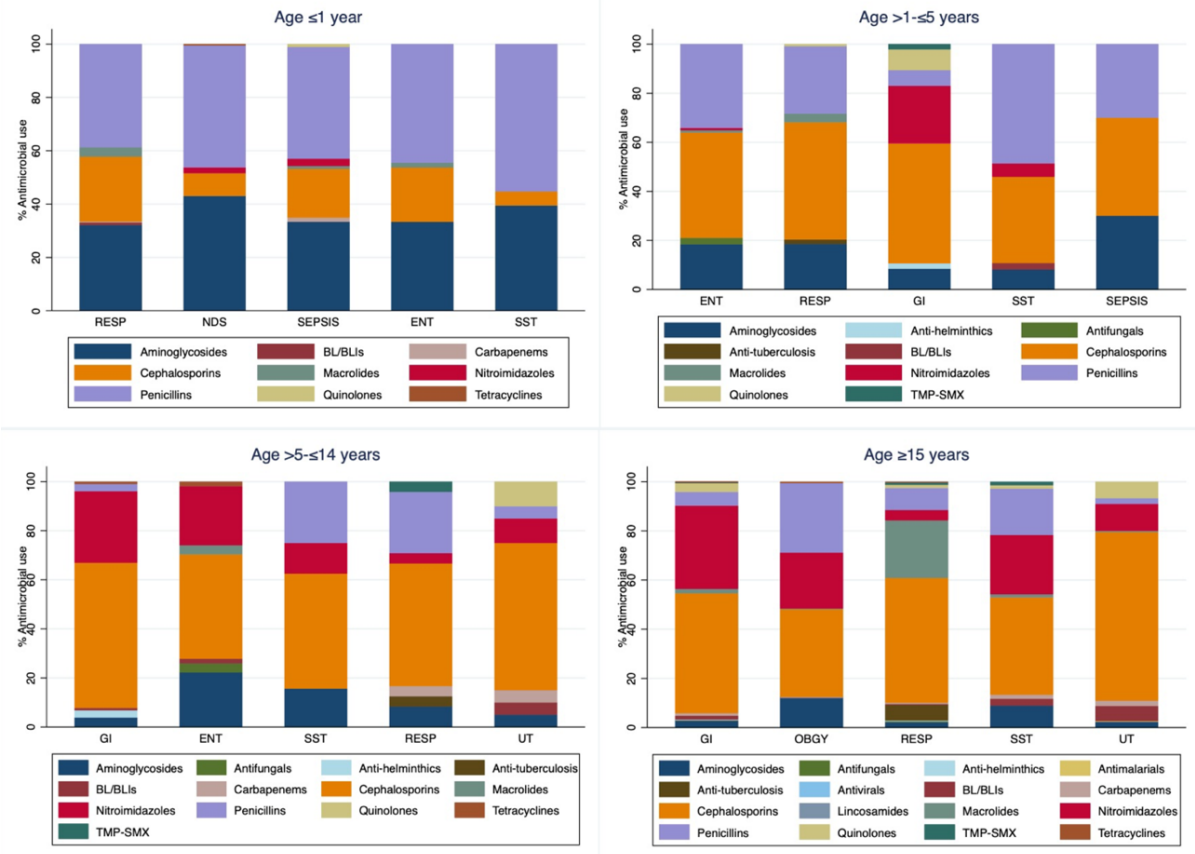
Figure 13: Antimicrobial use by type of indication in six survey hospitals from 2017 to 2020



Note: **BL/BLIs**=Beta-lactam/Beta-lactamase inhibitors; **MP**=medical prophylaxis; **TMP-SMX**=Trimethoprim-sulfamethoxazole.

The targeted organ systems of antimicrobial prescriptions varied by age. In infants (aged ≤1 year), antimicrobial prescriptions targeted the respiratory system in 230/754 (30%; 95% CI: 27-34). In older children and adults, prescriptions were most commonly for the gastrointestinal system at 103/317 (32%; 95% CI: 27-38) and 1,459/5,093 (29%; 95% CI: 27-30), respectively (Figure 14). Targeted therapy based on microbiology results was documented for 75/4,377 (2%; 95% CI: 1-2.1) patients or 88/6,555 (1.3%; 95% CI: 1.1-1.6) prescriptions. Culture results were only available for 58/75 (77%; 95% CI: 66%-86%) patients. Among those who had a culture taken, *Burkholderia pseudomallei* was identified in 28/58 (48%; 95% CI: 34-62) patients, followed by *Escherichia coli* in 8 (14%; 95% CI: 6-25), and *Staphylococcus aureus* in 7 (12%; 95% CI: 5-23). Among 75 patients with confirmed infections, tuberculosis was diagnosed in 17 (23%; 95% CI: 14-34) patients using either microscopy or GeneXpert (Table 14). Most confirmed diagnoses were made at Mahosot Hospital, accounting for 52/75 (69%; 95% CI: 58-79) patients.

Figure 14: Antimicrobial use for the top indications (by organ systems) for children and adults in six survey hospitals from 2017 to 2020



Note: **BL/BLIs**=Beta-lactam/Beta-lactamase inhibitors, **ENT**=Ear Nose and Throat, **GI**= gastrointestinal, **NDS**=non-defined site, **OBGY**=Obstetrics and Gynaecology, **RESP**=respiratory, **SST**= skin and soft tissue, **TMP-SMX**= Trimethoprim-sulfamethoxazole, **UT**= urinary tract.

Table 14: Targeted therapy based on laboratory results from six survey hospitals from 10 survey rounds during 2017 and 2020

Organism	Culture	Microscopy/ GeneXpert
Burkholderia pseudomallei	28	
Escherichia coli	8	
Staphylococcus aureus	7	
Cryptococcus spp.	5	
Klebsiella pneumoniae	3	
Pseudomonas aeruginosa	3	
Talaromyces marneffei	2	
Streptococcus anginosus	1	
Culture positive but the pathogen name was not recorded in patient's notes	1	
Mycobacterium tuberculosis	0	17
Total	58	17

Note: pathogens were isolated from various specimen types

The use of AWaRe antibiotics

The use of Access antibiotics over these four years made up 3,244/6,433 (50%; 95% CI: 49-52) prescriptions, while Watch antibiotics accounted for 3,156/6,433 (49%; 95% CI: 48-50). No Reserve group antibiotic prescription was captured in this study. However, antibiotics from the 'Not recommended" group of WHO AWaRe were prescribed to 33/4,255 (0.8%; 95% CI: 0.5-1.1) patients, including ceftriaxone-sulbactam in 30/33 (91%; 95% CI: 76-98) and cefoperazone-sulbactam in 3/33 (9%; 95% CI: 2-24).

Among the Watch group antibiotics used, 44/3,156 (1.4%; 95% CI: 1-1.9) were based on microbiology results while no prescriptions of antibiotics in the 'Not recommended' group were suggested by microbiology results. Access antibiotics were more commonly used in children 918/1,447 (63%; 95% CI: 61-66) than adults 2,326/4,986 (47%; 95% CI: 45-48) ($p<0.0001$). Access group use was highest in

infants aged ≤1 year at 578/754 (77%; 95% CI: 73-80) and at 199/384 (52%; 95% CI: 47-57) in children aged between >1 and ≤5 years, at 141/309 (46%; 95% CI: 40-51) in children aged between >5 and ≤14 years, and at 2,326/4,986 (47%; 95% CI: 45-48) in adults (Figure 15). Use of Access group antibiotics varied by hospitals in each survey and ranged from 44%-59% prescriptions. Use of WHO AWaRE 'Not recommended' antibiotics was only found in Mahosot in 33/2,029 (1.6%; 95% CI: 1.1-2.3) prescriptions (Figure 16).

Figure 15: WHO AWaRe group use by age category among inpatients in six survey hospitals from 2017 to 2020

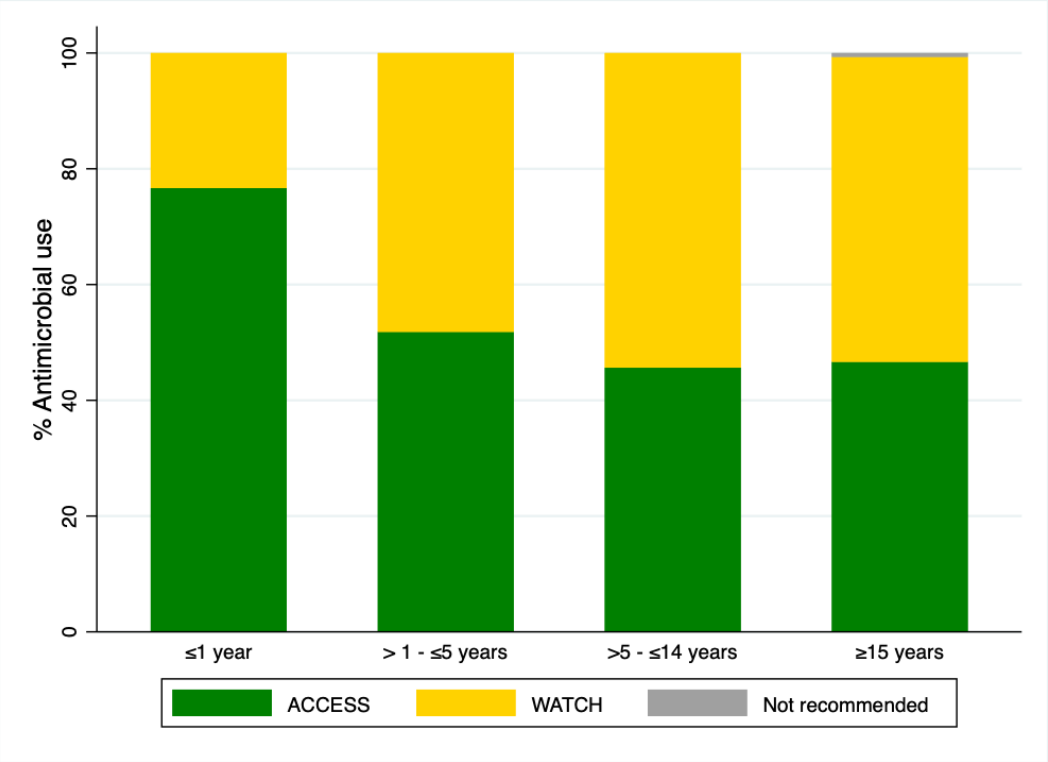
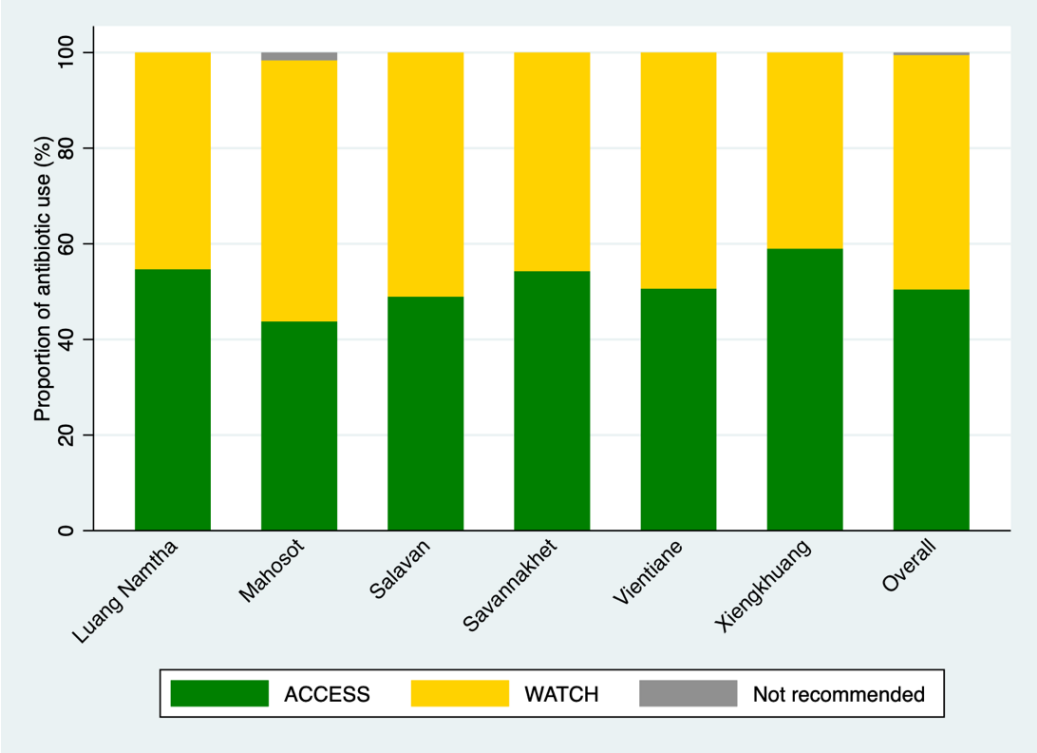


Figure 16: Overall use of antibiotics of AWaRe classification in six survey hospitals from 2017 to 2020



Adherence to the existing local treatment guidelines (pre-2021 guidelines)

Of 6,555 prescriptions, 4,397 (67%; 95% CI: 66-68) could be assessed as to whether the prescriptions adhered to the pre-2021 guidelines, whilst, 2,158 (33%; 95% CI: 32-34) were unable to be assessed because there was no guideline or prescribing indications were unknown/unclear. During this four-year monitoring period, 26% (1,136/4,397; 95% CI: 24.5-27) adhered to pre-2021 guidelines and nearly three-quarters of prescriptions (74% (3,261/4,397; 95% CI: 73-75)) did not adhere (Table 15).

Based on pre-2021 guidelines, adherence to the guidelines was more common among children aged ≤5 years at 44% (450/1,024; 95% CI: 41-47) than for older children aged >5 to ≤14 years and adults at 20% (686/3,373; 95% CI: 19-22).

Prescriptions not adherent to the guidelines were found most commonly in obstetric/gynaecology departments at 98% (637/648; 95% CI: 97-99), followed by surgery departments at 81% (1,011/1,248; 95% CI: 79-83). The five most common indications for prescriptions without guidelines to assess against, based on pre-2021 guidelines were eye, cardiovascular system, bone and joints, male genital conditions, and skin and soft tissue problems at 97% (33/34; 95% CI: 85-100), 94% (33/35; 95% CI: 81-99), 90% (162/180; 95% CI: 85-94), 89% (81/91; 95% CI: 81-95) and 76% (407/535; 95% CI: 72-80), respectively.

Table 15: Appropriate use of antimicrobials (based on pre 2021 guidelines) by age, department types and organ involved in six surveyed hospitals from 2017 to 2020

Characteristics	Adherence to guidelines; n=1,136 (26%)	Non-adherence to guidelines; n=3,261 (74%)
Age category:		
≤1	302/705 (43)	403/705 (57)
>1-≤5	148/319 (46)	171/319 (54)
>5-≤14	66/220 (30)	154/220 (70)
≥15	620/3,153 (20)	2,533/3,153 (80)
Department type:		
Intensive Care	136/409 (33)	273/409 (67)
Medicine	328/1,048 (31)	720/1,048 (69)
Obstetrics/gynaecology	11/648 (2)	637/648 (98)
Paediatrics	363/791 (46)	428/791 (54)
Surgery	237/1,248 (19)	1,011/1,248 (81)
Other	61/253 (24)	192/253 (76)
Targeted sites for prescriptions:		
Bone and Joint	4/18 (22)	14/18 (78)
Cardiovascular System	0	2/2 (100)
Central Nervous System	62/89 (70)	27/89 (30)
Ear-Nose-Throat	42/280 (15)	238/280 (85)
Ophthalmology	1/1 (100)	0
Gastrointestinal	291/1,198 (24)	907/1,198 (76)
Male genital tract	0	10/10 (100)
Obstetrics/Gynaecology	6/727 (1)	721/727 (99)
Respiratory tract	329/918 (36)	589/918 (64)
Sepsis	181/328 (55)	147/328 (45)
Skin and Soft Tissue	22/128 (17)	106/128 (83)
Urinary tract	75/366 (20)	291/366 (80)
No defined site	123/332 (37)	209/332 (63)
Indication for antimicrobial use		
Treatment of infection	1,082/2,953 (37)	1,871/2,953 (63)

Surgical prophylaxis	14/1,199 (1)	1,185/1,199 (99)
Medical prophylaxis-general	36/234 (15)	198/234 (85)
Medical prophylaxis-trauma	4/11 (36)	7/11 (64)
Medical prophylaxis-vaginal delivery	0	0

Pneumonia was the most common indication identified for antimicrobial prescription in both children and adults; the proportion of pre-2021 guideline adherence in children for which treatment guidelines were available was high, at 77% (166/216; 95% CI: 71-82) in those aged ≤1 year, 72% (76/105; 95% CI: 63-81) in children aged >1 to ≤5 years and 56% (10/18; 95% CI: 31-78) in children aged >5 to ≤14 years but it was much lower in adults at 6% (26/465; 95% CI: 4-8) ($p<0.0001$). The proportions of prescriptions adhering to the pre-2021 guidelines were 52% (157/304; 95% CI: 46-57) for sepsis, 69% (48/70; 95% CI: 56-79) for meningoencephalitis, 64% (35/55; 95% CI: 50-76) for suspected typhoid fever, 86% (67/78; 95% CI: 76-93) for suspected rickettsial infections, and 78% (52/67; 95% CI: 66-87) for melioidosis (both suspected and confirmed). Of 29 patients (all ages) with microbiologically confirmed melioidosis, antimicrobial prescriptions for two (7%; 95% CI: 0.8-23) patients did not adhere to the guidelines.

Discussion

These first assessments of AMU in Laos found that almost three-quarters of hospitalised patients were receiving antimicrobial treatment on the day of the survey. Third generation cephalosporins (42%), penicillins (17%), nitroimidazoles (16.8%), aminoglycosides (10.4%) and macrolides (3.2%) were the most commonly used antimicrobials. AMU prevalence varied across hospitals over time, and was as high as 88.4% in some hospitals on occasion. This is an alarming message for Laos. This prevalence is higher than reported from other regions of the globe. Our results show higher AMU than the overall proportion from the Global-PPS of 303 hospitals in 53 countries at 34%, in which the highest proportion was from African countries at 50%. The proportion of antimicrobial use in six East and South Asian countries (29 hospitals) was 37% and 42% in west and central Asian countries (27 hospitals in nine countries) (166). In neighbouring Thailand the proportion of hospital antimicrobial use in 183 hospitals in 2018 was 51.5% among 23,686 inpatients (176) and in Vietnam was 67.4% of 7,571 inpatients from 36 general hospitals in 2008 (171). Data from a single survey in two hospitals in Yangon, Myanmar, in 2019 showed that antimicrobial use in inpatients was 63.4% (1,255/1,980) (177). In six hospitals in Indonesia in 2019, 62% of 1,602 inpatients received antimicrobial(s) during the survey period (178). The high prevalence of antimicrobial use in Laos was similar to what has been documented in some low- and middle-income African countries recently, for example Botswana reporting AMU in 70.6% of 711 patients in one survey round in 10 hospitals (179), Uganda 74% of 1,077 patients in one survey round from 13 hospitals (180), and Nigeria 80.1% of 321 patients in one survey round in three hospitals (181).

Choice of antimicrobial varies by country. The prescription patterns in Laos resemble other LMICs (167, 171, 178, 182, 183), whilst surveys in high income countries (HICs) such as the USA, western and northern Europe showed that BL/BLIs (including, amoxicillin/clavulanic acid, ampicillin/sulbactam, piperacillin/tazobactam) were most commonly prescribed, followed by 3rdGC or 4thGC, fluoroquinolones or glycopeptides (166, 184). Chapter 1 showed that the proportion of ESBL-producing *Escherichia coli* among cultured isolates of *E.coli* is increasing year on year (141) (47% (42/90) from urine and 51% (56/109) from blood in 2020). Frequent use of cephalosporins may be contributing to increasing numbers of ESBL-producing *E. coli* in Laos. With rising levels of antibiotic resistance in Laos for some critical pathogens (141), choice of empirical antibiotic treatment must be carefully considered to ensure that patients receive the most appropriate treatment.

Antimicrobial use adherent to the local pre-2021 treatment guidelines in this study was 26%, while 33% of prescriptions could not be evaluated because of missing guidelines or unknown/unclear indications. These estimates of appropriate antimicrobial use were lower than other Asian countries. For instance, it was reported at 69.2% in Vietnam (2008), at 31.9% in Myanmar (2019), at 52.2% in Indonesia (2019), at 77.4% India (2017) assessed by choice of antibiotics (limited clarity from Vietnam and Myanmar publications) (171, 177, 178, 182). Globally, the appropriateness of antimicrobial prescriptions based on local guidelines (assessed by antibiotic choice) has been shown to range from 64.1% (Latin America) to 85.8% (North America) (166). This suggests that a key intervention to improve the appropriate use of antimicrobials in hospitals are comprehensive locally-informed antimicrobial prescribing guidelines which cover all infectious diseases, that are

regularly updated, and follow both international recommendations and local antimicrobial resistance patterns. The newly released 2021-guidelines (134, 135), and systematic monitoring and feedback on AMU in hospitals in Laos could hopefully lead to increased appropriate use of antimicrobials in Lao hospitals over time; which will be described in more detail in the next chapter. Existing evidence suggests that guidelines can improve the quality of antimicrobial prescribing. However other factors such as education, policy and public engagement also play important roles in sustainably improving the appropriateness of antimicrobial use (185-187).

Inappropriate surgical prophylaxis (99%) accounted for most inappropriate use. The latest local surgical prophylaxis guidelines were released in 1996 and have not been updated. Antibiotics of choice in the 1996 guidelines were mainly ampicillin (intravenous), cefalotin (intravenous), ± gentamicin or metronidazole; while our current study showed that the majority of the antimicrobial prescriptions for surgical prophylaxis were for ceftriaxone at 50%, whilst ampicillin accounted for 1% of prescriptions and no cefalotin prescriptions were captured. Cefazolin was commonly used in Oceania, North America, Western Europe for surgical prophylaxis, whilst ceftriaxone was used more often in Eastern and Southern Europe, Africa (166), Indonesia (178) and, as shown here, in Laos. Improving rational use of surgical antibiotic prophylaxis is challenging in low- and middle-income countries. Appropriate approaches such as comprehensive guidelines, monitoring, feedback and improving/updating physician's knowledge should be considered (188).

The WHO AWaRe list is being used increasingly in many countries to monitor the rational use of antibiotics (167, 178, 180, 189-191). The overall use of the Access

group in this study was 50%, which did not reach the WHO target recommendation (at least 60%) (189). However, the use of the Access group in infants and children reached 76.6% and 63%, respectively; which was slightly higher than equivalent data from 56 countries, which ranged from 7.8% to 61.2% (190). Use of the Access group antibiotics in adult patients in Laos was 46.7%, similar to data from Global-PPS from 69 countries in which the use of Access group ranged from 24.8% to 57.7% in adult patients (191). In Laos, 88% of the use of the 'Not recommended' group was in surgery departments and 83% was for urinary tract surgical prophylaxis. Antibiotics from this group are not included in the list of essential medicines of Laos (192). International recommendations for urologic surgical prophylaxis are fluoroquinolones or first or second generation cephalosporins, or aminoglycosides (193).

Limitation

This study has key limitations. The total duration of therapy was not captured because of the point prevalence survey methodology. There were no Lao guidelines for treatment or prevention of some infections meaning appropriateness could not be assessed in every patient. The assessment of appropriateness of antimicrobial use in this study was solely based on choice of antimicrobial(s), regardless of the dose, duration and route of administration; this could lead to an overestimate of the appropriateness of use. Data indicating antimicrobial use by hospital-acquired or community-acquired infections were not available. As we did not survey outpatient prescriptions, we do not have the complete picture of hospital antimicrobial use in the country from these results.

Conclusion

These results from repeated surveys over 41 months suggest that Laos has a consistently high prevalence of antimicrobial use in hospitals. Inappropriate use of antibiotics was highest by surgical and obstetrics/gynaecology specialties. The choice of available antibiotics to prescribe in Laos is limited. Some useful antibiotics (chloramphenicol, clindamycin or amikacin) are available but rarely used. Access to microbiology diagnosis is also limited outside Vientiane City but has been expanding to many provincial hospitals recently with the support of the Lao government and international funders. Antimicrobial stewardship activities to promote the rational use of antimicrobials in hospitals were sporadic over this survey period. As in many LMICs (194), Laos faces many challenges to its efforts to combat increasing AMR. The baseline data from this study for Laos present a good opportunity to implement appropriate evidence-based targeted antimicrobial stewardship interventions to improve the situation. These could include operational research to understand the reasons for excess use of antimicrobial prophylaxis, tailored antimicrobial stewardship education to health workers, expanding PPS nationwide with regular feedback from/to hospitals, regular updates of antimicrobial use guidelines in electronic format, and improving access to diagnostic microbiology facilities to support appropriate prescription. Reinforcement and empowerment of hospital drug and therapeutics committees and pharmacists to monitor antimicrobial use and suggest interventions to ensure compliance with guidelines would be an important step. These baseline data were an important for the development of an interventional study to promote the rational use of antimicrobials which will be described in the next chapter.

Chapter 3: Background, Rationale and Methods for Evaluating the impact of a Lao language mobile phone antimicrobial use guideline application on antimicrobial prescribing in Lao PDR

Abstract

Background:

The first Lao national comprehensive antimicrobial prescribing guidelines were released in 2021. The aim of this study was to compare the percentage of antimicrobial prescriptions adherent with these newly released prescribing guidelines delivered by a smartphone application versus the paper-based version in both in- and outpatients in six hospitals in Laos.

Methods: An open cohort stepped-wedge cluster randomized controlled 3-step trial was designed. The intervention was a smartphone application-based prescribing guideline and antimicrobial stewardship training (App-G). The reference was a paper-based version of the guidelines (PP-G). Adherence with the guidelines was defined as prescriptions using correct antimicrobial agent(s) and correct dose based on the provided prescribing guidelines. Primary outcome measurement was estimated by regular point prevalence surveys (PPS) of hospital antimicrobial use, at approximately 4-month intervals. A mixed-effects regression model, adjusting for the effect of time and clustering, was used to analyse the data.

Background, rationale and methods are presented in this chapter, with the results detailed in Chapters 4 and 5.

Background

Evidence-based guidelines have become essential tools for optimizing health delivery and patient care across global public health. More than 3,000 guidelines from many countries worldwide are available in the Guidelines International Network (GIN) library (https://g-i-n.net/), a resource created in 2002 which promotes "*trustworthy and accessible guidance for better health*". It is unclear how many antimicrobial prescribing guidelines are available in the GIN. Having antimicrobial use guidelines was one of the key assessments of the Tracking AMR Country Self-Assessment Survey (TrACSS). In 2023, TrACSS revealed that 113/177 surveyed countries (64%) had established national guidelines for appropriate use of antimicrobials (195). In high-income countries (HICs), institutional prescribing guidelines are common, in contrast to LMICs which often refer to national guidelines. Some international organisations have developed antimicrobial prescribing guidelines, for example WHO, European Centre for Disease Prevention and Control (ECDC), UK National Institute for Health and Care Excellence (NICE), Sanford, and the Infectious Diseases Society of America (IDSA) which have been widely used for several infectious diseases. Not every recommendation in these guidelines can be applied to all healthcare settings.

In many LMICs, using local evidence-based data to develop guidelines is less common and guidelines are not usually widely available (196). Added to this, some recommended antimicrobials may not be registered in LMICs. In 2022, WHO released an AWaRe antibiotic book to promote the rational use of antimicrobials worldwide in both primary healthcare and hospital settings (197). Chapter 6 discusses how the AWaRe book could be applied based on the context of Laos.

Situation of treatment guidelines in Laos

A table of treatment guidelines issued in Laos was presented earlier in this thesis (Table 9, Chapter 2, page 79-80). Two general guidelines, the National Standard Treatment Guidelines (STG) and the Pocket Book of Hospital Care for Children, provide disease management recommendations in Laos. The STG, established in 1998 with the latest edition in 2012, covers a range of conditions in medicine, surgery, and emergency care for adults and children but lacks guidance on antimicrobial stewardship and many common infections. It is currently used at the provincial and district levels and less in central levels. The Pocket Book of Hospital Care for Children, released in 2017 and translated from the WHO's 2013 edition, covers several common infectious diseases and it is widely used by paediatricians and distributed across hospitals in Laos, with initial usage assessments conducted in some hospitals in Laos (198).

In addition to the general treatment guidelines, two others have specifically addressed infectious diseases in Laos. The first, released in 2004 by the Institut de la Francophonie pour la Médecine Tropicale (IFMT), covered tropical diseases like typhoid, rickettsial infections, leptospirosis, malaria, and dengue. The second, the Mahosot Microbiology Review (MMR), reached its 7th edition in 2013 and provided antimicrobial treatment recommendations for common infections diagnosed at Mahosot Hospital's Microbiology Laboratory. Other specific treatment guidelines in Laos focus on diseases like malaria, tuberculosis, STIs, HIV/AIDS, kidney infections, infections in cancer patients, Covid-19, and hepatitis B and C. In 2020, the first Lao National antimicrobial prescribing guidelines for both children and adults were introduced, which will be discussed later in this chapter.

Regularly updating guidelines is uncommon in Laos due to various factors, including limited human and financial resources. Formal documentation of the guideline development process in Laos is currently lacking. Typically, a committee of senior clinicians and specialists oversees the process, with occasional involvement from external experts in a technical working group. A consulting team, often consisting of department or hospital directors, also guides the development process.

The timeline for guideline development in Laos is often unclear. Most treatment guidelines are national and endorsed by the MoH, with only a few being institutional, such as IFMT guideline, protocols d'antibioprophylaxis en chirurgie, and nephritis treatment guidelines. Developers' names are usually listed in the guidelines. These guidelines are predominantly available in printed format. The number of printed copies varies depending on the available support. In practice, a small number of copies of guidelines are distributed to each hospital, resulting in limited access for clinicians and prescribers, and awareness of the existence of the guidelines among hospital staff can be low. Most electronic versions (PDF) of guidelines are not readily accessible to healthcare providers. Requests for access typically need to be made directly to the relevant departments.

The need and the development of antimicrobial prescribing guidelines for Laos

Background of the guidelines

The National Strategic Plan on Antimicrobial Resistance in Laos, 2019-2023 was released in 2019 (199). The plan focused on five main objectives (based on the WHO Global Action Plan (11), including: 1. improving awareness and understanding of AMR, 2. strengthening the AMR surveillance system, 3. improving infection

prevention and control, 4. optimizing the use of antimicrobial agents in human and animals, and 5. improving coordination and budget support (199).

Strategic objective four comprised seven action plans, including: 4.1. Establish, update and enforce laws and regulations on antibiotic use, 4.2. Monitor antimicrobial consumption and AMU in humans, animals and animal feed, 4.3. Develop and revise an standard operating procedure (SOP) on antimicrobial use, 4.4. Provide capacity building on Rational Use of Drugs (RUD)/AMS for medical doctors, veterinarians and pharmacists, 4.5. Revitalize Drug and Therapeutics Committees (DTCs) to strengthen rational use of antimicrobials in hospitals, 4.6. Build capacity to check the quality of antimicrobials in Laos, and 4.7. Improve AMS to ensure the quality, efficacy, and safety of antimicrobials (199). This thesis focuses on action points two and three of Strategic objective four.

Before December 2020, there were no government-approved Lao evidence-based antimicrobial prescribing guidelines. A large survey of 386 doctors from 25 hospitals in three provinces and the capital in 2012 revealed that 65% of respondents favored local antimicrobial prescribing guidelines over international ones. Nevertheless, 22% noted that the existing local treatment guidelines made their decision-making process regarding antibiotic prescription (104) more challenging but the researchers did not provide the detailed discussion on this point. LOMWRU conducted a small survey on the need for antimicrobial prescribing guidelines among Lao Infectious Disease Society members in Laos in 2019; 70 Lao doctors from either central or provincial hospitals reported the main challenges to making decisions on the choice of antimicrobials were lack of access to a microbiology laboratory 31/70 (44%), no suitable antimicrobial prescribing guidelines 30/70 (43%) and poor availability of some antimicrobial agents 30/70 (43%). The majority of doctors used Lao treatment

guidelines 58/70 (83%) and guidelines from neighbouring countries 40/70 (57%) with a small proportion using European or US treatment guidelines 16/70 (23%). Only 17/70 (24%) had used any antimicrobial prescribing guideline/treatment guidelines delivered by a mobile application. Of these, 41% used the Medscape App (200) [LOMWRU, unpublished data].

Guideline development process and contents

The discussion regarding the necessity of having antimicrobial prescribing guidelines in Laos in 2019 centred on several factors, including the absence of antimicrobial prescribing guidelines based on local scientific evidence of AMR and AMU, as well as language barriers (the majority of available international guidelines are in English). Moreover, the initiative aimed to fulfill action three of National strategic objective four.

The guideline development came out of an agreement between the Department of Healthcare and Rehabilitation (DHR) and the Department of Communicable Disease Control (DCDC) within the Lao MoH, along with other stakeholders. Dr. Vilada Chansamouth, as a government staff member and a member of the Lao Infectious Diseases Society, was appointed by MoH to draft the initial version (paediatric and adult versions), and subsequently facilitated discussions within national and external experts in several technical meetings, ultimately leading to the finalization of the guidelines under the supervision of the DHR, MoH.

National experts included specialists in infectious disease, obstetrics & gynaecology, surgery, paediatrics, emergency medicine/ICU, and microbiology from different central hospitals, and committees such as the Lao Infectious Diseases Society, the paediatric committee and obstetrics & gynaecology committee. External experts included experts in microbiology, infectious diseases,

medicine quality and public health from the United Kingdom (UK), who served as technical consultants during the development of the guidelines. They had experience of working in LMICs and were familiar with the healthcare landscape in Laos for decades. The guidelines also included the names, positions, and affiliations of both national and international consultants. The timeline from the initiation of guideline development to its final approval for use by the DHR was almost two years (from Jan 2019 to December 2020).

The main objectives of developing these guidelines were to support and guide the rational use of antimicrobials to optimize treatment and prophylaxis of infectious diseases and to control the spread of antimicrobial resistance in Laos. Most recommendations were for empiric treatment before laboratory results were available. Guidelines were developed based on common infectious disease pathogens and syndromes for which local data were available, common causative pathogens and antimicrobial susceptibilities for some available pathogens are provided as a guide. This guideline also referred to some specific Lao treatment guidelines (to avoid duplication) and international prescribing/treatment guidelines. The guidelines were separated into paediatric and adult guidelines for ease of use (Figure 17). Common and important infectious diseases were arranged by involved organ systems. Each infectious disease section included causative pathogen(s) of the diseases, choices of antimicrobial regimen (primary and alternative), doses, duration and important notes on allergy or toxicity or to help guide treatment. In the adult guideline, there were 90 infectious disease topics included, covering treatment of infections, along with ten topics addressing surgical prophylaxis and two focusing on medical prophylaxis (e.g., infective endocarditis or asplenia). Meanwhile the paediatric guideline included 66 infectious disease topics for treatment of infection,

eight for surgical prophylaxis and five for medical prophylaxis. Both paediatric and adult guidelines included an antibiotic stewardship section and a section on dose-adjustment in the event of renal impairment. Additionally, the guidelines included a list of notifiable diseases and sources of information (Appendix 5). Both paediatric and adult antimicrobial prescribing guidelines were transferred to the MicroGuide mobile phone application platform (Figure 18).

Figure 17: Paediatric and adult antimicrobial prescribing pocketbook guidelines

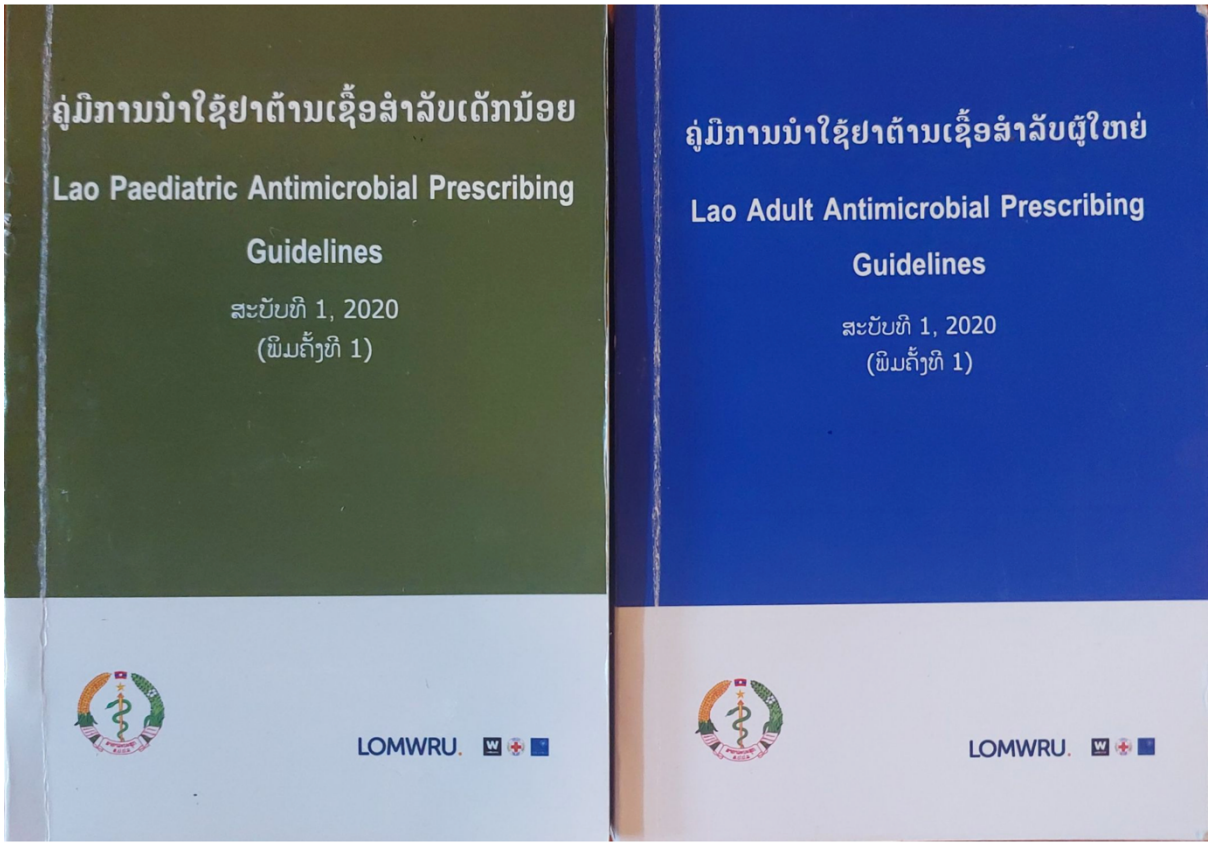
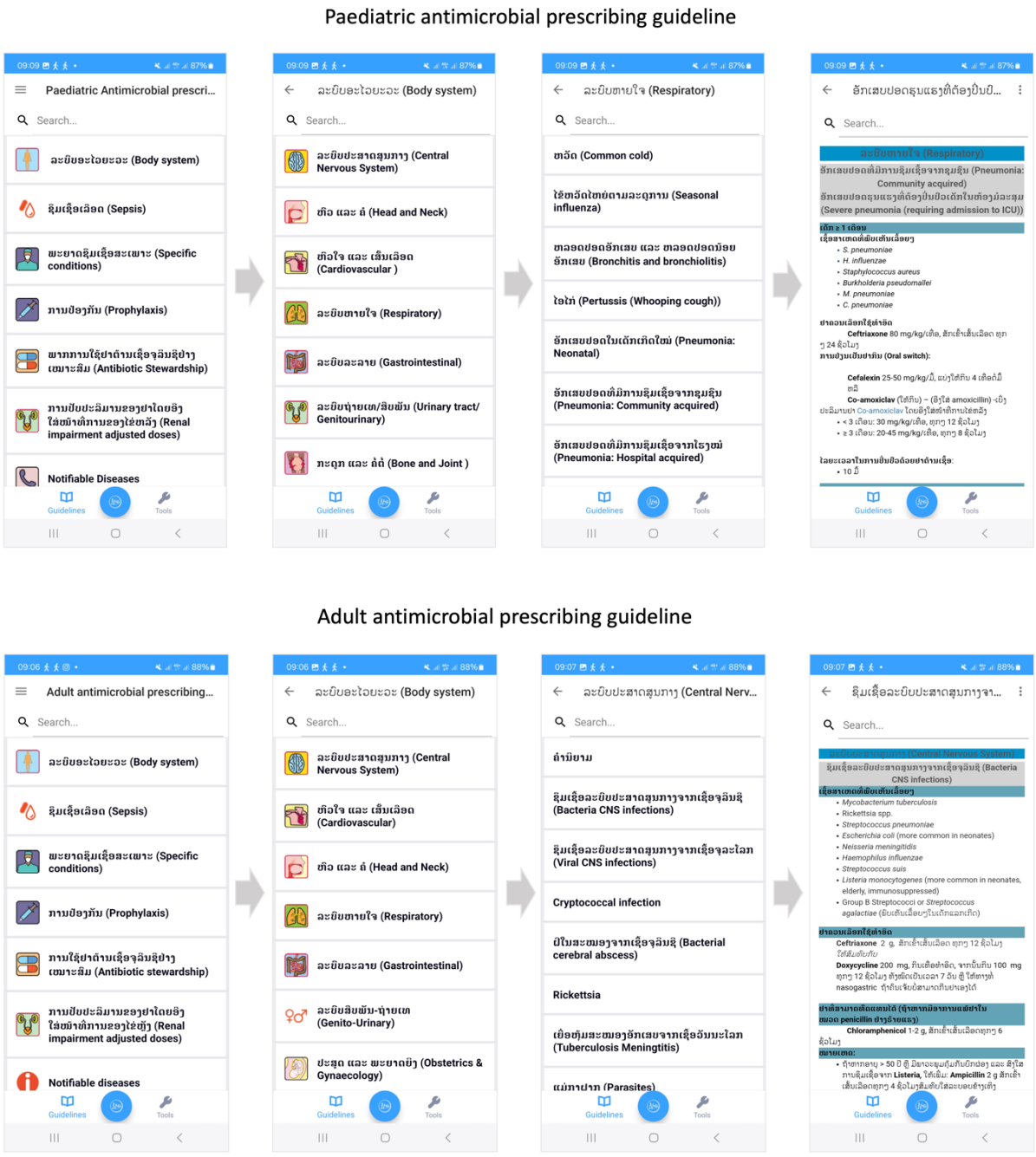


Figure 18: Paediatric and adult antimicrobial prescribing guideline mobile phone application (MicroGuide)



Overview of the use of mobile phone applications in the healthcare sector

Mobile health or mHealth is widely used across various healthcare domains, such as diagnostics and clinical decisions, delivery of medical education, chronic disease management or health tracking (201). WHO defines mHealth as "*Medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, Personal Digital Assistants (PDAs), and other wireless devices*" (202). By 2022, the number of global smartphone network subscriptions was approximately 8.36 billion (203). However, the exact number of healthcare mobile phone applications available worldwide remains uncertain. By the end of 2022, there were approximately 41,517 and 54,546 healthcare or medical applications available on the Apple app store and the Google play store, respectively (204).

A systematic review of healthcare applications for mobile phones, published in 2012 (data from 2003 to 2011), identified 83 applications from 55 peer-reviewed articles. Among 83 applications, 57 targeted healthcare professionals (e.g., disease diagnosis, drug reference, medical calculator), 11 were for medical or nursing students and 15 were for patients (i.e., disease management with chronic conditions). Among disease diagnosis applications, some infectious disease handbooks are also available in the format of mobile phone applications for example, Johns Hopkins Antibiotic Guide (205), Sanford Guide to Antimicrobial Therapy (206), and Harrison's Manual of Medicine (207). UpToDate (208) was commonly mentioned in several articles as a useful tool to support patient-management decisions (209). While these apps offer great benefits, most require a subscription for full access, which can be costly for users in many LMICs. The total number of mobile phone applications related to clinical practice for physicians is

unknown but is likely to have increased steadily since 2012, particularly since the advent of large-language models.

A systematic review of 41 studies to understand how physicians used mobile phone or tablets in their clinical settings from 2012 to 2021 showed that 80% of participants (ranged from 36-3,306 participants/study) used their mobile phones during their clinical practice and that use has been increasing (210). Overall, the purposes of mobile phone usage within physicians' clinical practice were for communication and consulting, documentation and monitoring (e.g, information and time management, patient monitoring), diagnostic and therapeutic decision support, and medical education and training. Several applications were available such as UpToDate (208), Medscape (200), Epocrates (211), MedCalc (212), Laborwerte (213), Dynamed (214). The most common use of mobile phone devices was for searching for drug information, for example: dosages, preparation, and indications for use. Following this, accessing medical calculators emerged as another common use (210, 215, 216). Accessing electronic guidelines or handbooks via mobile phone was also emphasized. However, most reports came from HIC settings (210).

There is growing interest of the use of healthcare mobile phone applications in LMICs, especially since the Covid-19 pandemic (217-219). Use of mHealth in clinical management has been reported in maternal and neonatal healthcare, sexual and reproductive health, antimicrobial stewardship and chronic condition management (218, 220, 221). Mobile phone applications have gained attention across various medical fields due to their convenience, ability to support clinical decision-making, enhanced documentation accuracy, and optimized workflow (210, 215, 216). However, data security, negative impact on physician-patient

interactions, and quality of the application or accessibility remained concerns (210, 215).

Evidence of antimicrobial prescribing guidelines mobile phone applications improving antimicrobial prescribing

While traditional paper-based guidelines are informative, they often suffer from limited accessibility, bulkiness and an inability to provide real-time updates. In contrast, mobile phone applications offer a promising solution by providing healthcare professionals with instant access to the latest guidelines, recommendations, and decision-support tools. Recent studies have highlighted the potential of mobile phone applications to improve adherence to clinical guidelines across various healthcare settings. (222-230).

To date, nine publications have examined whether the use of mobile phone applications enhances prescription practices and adherence to prescribing guidelines. The majority of these studies employed a pre- and post-intervention design (Table 16). Charani et al. (2017) conducted an interrupted time series study spanning from 2010 to 2014 among hospitalized patients in one UK hospital, comparing a three-year period before and after the implementation of the IAPP app (Imperial College Antibiotic Prescribing Policy Application) (231). This app contained local therapeutic antimicrobial guidelines to enhance guideline adherence in both surgical and medical wards. Following its introduction, the overall increase of guideline adherence was improved in the surgical wards 6.6% (95% CI: 0.15 to 13.10), but it was not in the medical wards at 6.5% (95% CI: -1.25 to 14.20) in medical wards (223).

In Bangladesh, Haque et al. (2017) demonstrated a significant increase in guideline adherence using the Rehydration calculator app in patients with acute watery diarrhoea, when focusing on azithromycin as the recommended antibiotic for cholera. Adherence rose from 13% before the app implementation to 87% ($p<0.0001$) afterwards at district hospital level. Additionally, prescriptions for non-recommended antibiotics sharply decreased, with ciprofloxacin dropping from 70% to 5% ($p<0.0001$) and metronidazole from 40% to 0% ($p<0.0001$) (224). Rambaud-Althaus et al. (2017) reported positive outcomes with the ALMANACH (Algorithm for the Management of Childhood illness) decision support app in a 2011 cluster-randomized controlled trial conducted in primary healthcare outpatient settings in Tanzania. App use was significantly associated with reduction in the proportion of children prescribed antibiotics, with the intervention groups showing prescription rates of 26% and 25%, compared to 70% in the control group (227).

Between 2010 and 2015, Tuan et al. (2017) observed the effects of a local therapeutic antimicrobial guideline app on meropenem consumption and susceptibility of Gram-negative bacilli bacteria in a Brazilian hospital. Twelve months after the app's implementation, meropenem consumption significantly decreased ($p=0.007$), and susceptibility patterns to meropenem improved from 73% to 83% ($p<0.05$) (228). Similarly, Antonello et al. (2019) reported improvements in antimicrobial prescriptions for pyelonephritis in pregnancy at a Brazilian hospital. The ATB Fêmina app (232) facilitated correct antimicrobial use, which increased from 74.4% in 2010 to 100% in 2015 after its introduction (222).

In New Zealand, multiple studies by Yoon et al. (2019; 2023), and Primhak et al. (2023) evaluated the SCRIPT (Standardized Clinical Resource to Improve Pathway

Targets) app's effectiveness. This app, which incorporates local therapeutic antimicrobial guidelines, showed significant improvements in guideline adherence for community-acquired pneumonia (CAP) treatment and overall antibiotic prescriptions (226, 229, 230). Yoon et al. (2019 and 2023) described guideline adherence among patients with urinary tract infection (UTI) and CAP. Antimicrobial prescription adherence to the guideline six-months post app implementation described in Yoon et al. (2019) showed an improvement of 19-27% ($p=0.04$). In addition, the guideline adherence among severe pneumonia patients increased from 7% to 29% ($p=0.03$) post intervention. Adherence to prescribing guidelines for UTI treatment remained unchanged before and after intervention implementation (229). When focusing on sustained improvements, results from Yoon et al. (2023) revealed that guideline adherence among patients with CAP continuously increased from 23% at baseline to 31% at 3-months post-app, peaking at 34% at 12 months before stabilizing at 31% at month-24 (230). Primhak et al. (2023) continued to evaluate the SCRIPT app, focusing on hospitalized paediatric patients. The researchers collected data at baseline, 4-months and 12-months post app implementation. The findings showed that the adherence increased from 69% at baseline to 84% at four months ($p<0.001$) and to 81% at twelve months ($p<0.001$). This improvement was seen as early as four months post-app introduction in medical (78%-90%, $p=0.005$) and emergency departments (59%-79%, $p=0.006$), with significant improvements in surgical prescribing observed at twelve months (63%-76%, $p=0.045$) (226).

A recent study by Luedtke et al. (2023) evaluated the GADSA app (Gamified Antimicrobial Stewardship Decision Support App) in Nigerian hospitals, focusing on surgical antibiotic prophylaxis (SAP) practices of surgeons. The findings revealed

that the app significantly improved surgeons' compliance with SAP guidelines, particularly in determining the necessity of SAP. The majority of surgeons (89%) made the correct decision regarding SAP administration both before and after the app's implementation. Among those who initially made inappropriate decisions, there was a 10% improvement in making the correct decision post-app implementation. However, the overall correct choice of antibiotics only improved by 6%. For example, out of 85 surgeries where first-generation cephalosporins were recommended, only 4 surgeries adhered to the guidelines (225).

The evidence suggests that introducing an antibiotic guideline via a mobile phone application can increase adherence to antimicrobial prescription guidelines compared to paper-based guidelines among prescribers. Additionally, it positively impacts antibiotic stewardship by reducing costs, altering microbiological susceptibilities, and lowering antimicrobial consumption (228). Various apps' implementation did not consistently show significant improvements, and improvement was not always sustained across several studies (223, 225, 227, 230).

Table 16: Research publications on the impact of antimicrobial prescribing guidelines delivered by mobile phone applications on guideline uptake and prescribing improvement

Author (year); study period	Setting/ Country	Study design/ control-intervention	App name/ content	Target	Definition of adherence	Guideline adherence improvement
Charani et al. (2017); 2011 (223)	Hospital, hospitalized patients/ United Kingdom	Interrupted time series (3 years pre-intervention and 3 years post-intervention: baseline, 6, 12, and 24-month post app implementation	IAPP [a]/ Local therapeutic antimicrobial guidelines, calculator	Improvement in adherence to antibiotic prescription guidelines in surgery and medicine wards	Correct choice of antibiotic	There was a minor change in the percentage of guideline adherence in the surgery ward post-intervention: 6.71% (95% CI: -0.06-13.48) at month 6, 6.8% (95% CI: -1.6-15.2) at month 12 and 6.96% (95% CI: -6.55-20.48) at month 24. However, guideline adherence improvement was not observed in the medicine wards with 4.7% (95% CI: -3.55-12.96) at month-6, 2.93% (95% CI: -7.96-13.83) at month-12, -0.61% (95% CI: -19.21-18)) at month-24 after the implementation of the IAPP.
Haque et al. (2017); 2015 (224)	Hospital, hospitalized patients/ Bangladesh	Pre and post intervention (6 week-pre-intervention & 6 weeks intervention with 10-day post-intervention follow-up)	Rehydration calculator [a] / Therapeutic WHO guideline, calculator	Impact of mobile app on enhancing diarrhoeal disease management with a focus on azithromycin prescriptions	Correct choice of antibiotic	The proportion of prescriptions adhering to the guidelines for azithromycin increased significantly from 13% pre-intervention to 87% post-intervention ($p< 0.0001$). Besides this, the prescriptions for non-recommended antibiotics decreased significantly: ciprofloxacin prescriptions dropped from 70% pre-intervention to 5% post-intervention ($p<0.001$), and metronidazole

						prescriptions fell from 40% pre-intervention to 0% post-intervention (p<0.001).
Rambaud-Althaus et al. (2017); 2011 (227)	Primary healthcare, outpatients/ Tanzania	Cluster-randomized controlled study (standard practice vs paper ALMANACH vs ALMANACH smartphone)	ALMANACH [b]/ clinical algorithm for management of childhood illness	Improvement of rational antimicrobial prescriptions for childhood illnesses	NA	The percentage of children prescribed antibiotics was significantly lower in the intervention groups compared to the standard practice group. In the standard practice group, 70% of children received antibiotics (range: 60-85%). While, the paper-based intervention group had a prescription percentage of 26% (14-37%, OR 0.4 (95% CI: 0.2-0.6)), and the electronic intervention group had a rate of 25% (17-33%, OR 0.3 (95% CI: 0.2-0.5)).
Tuan et al. (2017); 2014 (228)	Hospital, hospitalized patients/ Brazil	Pre and post intervention (12 months before and 12 months after the app implementation)	NA/local therapeutic antimicrobial guidelines & susceptibility results	Improvement of antibiotic prescriptions and assessment of the antimicrobial resistance patterns	NA	Following the implementation of the app, meropenem consumption significantly decreased (p=0.007), as did piperacillin/tazobactam consumption (p=0.016). Additionally, the susceptibility of Gram-negative bacilli to meropenem improved from 73% to 83% (p<0.05)
Antonello et al. (2019); 2010-2015 (222)	Hospital, hospitalized patients/ Brazil	Cross-sectional	ATB Fêmina [a] /local diagnostic & therapeutic antimicrobial guidelines	Improvement of antimicrobial prescriptions for pyelonephritis in pregnancy	Correct choice, route, dosage and interval between doses	Improvements were observed in the appropriate use of antimicrobials over the study periods. Completely appropriate prescription increased from 74.7% in 2010 to 91.4% in 2013, reaching 100% in 2015, among pre-guideline period, introduction of the guideline, and after the app implementation, respectively.

Yoon *et al*. (2019); 2016 (229)	Hospital, hospitalized patients/ New Zealand	Pre and post intervention (initial antibiotic prescription(s) in the first 24 hours of admission 6 months before and after the app implementation)	SCRIPT [a] /Local therapeutic antimicrobial guidelines	Improvement of guideline adherence among inpatients with community-acquired pneumonia (CAP) or urinary tract infections (UTI)	Correct choice, dosage and route	Adherence to antibiotic guidelines for CAP improved from 19% (37/199) to 27% (64/237) during the intervention period (p=0.04). Adherence in severe pneumonia cases increased significantly from 7% in the baseline period to 29% in the intervention period (p=0.03). The guideline adherence among patients with UTI remained unchanged pre- and post-intervention.
Luedtke et al. (2023); 2019 (225)	Hospital, hospitalized patients/Nigeria	Longitudinal study	GADSA [a]/ W HO and Sanford prescribing guideline on surgical antibiotic prophylaxis (SAP)	Improving surgical antibiotic prophylaxis practice	Decision to give SAP, choice of antibiotic and duration	Surgeons' adherence to guidelines showed an improvement after the app's implementation. The decision to administer SAP improved by 10%, the choice of antibiotics for SAP improved by 6%, and the duration of SAP improved by 5%.
Yoon et al. (2023); 2016-2018 (230)	Hospital, hospitalized patients/ New Zealand	Pre and post intervention, retrospective (baseline=6 months before app implementation vs immediately post-app vs 12-month post-app vs 24-month post-app)	SCRIPT [a] /Local therapeutic antimicrobial guidelines	Long-term impact of the app on antibiotic prescriptions adherent to the guidelines in patients with community-acquired pneumonia	Correct choice, dosage and route	Adherence to antibiotic prescription guidelines was fluctuated after the app implementation. At baseline, 23% (46/200; 95% CI: 17.4-29.5) of prescriptions adhered to the guidelines. This increased to 31% (73/237; 95% CI: 25-37.1) at 3 months and 34% (69/200; 95% CI: 27.9-41.5) at 12 months, before slightly declining to 31% (62/200; 95% CI: 24.7-37.9) at 24 months.
Primhak et al. (2023);	Hospital, hospitalized	Pre and post intervention (Baseline vs 4	SCRIPT [a] /Local therapeutic	Improvement of guideline adherence	Correct choice,	Adherence to the guidelines showed a significant increase, rising from 47% (95% CI: 41.2-51.9) initially to 58%

2019 (226)	patients/ New Zealand	months and 1 year after app implementation)	antimicrobial guidelines	relating to infectious diseases in paediatrics and adults	route and dosage	(95% CI: 52.6-63.1, p= 0.003) after four months (p < 0.0001). This improvement was sustained after one year, with adherence remaining high at 62% (95% CI: 15.1-23.9, p<0.001).

Note: [a] converting from existing paper-based guideline to mobile phone app format, [b] brand new guidelines, **ALMANACH**=Algorithm for the Management of Childhood illness, **CI**=Confidence Interval, **GADSA**=Gamified Antimicrobial Stewardship Decision Support, **IAPP**=Imperial College Antibiotic Prescribing Policy Application, **NA**=Not Applicable, **OR**=Odds Ratio, **SCRIPT**=Standardized Clinical Resource to Improve Pathway Targets.

Study rationale

As approximately 90% of Lao doctors from provincial hospitals have smartphones [unpublished data], this could make apps a more attractive option for physicians compared to bulky handbooks. However, this is a novel approach for Laos, as the local antimicrobial prescribing guidelines were released fairly recently and delivering a guideline via mobile phone applications in Laos is new. As reviewed above, evidence indicates that antibiotic guidelines on a mobile phone app can increase guideline adherence among prescribers and reduce unnecessary antibiotic use in hospitals. This section describes the design and methods of a stepped-wedge cluster randomized controlled trial comparing antimicrobial prescribing guidelines delivered by paper-based and mobile phone-based guidelines.

Study objective

Primary objective

To compare the proportion of antimicrobial prescriptions adherent with prescribing guidelines delivered by mobile phone application (app) versus paper-based prescribing guidelines in both in- and outpatients in six general hospitals in Laos

Secondary objectives

1. To compare the percentage of patients admitted to hospital receiving an antimicrobial prescription before and after introduction of the paper-based prescribing guidelines; and the mobile phone app prescribing guidelines + AMS training
2. To compare the change in antimicrobial defined daily doses (DDDs) in both in- and out patients after introduction of paper-based versus mobile phone

app prescribing guidelines plus antimicrobial stewardship (AMS) training to prescribers

3. To compare the change in proportion of inpatients and outpatients receiving antimicrobials via the intravenous (IV) route between paper-based and mobile phone app prescribing guidelines + AMS training
4. To compare the AMS knowledge level of the prescribers before and after prescribing guidelines delivered by mobile phone app and AMS training
5. To compare the prescriber satisfaction with/acceptability of paper-based prescribing guidelines versus mobile phone app prescribing guidelines

Methods

Study design

A stepped wedge cluster randomized controlled trial (SW-CRCT) was conducted in six central/provincial hospitals across Laos. SW-CRCT was chosen as the most appropriate design in the Lao context because it required fewer sites than a parallel cluster trial, but had similar observational periods for control and intervention phases. As the interventions were delivered by one team travelling to each cluster in turn, implementing in stages was more practical. The trial was registered at clinicaltrials.gov (NCT04914793).

Study sites

Six hospitals (two referral (200-450 beds) and four provincial hospitals (60-100 beds) were purposively selected based on their capacity, location, and previous participation in our PPS program (Chapter 2) (Table 17 and Figure 9 – Chapter 2, page 75).

Table 17: Stepped wedge cluster randomized controlled trial (SW-CRCT) study sites

Study sites	**Mahosot (MS)**	**Vientiane Province (VTP)**	**Xiengkhuang (XK)**	**Luang Namtha (LNT)**	**Salavan (SV)**	**Savannakhet (SVK)**
Region	Centre	Centre	North	North	South	South
Location (above mean sea level)	17º95'N 102º 61'E, 268m	18º 47'N 102º48'E 497m	19°27'N 103°10'E, 1,150m	21°00'N 101°24' E; 570m	15°43'N 106°25' E; 184m	16°55'N 104° 74'E; 726 m
Type of hospital	Central referral	Provincial	Provincial	Provincial	Provincial	Regional
Number of beds	450	100	150	50	70	200
Number of staff	968[a]	211[b]	305[c]	117[b]	191[b]	293[c]
Physician	222	30	66	18	30	60
Number of wards and OPD	18 wards and 1 main OPD and small number of OPDs within in-patient wards	6 wards and 1 OPD	11 wards and 1 main OPD and a small number of OPDs within in-patient wards	6 in-patients wards and 1 OPD	7 in-patients wards and OPDs within in-patient wards	9 wards and 1 main OPD and small number of OPDs within in-patient wards

Note: [a] data from 2020, [b] data from 2018, [c] data deom 2019, **N**=North, **E**=East, **OPD**=Outpatient Department

Sample size and power calculation

A PPS of hospital antimicrobial use in four general hospitals in Laos in 2017 showed 13% compliance to Lao treatment guidelines but previous guidelines did not contain much information on antibiotic prescribing, and therefore reliable baseline data were lacking. The sample size of six hospitals was estimated assuming 30% of antimicrobial prescription adherence with the paper-based prescribing guideline (reference), and assuming 0.05 intra-cluster correlation coefficient. This gave 80% power to be able to detect a 15% difference in adherence after introduction of the mobile phone app prescribing guidelines the at the 0.05 significance level.

Randomization and blinding

The six participating hospitals (cluster) were divided into three pairs based on the geographical location and convenience for conducting the surveys. The first paired hospitals included two hospitals from the north of Laos (LNT and XK), the second pair included hospitals in the centre (MS and VTP). The third pair included two hospitals from the south of Laos (SVK and SV).

As there were only three orders (sequence) to be assigned, hospitals were assigned to one of three start dates to have access to the study intervention using simple random sampling. Names of three paired hospitals (LNT+XK, MS+VTP and SVK+SV) were written on three different paper slips (similar paper size and paper texture). All slips were folded to the same size and put in a non-transparent container, covered firmly and mixed well. A person who was not involved in study implementation was asked to pick out a paper slip one by one and read out to the principal investigator (PI) and a co-investigator.

Neither hospitals nor investigators were blinded to the introduction of the intervention.

Study intervention and reference

Before starting the project, the PI, co-investigators and research team visited each participating hospital to discuss the project's planned objectives and activities during 16 months with the directors. These six hospitals had already participated in PPS of antimicrobial use, led by the same research team of this project. Hospital staff were informed about the study by the PI and the directors of the hospitals before starting the project and all prescribers in participating hospitals were encouraged to participate in the training and surveys.

1. Pre-guideline

Antimicrobial prescription data (see Appendix 6 for in- and outpatient PPS CRFs) were collected at month-0 as baseline data with the report (see Appendix 7 for PPS report) provided approximately one month later. Then prescribers from each participating hospital were asked to complete an antimicrobial stewardship (AMS) knowledge survey (see Appendix 8 for AMS knowledge survey questionnaires) and pre-guideline prescribing behaviour survey (Appendix 9). These pre-guideline data were used to compare with both paper-based guidelines (PP-G) and app-based guideline (App-G) periods.

2. Reference (PP-G)

After baseline data collection, paediatric and adult versions of the PP-G (Figure 17) were distributed to all prescribers at participating hospitals, followed by a session focused solely on guideline use (see Appendix 10.1 for training materials). No

training on diagnosing infectious diseases or prescribing antimicrobials was provided. Once the PP-G was introduced, all six hospitals officially entered the reference (PP-G) period. The research team did not influence any antimicrobial prescribing decisions. The guidelines included the PI's contact details for any needed clarifications. Regular PPS and a feedback survey on the PP-G were conducted just before each hospital transitioned to the intervention (App-G) period (at months 4, 8, and 12 after PP-G introduction). See activities during PP-G period in Figure 19.

3. Intervention (App-G)

The interevention included introduction of the app-based guidelines, accompanied by a training of their use (Appendix 10.2) and an AMS session (Appendix 11). This set of activities was collectively referred to as "App-G" for simplicity. All activities during the App-G period are found on Figure 19.

Antimicrobial prescribing guidelines mobile phone application (MicroGuide)

The App-based version of the guidelines (Figure 18) was installed on the personal smartphones of local prescribers by the PI and a research assistant. The project did not provide smartphones to physicians who did not already have one, which affected fewer than 10% of physicians in provincial hospitals (unpublished data). The contents of the guidelines in the application were the same as the pocketbook versions but used a different interface. The process to finalize the mobile phone application for the prescribing guidelines took approximately one month. MicroGuide was launched in 2013 and has been adopted by 114 medical organizations, with more than 100,000 users in 173 countries. MicroGuide is an offline application, free-of-charge for individual users, although institutions pay license and maintenance fees. There are pricing concessions for LMICs. The app

can monitor the number of users and which guidelines are being accessed. This is the first mobile phone application-based guideline for antimicrobial prescribing available in Laos. In 2024, the MicroGuide platform changed its name to Eolas Medical.

Antimicrobial stewardship (AMS) training

The aim of the AMS training was to increase knowledge and awareness of rational antimicrobial prescription among Lao prescribers. AMS training sessions were given to all prescribers in participating hospitals when they first entered to the intervention phase. This session was given alongside an introduction of the app-based guideline. The training details were based on the existing information in the therapeutic and prophylactic antimicrobial prescribing guidelines. The main part of the training focused on good practices of antimicrobial prescription. Prescribers could also access information on AMS in both PP-G and App-G by themselves (Appendix 11).

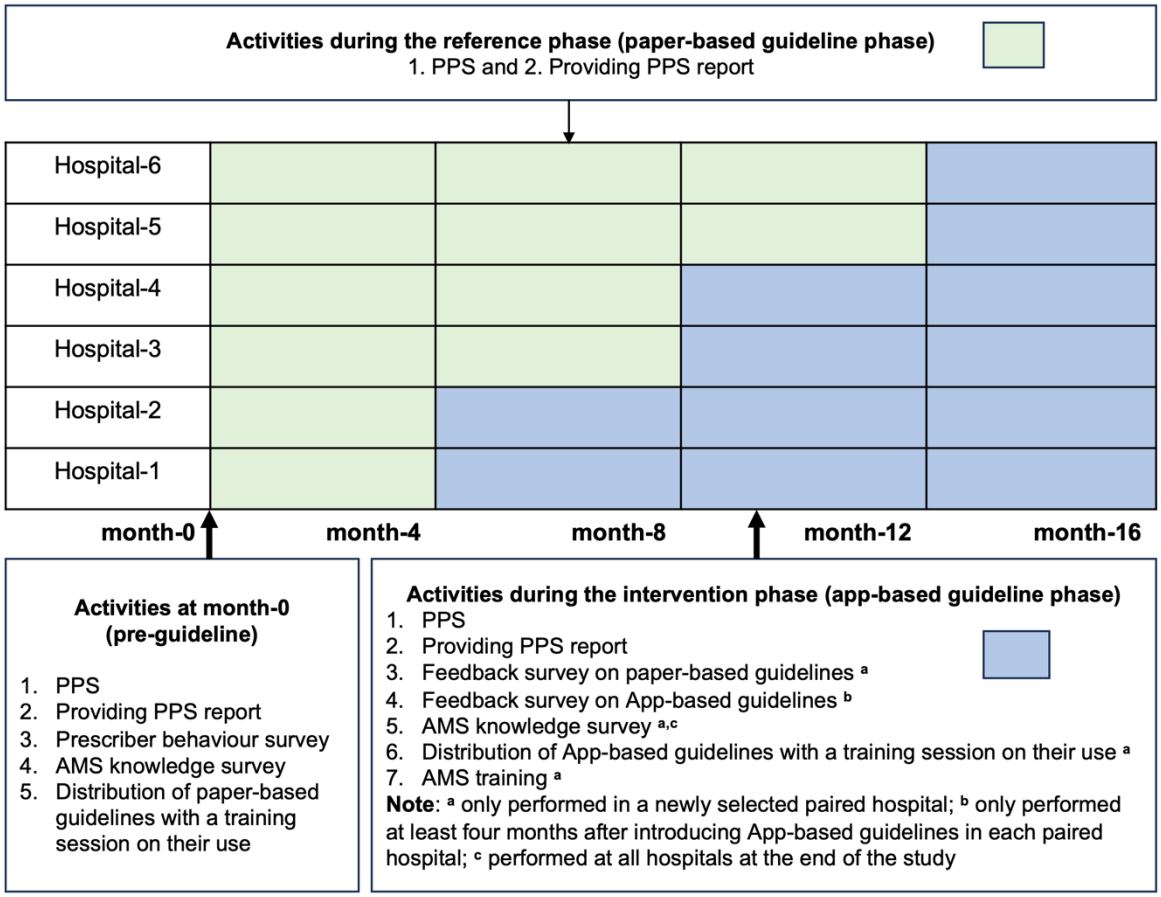
Intervention delivery

At month-4 after the start of the project, the intervention was introduced to the first selected hospital pair, then every four months each pair of hospitals was rolled out from the reference phase to the intervention phase until all had implemented the intervention. This gave a 1:1 ratio of intervention *vs* reference period of observation (Figure 19). We could therefore compare the effects of the PP-G and App-G over a reasonable period of time. During the App-G period, prescribers in participating hospitals still had access to PP-G distributed at the start of the study.

At month-4, after the first two selected hospitals had officially entered to the intervention phase, prescribers from this paired hospital were invited to provide

feedback on the PP-G, and then participated in the AMS knowledge survey. Following this, they received training on how to use the App-G and AMS training before installing the App-G on their mobile phones. These procedures were repeated in the two newly selected hospital pairs at month-8 and month-12. All prescribers who had access to App-G, were invited to give feedback on the app at least four months after their initial access. By month-16, all hospitals had entered the intervention period, for at least four months. The last pair of hospitals was invited to give feedback on the App-G. Additionally, AMS knowledge survey was performed at all hospitals during this stage (Figure 19).

Figure 19: Study procedures of SW-CRT on evaluation of Lao-language antimicrobial use guidelines mobile app



Note: All hospitals continued to have access to paper-based guidelines after entering the intervention phase; the numbers in the activity boxes indicate the sequence of activities within each phase, **PPS**=Point Prevalence Survey, **AMS**=Antimicrobial Stewardship.

Risk of Contamination between hospital pairs

Although the hospitals were geographically quite remote from each other, travel and communications between prescribers in Laos is frequent. While thought to be unlikey, there was a possibility of contamination of the App-G to the PP-G. If it occurred, the research team recorded it, e.g., doctors from the App-G moved to the PP-G for any possible reason (training or changing workplace).

To avoid or reduce the posibility of contamination, at the start of the intervention phase, all participating hospitals were requested to avoid sharing the App-G to

anybody outside their hospitals while they were still under evaluation. The PI installed the App-G using a code, thereby restricting access to the app for prescribers outside the study sites. The functional system, security and app maintenance were controlled by the MicroGuide team and PI of the project.

Endpoints

Primary endpoint

The proportion of antimicrobial prescriptions adherent with prescribing guidelines delivered by mobile phone app versus paper-based prescribing guidelines at month 16.

Secondary endpoints

1. Proportion of patients admitted to hospital receiving an antimicrobial prescription before and after introduction of the paper-based prescribing guidelines; and the mobile phone app prescribing guidelines + AMS training at month 16
2. Total antimicrobial defined daily doses (DDDs) prescribed in mobile phone app versus paper-based groups at month 16
3. Proportion of patients prescribed antimicrobials by the intravenous route in mobile phone app versus paper-based groups at month 16
4. AMS knowledge level of prescribers prescribed in mobile phone app versus paper-based groups at month 16
5. Prescriber satisfaction/acceptability of the prescribing guidelines in mobile phone app versus paper-based groups after at least 4 months' exposure in each group

Definitions of adherence to the guidelines

1. Full adherence with the guidelines = using correct antimicrobial agent(s) and correct dose based on the provided antimicrobial prescribing guidelines. For elective surgical prophylaxis antimicrobial duration was incorporated in the definition since it should only be administered pre-operatively or intra-operatively (using correct antimicrobial agent(s), correct dose and correct duration based on the provided antimicrobial prescribing guidelines)
2. Partial adherence with the guidelines = using correct antimicrobial agent(s) only based on the provided antimicrobial prescribing guidelines
3. Non-adherence with the guidelines = using a different antimicrobial agent(s) compared to that suggested in the provided antimicrobial prescribing guidelines

Outcome measurements

Outcomes of this study were measured using:

- PPS of hospital antimicrobial use
- Prescriber surveys:
    - Prescriber behaviour survey (pre-guideline survey)
    - AMS knowledge surveys of prescribers
    - Feedback survey on paper-based and app-based version of the guidelines

Each data collector received training on the study purpose/processes and the use of the data collection instruments before starting the project.

1. Point prevalence survey procedures

The Open Data Kit (ODK) system was used as the data collection tool for PPS. Outcomes were measured by regular PPS of hospital antimicrobial prescribing in both in- and outpatients at all six hospitals during visits approximately four monthly (five visits including one baseline data collection – Figure 19). Data were collected using separate electronic questionnaires for in- and outpatients.

IPD and OPD PPS data were collected using the ODK platform to gather information on patients' characteristics and treatment status, including age, sex, body weight, wards, antimicrobial agent(s), administration, dosage, unit, diagnoses, prescribing indication and antimicrobial start date. IPD PPS data were collected directly from hospital charts and OPD PPS data were obtained from scanned prescription sheets.

1.1. Inpatient point prevalence survey

Procedures of PPS in inpatients was described in the methodology of Chapter 2.

1.2. Outpatient point prevalence survey

Survey site – In most hospitals, many wards have their own outpatient departments (OPDs). However, in this study, we focused on three primary departments, including paediatrics, medicine, and surgery within the main OPD areas of the hospitals, as these were anticipated to have the highest volume of antimicrobial prescribing. However, some hospitals do not classify their outpatient departments by specialty. Therefore, we classified these departments as general outpatients.

Survey dates and times – OPD PPS was performed for five consecutive working days in total in all six hospitals. All outpatient prescriptions were screened between

8:00 o'clock in the morning and 4:00 o'clock in the afternoon on the day of survey (working hours). Survey days excluded public holiday and weekends.

Inclusion and exclusion criteria

Inclusion criteria

1. All patients consulting at OPD of paediatrics, medicine and surgical wards of all participating hospitals during 8:00am to 4:00pm of a survey day were counted as the denominator
2. All patients consulting at OPD of these three wards of all participating hospitals who were prescribed antimicrobial(s) between 8:00am and 4:00pm on a survey day were counted as the numerator
3. If the same outpatient came back for consultation during the same survey period (same round, any day during these five days) this patient was also included in the survey and was defined as a new consultation.

Exclusion criteria

- Patients who came for consultation outside the survey time (before 8:00am or after 4:00pm) of the survey day
- Patients who were prescribed topical antimicrobial(s) only were excluded from the numerator but they were still in the denominator

Study setting

Hospital directors of each hospital were informed at least three days before the survey. Heads of OPD were informed about the survey on the same day as the survey day. Data were collected from an OPD prescription sheet at the OPD pharmacy.

The OPD prescription sheets from patients were scanned and saved as an electronic file for data entry by research staff on the same day. The reason for

scanning OPD prescription sheets was to avoid disrupting the OPD workflow during busy times in each participating hospital. The total number of OPD patients (denominator) was collected from the OPD logbook at the end of each survey day. There were different systems of OPD data recording in each hospital. This project did not create a new system for the hospital but followed the existing routine systems of each hospital, ensuring that we could capture all antimicrobial prescription data and the denominators. Scanned prescription files were securely kept and discarded one month after the scanned date. For more details of the outpatient PPS data collection form, see Appendix 6.

2. Prescriber survey

Paper case report forms (CRF) in Lao language were used for the prescriber surveys (Appendix 8 – AMS knowledge survey questionnaires, Appendix 12 for PP-G feedback survey and Appendix 13 for App-G feedback survey). Basic information (age, sex, specialty, departments, and graduated year) of prescribers and their prescribing behaviours were also collected. All completed survey forms by prescribers were returned to the study team on the same day as the survey day. All data were entered to the MACRO system. Data on the frequency of use of the mobile app could also be downloaded from the MicroGuide App.

2.1. Prescriber behaviour survey (pre-guideline survey)

The survey aimed to assess how prescribers used antimicrobial guidelines in their routine work and their opinions on the provided guidelines. It was conducted once at month-0 before the PP-G introduction, with all prescribers at each study hospital invited to participate (Appendix 9). The form contained six questions and it took approximately five minutes to complete.

2.2. Antimicrobial stewardship (AMS) knowledge survey

An AMS knowledge survey was conducted three times at each hospital during the study, including one before the introduction of PP-G (month 0), one approximately every four months before implementing App-G, and one at month 16, before the study concluded. This survey assessed prescribers' knowledge of rational antimicrobial prescribing before and after exposure to PP-G and App-G. Each survey consisted of eight multiple-choice questions, which were randomly selected from a set of 18 questions (Appendix 8). A simple random sampling method was employed using a computer-generated random allocation sequence in Excel to assign a unique set of questions to each survey. The completion time for each survey was approximately ten minutes.

2.3. Prescriber feedback survey on paper-based and App-based prescribing guidelines

The PP-G feedback survey (Appendix 12) was conducted once before each hospital transitioned to App-G, and once while the App-G survey (Appendix 13) was done, after hospitals had at least four months of App-G access. These surveys aimed to gather prescribers' feedback on both guidelines and assess changes in their prescribing practices. Completed surveys were collected from all prescribers on the day of administration.

Ethics

Ethical approval for this project was obtained from the University of Health Sciences Ethics Committee, Lao PDR (Ref: 105/REC, 27 October 2020) and the Oxford Tropical Research Ethics Committee, University of Oxford (OxTREC Ref: 541-20, 16 July 2020). For PPS data, the study involved collecting data solely from patients'

documents and outpatient prescriptions, with no interviews or biological sample collection, so written informed consent from patients was not required. Verbal consent to participate was obtained from the directors of each hospital, and prescribers were informed about the study and its purpose.

Data management and monitoring

All data were entered by the PI and trained research staff. All completed survey forms were kept securely in a locked filing cabinet. Only the PI of the project and project data management team had access to the raw data. All electronic data were kept securely, protected by password access with automatic daily backup on the server at the LOMWRU office and regular offsite tape backups. All scanned OPD prescription sheets were appropriately destroyed within one month of the scanned date. Anonymized data from PPS were fed back to the participating hospitals and MoH through a project-generated computer dashboard and reports one month after each PPS in each hospital. Data checking and cleaning were done by the PI after each survey. Data inconsistencies were discussed with the research team immediately and resolved through discussion.

Statistical analysis

A statistical analysis plan was drafted by PI and reviewed by statisticians (Mavuto Mukaka and Sue Lee) and all supervisors before the actual data analysis (Appendix 14). Results were analysed and reported separately for inpatients and outpatients.

Reporting baseline characteristics

Characteristics of variables (from OPD and IPD PPS; and prescriber surveys) from each hospital and sequence were presented and compared on tables/charts as appropriate. Normally distributed continuous baseline characteristics were summarized with means and standard deviation or 95% CI. Skewed continuous data were summarized using median and IQR (± range). Categorical data were presented as frequency and percentages and compared using test of trend, Chi-square or Fisher's exact tests. Variables such as years since medical graduation, specialty, and departments where prescribers were based were summarized by hospital.

Analysis of primary outcome

A mixed-effects logistic regression model (to adjust for clustering) was used to compare the proportion of antimicrobial prescriptions adherence measured at month-0, 4, 8, 12 until month 16. The model compared all steps in the App-G from month 4 to month 16 with all steps in the PP-G from month-0 to month-12. Odds ratios (OR) and the corresponding 95% CI are reported. Tests of significance were performed at the 5% level.

Calendar time is a potential confounder in stepped wedge design. Therefore, the model was adjusted for the effect of time. The duration of exposure of each hospital to the PP-G or App-G was included in the model as an interaction term with the study arm in order to assess whether duration of exposure was an effect modifier. Initially a model with fixed effect for time, implying a common secular trend across steps and clusters, was analysed with adherence to guidelines as the outcome. Models adjusting for time as a random effect were also considered, when

necessary, particularly to address issues such as collinearity. The model considered the correlation among the outcome's measurements from the same hospital (cluster) by adjusting for clustering in the model.

Sensitivity analysis explored seasonal variations and variations in secular trends across clusters and allowed the guideline effect (i.e., effect of paper-based or mobile phone application on adherence) to vary across clusters and time. For example, a fixed effect interaction between time and each pair of hospitals (strata) for examining varying secular trends across clusters would be added to the model or the model incorporated a random effects component between time and cluster. Heterogeneity in adherence across clusters was considered as a fixed effect interaction between the intervention and strata or, by incorporating a random effect term for the intervention and for each pair of hospitals (strata). Sensitivity analysis also considered whether adherence varied over time using a fixed effect term for the interaction between intervention and time. This model was only estimable at time periods that had both intervention and control phases (weeks 4 to 16).

An *a priori* set of variables were considered for inclusion in multivariable models. Interactions were considered, as appropriate. The results were reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) extension for SW-CRT(233) .

Analysis of secondary outcomes

A mixed effects logistic regression model, as described above (for primary outcome) was used to compare the overall proportion of antibiotics prescribed to be given by the intravenous route. Duration of exposure to intervention arm was included in the model as an interaction term with study arm. Hospital was fitted as a random effect

to account for clustering for both secondary outcome 1 and secondary outcome 3. Defined daily doses (DDDs) were calculated using data (antibiotic agent, start date, dose and DDD of each antibiotic from www.whocc.no) from PPS in both IPD and OPD for secondary outcome 2.

For secondary outcome 4, AMS knowledge level of prescribers was assessed using questionnaires based on information in the prescribing guidelines. The overall percentage of correct answers at each time point were compared. The scores were coded as 0/1, where 1=correct and 0=incorrect. Then the knowledge level was assessed using sum of a total score.

For secondary outcome 5, frequency of use of PP-G and App-G and frequency of use of other antimicrobial prescribing guidelines were described at month-0, 4, 8, 12 until month 16. The frequency of use of the App-G could also be collected from the MicroGuide app directly, as well as which topics the prescribers commonly visited. Likert scale analysis was used to evaluate prescriber satisfaction with/acceptability of PP-G compared to App-G. The satisfaction/acceptability scale had six categories, including (strongly agree=5, agree=4, neutral=3, disagree=2, strongly disagree=1, no opinion/not use=0). The Mann-Whitney U test was used to assess the differences between paper-based population and mobile phone app population. The satisfaction/acceptability scale was also stratified by prescriber specialty, departments where they were based and years since medical graduation.

Safety considerations/Adverse events

This study was more likely to benefit than harm patients or clinicians. The intervention was the introduction of antimicrobial prescribing guidelines delivered by a mobile app in line with national and international recommendations. No adverse event monitoring was planned.

Benefits

This study described the introduction of the first therapeutic and prophylactic antimicrobial prescribing guidelines in Laos. The guidelines encouraged the rational use of antimicrobials. This helped to improve clinical decision of doctors and consistency of care. This gave the potential to improve health outcomes of patients, reduced morbidity and mortality and gave value for money.

Risks

There was risk of cross-contamination in this study as Lao doctors frequently travel from one hospital to another for training, workshops and conferences (not related to this project). In addition, an AMR program supported by the Fleming Fund was conducted in five participating hospitals (VTP, SV, SVK, XK, and LNT) to improve the quality of infectious disease diagnosis in these hospitals. It is possible that this program may have influenced the results of this study, as they could have had positive effect on antimicrobial stewardship knowledge of Lao doctors.

Patient and doctor confidentiality

No personal details of patients or staff were recorded. Only age, gender, weight, and antimicrobial prescription data were collected from hospital charts. There was no direct interaction between the research team and patients. The study focused on prescriber behaviour rather than individuals. Only prescribers' age, specialty, and year of graduation were recorded. Neither the research team nor the PI could identify individuals from the survey forms or prescription records.

Trial insurance

The University of Oxford had a specialist insurance policy in place: Newline Underwriting Management Ltd, at Lloyd’s of London, which would operate in the

event of any participant suffering harm as a result of their involvement in the research.

Summary

This study was the first SW-CRCT to evaluate the impact of Lao antimicrobial prescribing guidelines in both pocketbook and mobile app formats. It aimed to provide robust data to strengthen antimicrobial stewardship in Laos, reduce inappropriate use, and improve patient outcomes. The study also sought to identify the most effective format for widespread adoption. Chapter 4 presents the results of the primary objective and secondary objectives 1, 2 and 3, while Chapter 5 focuses on secondary objectives 4 and 5, along with a qualitative study on Lao prescribers' practices and guideline uptake.

Chapter 4: Results and Discussion: Evaluating the impact of a Lao language mobile phone antimicrobial use guideline application on antimicrobial prescribing in Lao PDR

Abstract

Primary objective:

This trial aimed to compare the proportion of antimicrobial prescriptions adherent with the Lao prescribing guidelines delivered by a smartphone application (App-G) versus the paper-based version (PP-G) in both inpatients and outpatients in six hospitals in Laos.

Results:

Among hospitalized patients, guideline adherence was 18% (95% CI: 15-20%) in the pre-guideline, 17% (15-19%) in the PP-G group, and 26% (23-28%) in the App-G group. Adherence to guidelines in the App-G group was 68% higher than the PP-G group with unadjusted odds ration (OR) of 1.68 (1.38-2.05, p<0.0001). Despite the trend towards increased adherence in the App-G group, after accounting for random effects of time and cluster and adjusting for potential confounders, the adherence was not explained by the mode of guideline delivery (aOR=1.27, 95% CI: 0.84-1.90, p=0.249). For outpatients, adherence was 22% (95% CI: 19-25) in the pre-guideline, remained 22% (19-24) in the PP-G group, and was 23% (21-25) in the App-G group, with no difference between PP-G and App-G (aOR=0.90, 95% CI: 0.74-1.09, p=0.299).

Conclusion:

This study demonstrated that mobile phone technology for antimicrobial prescribing guidelines can be implemented effectively in LMICs like Laos. However, there was insufficient evidence to suggest that the mobile app had a greater impact on adherence than paper-based guidelines. While guidelines offer valuable recommendations, adherence depends on multiple factors beyond their availability.

Overview of study participants

Between January and March 2021, the SW-CRCT was formally initiated in six hospitals across Laos. Savannakhet (SVK) was the first hospital to receive the PP-G, followed by Salavan (SV), Xiengkhuang (XK), Luang Namtha (LNT), Vientiane Province (VTP), and Mahosot (MS). The median duration for the implementation of the PP-G and the prescriber surveys in one hospital was 3.5 days (range: 2-8 days), with SVK at 4 days, SV at 3 days, XK at 4 days, LNT at 3 days, VTP at 2 days, and MS at 8 days.

The trial operated over 22 months, from January 2021 to October 2022. The baseline data collection (pre-guideline) and implementation of the paper-based guideline (PP-G) occured from January-March 2021. The first pair of hospitals (XK and LNT) received the intervention in June-July 2021 (sequence-1), the second pair (SV and SVK) in November-December 2021 (sequence-2), and the last pair (VTP and MS) in April 2022 (sequence-3), with five-to-six-month intervals between each (Figure 20).

A total of 16,878 patient records, including inpatient documents and OPD prescription forms, were screened for antimicrobial use across six hospitals over 22 months. Of these, 13,711 (81%; 95% CI: 80.6-81.8) were OPD prescription forms, with a median of 377 forms (range: 79-1,356) per survey per hospital. The remaining 3,167 (19%; 95% CI: 18.2-19.4) were inpatient documents, with a median of 95 documents screened (range: 8 patients in LNT to 225 patients in MS) per survey per hospital (Table 18).

Figure 20: Study timeline overview

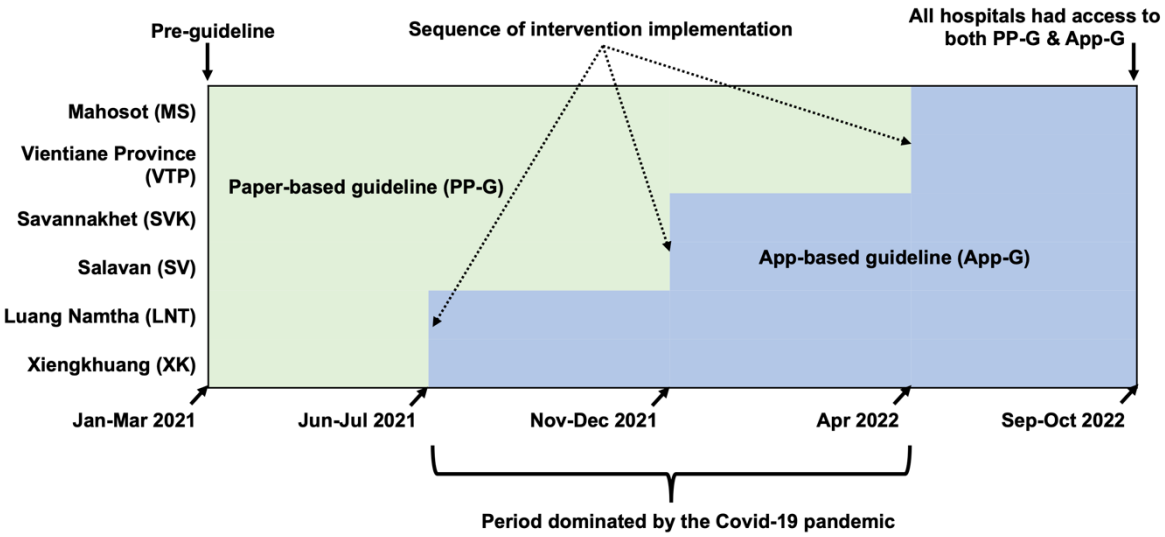


Table 18: Total number of screened patient's documents and OPD prescriptions in each survey in six hospitals

Hospital	Period 1		Period 2		Period 3		Period 4		Period 5	
	IPD	OPD	IPD	OPD	IPD	OPD	IPD	OPD	IPD	OPD
XK	111	274	110	438	34	266	45	321	123	343
LNT	56	79	56	288	8	92	44	280	48	188
SV	86	464	89	641	62	376	74	406	130	565
SVK	218	378	197	340	126	179	148	230	170	415
VTP	94	750	117	493	56	196	44	348	96	576
MS	192	1,131	167	898	83	582	158	818	225	1,356
Total	**757**	**3,076**	**736**	**3,098**	**369**	**1,691**	**513**	**2,403**	**792**	**3,443**

Note: XK=Xiengkhuang, **LNT**=Luang Namtha, **SV**=Salavan, **SVK**=Savannakhet, **VTP**=Vientiane Province, **MS**=Mahosot, **IPD**=inpatient, **OPD**=outpatient department, **Period 1**=Pre-guideline, **Period 2**=Month-6 after PP-G implementation (all hospitals), **Period 3**=First survey after App-G implementation in XK&LNT or month-11 after PP-G introduction, **Period 4**=Second survey post-App-G for XK&LNT, first survey post-App-G for SV & SVK, or month-17 after PP-G introduction, **Period 5**=final survey after all clusters had App-G access or month-22 after PP-G introduction.

1. Hospitalised patients

Among inpatients, the percentage of antimicrobial prescriptions was similar across all groups, with 74% in the pre-guideline group (560/757 patients, 95% CI: 70.7-77.1), 75% in the PP-G group (952/1,265, 95% CI: 72.8-77.6) and 71% in the App-G group (814/1,145, 95% CI: 68.4-73.7). The majority of patients were aged ≥15 years which is the age of admission to adult wards in Laos: 76.2% (95% CI: 72.5-79.7) in the pre-guideline group, 83.7% (95% CI: 81.2-86) in the PP-G group, and 74.9% (95% CI: 71.8-77.9) in the App-G group. Nearly half of all patients received more than one antimicrobial: 45% (95% CI: 42.6-51) in the pre-guideline group, 47% (95% CI: 43.4-49.9) in the PP-G group, and 40.5% (95% CI: 37.2-44) in the App-G group. Most prescriptions were for treating infections: 54% (95% CI: 50.5-57.3) in the pre-guideline, 53% (95% CI: 50.8-55.9) in the PP-G, and 59% (95% CI: 56.1-61.7) in the App-G group. Nearly all prescriptions were empirical: 99% (844/852, 95%CI: 98.2-99.6) in the pre-guideline, 98% (1,460/1,492, 95%CI: 97-98.5) in the PP-G, and 94% (1,147/1,217, 95%CI: 92.8-95.5) in the App-G group. Few patient documents mentioned review or end date of the antimicrobial prescription (Table 19).

2. Outpatients

Out of 13,711 OPD patients included, 3,484 (25.4%; 95% CI: 24.7-26.2) received antimicrobials. This included 27% (841/3,076; 95% CI: 25.8-28.9) in the pre-guideline group, 21% (1,184/5,597; 95% CI: 20.1-22.2) in the PP-G group, and 29% (1,459/5,038; 95% CI: 27.7-30.2) in the App-G group. Most patients were aged ≥15 years: 56.1% (95% CI: 52.7-59.5) in pre-guideline, 69.3% (95% CI: 66.5-71.9) in PP-G, and 54.1% (95% CI: 51.6-56.7) in App-G. Nearly all OPD patients received a single antimicrobial, with 9% (95% CI: 6.8-10.7) in pre-guideline, 13% (95% CI: 10.8-14.6) in PP-G, and 10.1% (95% CI: 8.6-11.7) in App-G receiving more than one. Ear, Nose, Throat conditions were the most common target for prescriptions across all groups (Table 19).

Table 19: Characteristics of antimicrobial prescriptions in six hospitals in the pre-guideline, PP-G and App-G groups

Characteristics	Pre-guideline group, n (%)		PP-G group, n (%)		App-G group, n (%)	
	Inpatient (n-%)	Outpatient (n-%)	Inpatient (n-%)	Outpatient (n-%)	Inpatient (n-%)	Outpatient (n-%)
Screened patient documents [a] n	757	3,076	1,265	5,597	1,145	5,038
Patients with antimicrobial(s) prescribed - n (%)	560 (74)	841 (27)	952 (75)	1,184 (21)	814 (71)	1,459 (29)
Antimicrobial use by hospital – n/N (%) [b]						
Xiengkhuang Provincial Hospital (XK)	79/111 (71.2)	134/274 (48.9)	74/110 (67.3)	124/438 (28.3)	129/202 (63.9)	358/930 (38.5)
Luang Namtha Provincial Hospital (LNT)	40/56 (71.4)	46/79 (58.2)	35/56 (62.5)	99/288 (34.4)	61/100 (61)	145/560 (25.9)
Salavan Provincial Hospital (SV)	72/86 (83.7)	248/464 (53.5)	118/151 (78.2)	372/1017 (36.6)	139/204 (68.1)	531/971 (54.7)
Savannakhet Provincial Hospital (SVK)	162/218 (74.3)	77/378 (20.4)	255/323 (78.9)	62/519 (11.9)	268/318 (84.3)	79/645 (12.3)
Vientiane Provincial Hospital (VTP)	70/94 (74.7)	84/750 (11.2)	167/217 (76.9)	153/1037 (14.8)	59/96 (61.5)	105/576 (18.2)
Mahosot Hospital (MS)	137/192 (71.4)	252/1131 (22.3)	303/408 (74.3)	374/2298 (16.3)	158/225 (70.2)	241/1356 (17.8)
Antimicrobial use by sequence of intervention implementation – n (%)						
Sequence 1 (XK + LNT)	119 (71.3)	180 (50.9)	109 (65.7)	223 (30.7)	190 (62.9)	503 (33.8)
Sequence 2 (SV + SVK)	234 (76.9)	325 (38.6)	373 (78.7)	434 (28.3)	407 (77.9)	610 (37.8)
Sequence 3 (VTP + MS)	207 (72.4)	336 (17.9)	470 (75.2)	527 (15.8)	217 (67.6)	346 (17.9)
Age, median (IQR) years	31 (16.5-50)	22 (4-43)	38 (22.5-57)	30 (9-48)	32 (14-54)	20 (3-40)
Age category - n (%) [a] ≤ 1 year	66 (11.8)	100 (11.9)	75 (7.9)	68 (5.7)	107 (13.1)	157 (10.8)
> 1 to ≤ 5 year	43 (7.7)	159 (18.9)	36 (3.8)	160 (13.5)	60 (7.4)	315 (21.6)
> 5 to <15 years	24 (4.3)	110 (13.1)	44 (4.6)	136 (11.5)	37 (4.6)	197 (13.5)
≥ 15 years	427 (76.2)	472 (56.1)	797 (83.7)	820 (69.3)	610 (74.9)	790 (54.1)

Sex						
Male	270 (48.2)	409 (48.6)	447 (46.9)	579 (48.9)	380 (46.7)	699 (47.9)
Female	290 (52.8)	432 (51.4)	505 (53.1)	605 (51.1)	434 (53.3)	760 (52.1)
Department - n (%) [a,c]						
Intensive Care	50/60 (83.3)	-	86/116 (74.1)	-	89/106 (83.9)	-
Paediatrics	89/107 (83.2)		92/126 (73)	-	124/171 (72.5)	-
Obstetrics & Gynaecology	97/117 (82.9)	-	159/185 (85.9)	-	111/171 (64.9)	-
Medicine	136/245 (55.5)	-	253/421 (60.1)	-	223/377 (59.2)	-
Surgery	147/168 (87.5)	-	277/300 (92.3)	-	169/186 (90.9)	-
Other	41/60 (68.3)	-	85/117 (72.7)	-	98/134 (73.1)	-
General practice	-	841/3,076 (27.3)	-	1,184/5,597 (21.2)	-	1,459/5,038 (28.9)
Number of antimicrobial(s) – n (%)[a]						
One	298 (53)	769 (91)	508 (53)	1,035 (87)	484 (59)	1,312 (90)
Two	234 (42)	60 (7)	351 (37)	126 (11)	276 (34)	131 (9)
≥ Three	28 (5)	12 (2)	93 (10)	23 (2)	54 (7)	16 (1)
Number of prescriptions - n	**852**	**926**	**1,492**	**1,357**	**1,217**	**1,622**
Route of administration – n (%)[d] Oral	119 (14)	926 (100)	225 (15.1)	1,355 (99.8)	274 (22.5)	1,615 (99.6)
Parenteral	733 (86)	0	1,267 (84.9)	2 (0.2)	943 (77.5)	7 (0.4)
Number of antibiotic prescription - n (%) [d]	842 (99)	826 (89)	1,446 (97)	1,197 (88)	1,145 (94)	1,503 (93)
AWaRe antibiotics - n (%) [d]						
Access	423 (50)	561 (68)	694 (48)	743 (62)	511 (45)	1,030 (69)
Watch	416 (49)	265 (32)	750 (52)	454 (38)	634 (55)	473 (31)
Reserve	0	0	0	0	0	0
Not recommended	3 (0.4)	0	2 (0.1)	0	0	0
Indication - n (%) [d]						

Treatment of infection	459 (54)	757 (82)	795 (53)	1,049 (77)	717 (59)	1,341 (83)
Medical prophylaxis-general	50 (6)	3 (0.3)	79 (5)	2 (0.2)	58 (5)	5 (0.3)
Medical prophylaxis-trauma	25 (3)	6 (0.7)	29 (2)	2 (0.2)	20 (2)	2 (0.1)
Medical prophylaxis-vaginal delivery	42 (5)	0	72 (5)	1 (0.1)	58 (5)	0
Single dose surgical prophylaxis	13 (1)	0	13 (1)	0	12 (1)	0
24-hours-surgical prophylaxis	32 (4)	0	11 (1)	0	35 (3)	0
More than 24 hours-surgical prophylaxis	131 (15)	3 (0.3)	307 (21)	2 (0.2)	202 (17)	1 (0.1)
Unclear indication	18 (2)	21 (2)	35 (2)	35 (3)	17 (1)	38 (2)
Unknown	82 (10)	136 (15)	151 (10)	266 (20)	98 (8)	235 (14))
Indication documented in patient records – n (%)[d]	752 (88)	769 (83)	1,306 (88)	1,056 (78)	1,102 (91)	1,349 (83)
Treatment – n (%) [d]						
Empirical	844 (99)	924 (99.8)	1,460 (98)	1,357 (100)	1,147 (94)	1,622 (100)
Targeted [e]	8 (1)	2 (0.2)	32 (2)	0	70 (6)	0
Stop/review date documented - n (%) [d]	0	855 (92.3)	0	1,339 (98.7)	50 (4.1)	1,445 (89.1)
Focused organ system - n (%) [d]						
Bone and Joint	25 (3)	22 (2)	30 (2)	28 (2)	33 (3)	17 (1)
Cardiovascular System	8 (1)	3 (0.3)	14 (1)	9 (1)	8 (1)	5 (0.3)
Central Nervous System	39 (5)	6 (0.7)	32 (2)	4 (0.3)	40 (3)	6 (0.4)
Ear-Nose-Throat	34 (4)	330 (36)	44 (3)	318 (23)	59 (5)	630 (39)
Gastrointestinal	195 (23)	142 (15)	433 (29)	271 (20)	251 (21)	238 (15)
Male genital tract	10 (1)	9 (1)	16 (1)	36 (3)	10 (1)	18 (1)
Obstetrics/Gynaecology	162 (19)	57 (6)	311 (21)	112 (8)	234 (19)	70 (4)
Ophthalmology	4 (0.5)	1 (0.1)	15 (1)	3 (0.2)	1 (0.1)	0
Respiratory tract	140 (16)	164 (18)	173 (12)	156 (12)	254 (21)	222 (14)
Sepsis	64 (8)	2 (0.2)	97 (7)	1 (0.1)	94 (8)	4 (0.3)
Skin and Soft Tissue	59 (7)	61 (7)	102 (7)	146 (11)	57 (5)	113 (7)
Urinary tract	42 (5)	60 (6)	104 (7)	153 (11)	77 (6)	152 (9)
Not defined	70 (8)	69 (7)	121 (8)	120 (9)	99 (8)	147 (9)

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**=group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training. [a] denominator was number of patients with antimicrobial(s), [b] denominator was number of screened patient documents in each hospital, [c] denominator was number of prescribers from each ward/department, [d] denominator was number of prescriptions, [e] targeted treatment referes to prescribing based on confirmed microbiological results (e.g., conventional culture or Gene-Xpert for tuberculosis), **Other department**=including VIP departments, ENT-EYE (Ear, Nose, Throat and Eyes).

Part I: Primary Endpoint - Guideline adherence and their impact on antimicrobial prescriptions

1. Hospitalised patients

1.1. Overall percentage of antimicrobial prescriptions fully adherent to prescribing guidelines between PP-G and App-G among inpatients

Of 3,561 inpatient prescriptions, 3,242 (91%; 95% CI: 90-92) had sufficient information to assess guideline adherence, while 319 (9%; 95% CI: 8-10) could not be assessed. Of the unassessable prescriptions, 22% (90/319, 95% CI: 17-27) lacked clear prescribing indications, and 78% (249/319, 95% CI: 73-82) involved conditions not covered by guidelines. The most common topics not covered by the guidelines were gastrointestinal conditions (34%; 86/249, 95% CI: 29-41), CNS conditions (18%; 44/249, 95% CI: 13-23), and non-specific site conditions (14%; 36/249, 95% CI: 10-19).

The overall adherence to the prescribing guidelines in the PP-G group was 17% (231/1,360; 95% CI: 15-19). This adherence was significantly lower compared to the App-G group, at 26% (285/1,112; 95%CI: 23-28); $p<0.0001$ (Figure 21a). The percentage of guideline adherence in each hospital (cluster) varied across the survey periods, ranging from 7% (9/134; 95%CI: 3-12) at VTP in period-2 to 36% (77/214; 95%CI: 30-43) at SVK in period five (Figure 21b, Figure 22 & 23).

Guideline adherence among inpatients increased to 28% (95% CI: 25-31) by the end of the study, compared to 18% (95% CI: 15-20) in the pre-guideline group ($p<0.0001$, Figure 21c). By sequence of intervention implementation (order of intervention delivery), adherence improved in the paired hospitals of sequence-1

and sequence-2 after intervention, but in sequence-3, it went from 19% (95% CI: 14-24) to 13% (95% CI: 10-15) after PP-G implementation, then rose to 20% (95% CI: 16-25) with App-G by the study's end (Figure 21d).

1.2. Comparison of full adherence to the prescribing guidelines between PP-G and App-G among inpatients

During the guideline implementation period, adherence in the App-G group (26%, 95% CI: 23-28) was 68% higher than in the PP-G group (17%, 95% CI: 15-19), with an unadjusted odds ratio (OR) of 1.68 (95% CI: 1.38-2.05, p<0.0001). Adherence to the guidelines was associated with sequence of intervention implementation, time, the patient's age, gender, department, prescribing indications, and types of prescription (empiric or targeted) (Table 20). However, time was strongly correlated with the outcome, resulting in collinearity. To distinguish the effects of these variables on guideline adherence, therefore the model included time and hospitals (clusters) as random effects. The adjusted OR (aOR) for antimicrobial prescriptions adherence to guidelines showed that the adherence in the App-G group was 27% higher than the PP-G group (aOR=1.27, 95% CI: 0.84-1.90, p=0.249). Though the model showed higher adherence in the App-G group after adjusting for potential confounders and accounting for random effects, the evidence was insufficient to conclusively demonstrate that adherence in the App-G group was better than in the PP-G group (Table 21).

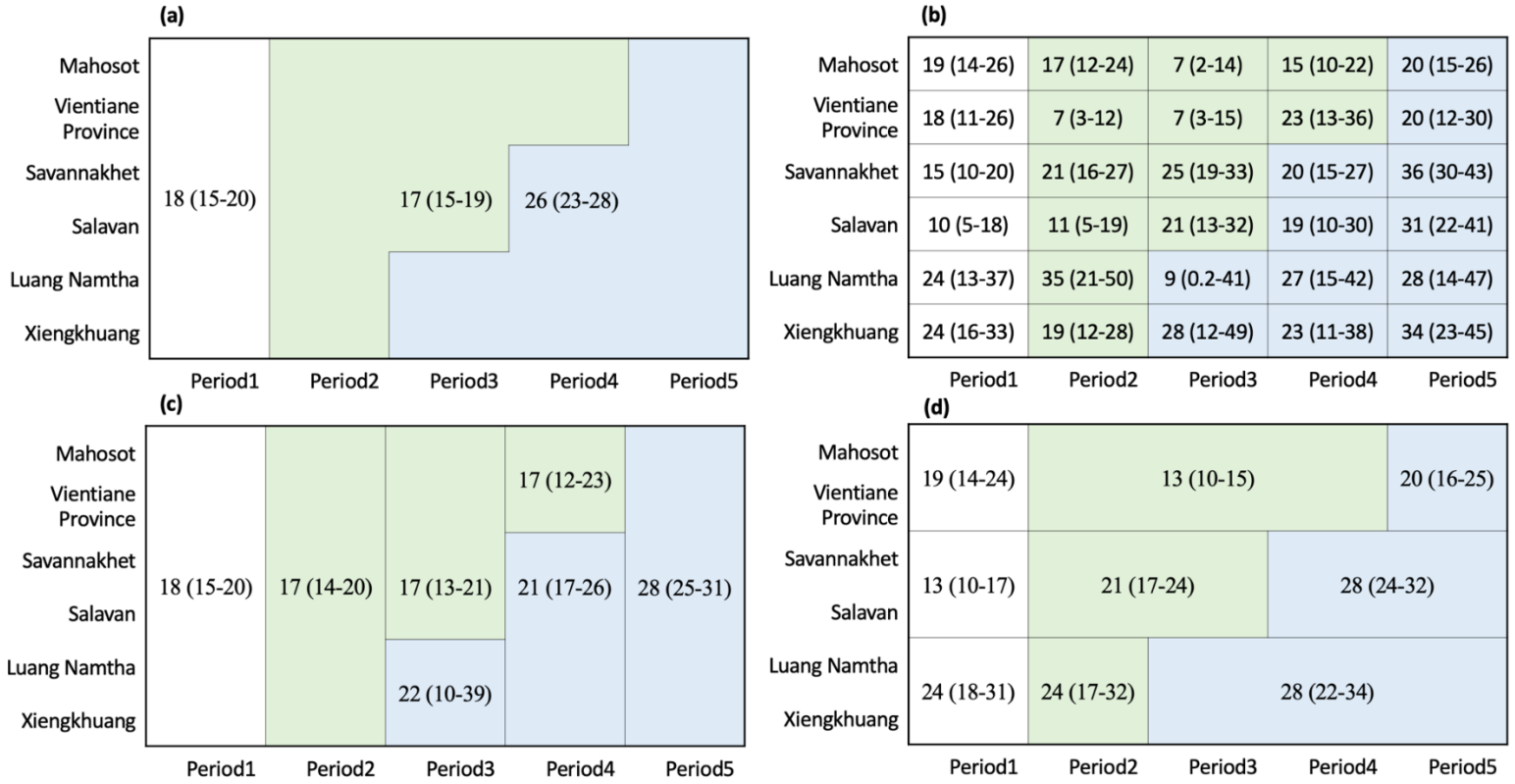
However, the first paired hospitals with access to App-G (sequence 1) showed twice the guideline adherence (28%, 95% CI: 22-34) compared to the last paired hospitals or sequence 3 (20%, 95% CI: 16-25), aOR=2.03, 95% CI: 1.20-3.43, p=0.008. The second pair or sequence 2 (28%, 95% CI: 24-32) had 60% higher adherence

compared to the last pair (aOR=1.60), though the CI included one (95% CI: 1.00-2.55, p=0.049). By department, medical wards had 70% higher adherence than surgical wards (aOR=1.70, 95% CI: 1.23-2.35, p=0.001)). ICU wards also showed an 82% increase (aOR=1.82, 95% CI: 1.13-2.94, p=0.014). While, OBGY had 63%

lower adherence (aOR=0.37, 95% CI: 0.19-0.72, p=0.004) than surgical wards. Prescriptions for known pathogens or confirmed microbiology results were more adherent (aOR=12.21, 95% CI: 6.91-21.51, p<0.0001) than empiric prescriptions. Prescriptions for treating infections more than twice as adherent compared to prophylaxis prescriptions (aOR=2.50, 95% CI: 1.78-3.53, p<0.0001) (Table 21).

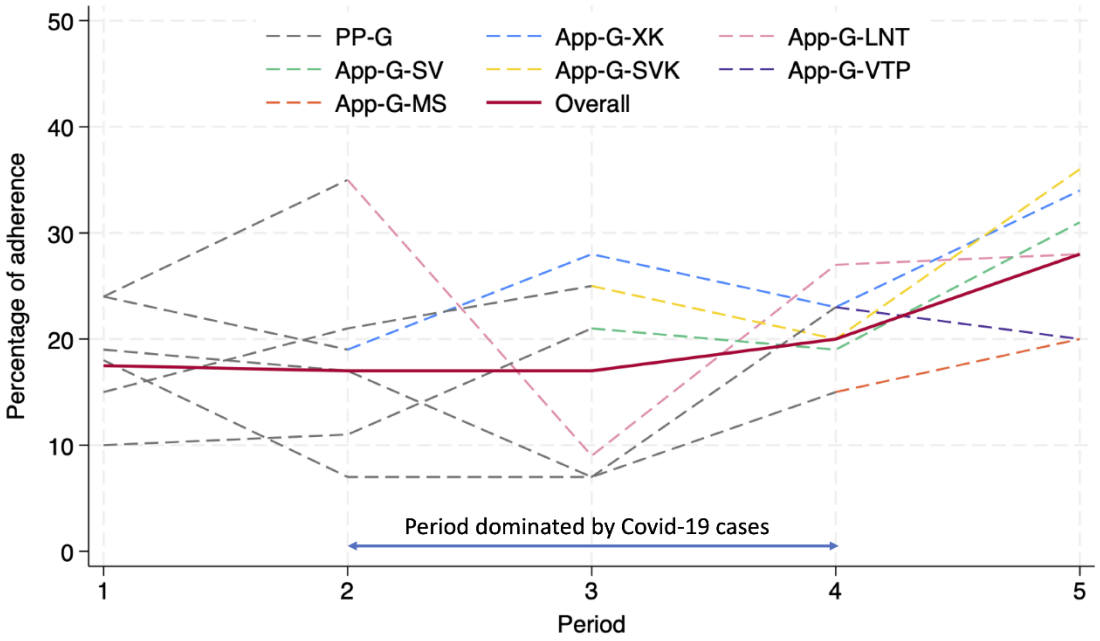
Among inpatient prescriptions, guideline adherence was 4% (31/743, 95%CI: 3-6) for surgical prophylaxis and 16% (48/306, 95% CI: 12-20) for medical prophylaxis. For non-adherence in surgical prophylaxis, 87.6% (624/712, 95% CI: 85-90) involved prescribing the wrong antibiotic, 0.6% (4/712, 95% CI: 0.1-1) prescribed the correct antibiotic but with the wrong dose and duration, and 11.8% (84/712, 95% CI: 9-14) prescribed the wrong duration. Additionally, those who used the wrong antibiotics often continued surgical antimicrobial prophylaxis for more than 24 hours. In medical prophylaxis, 63% (162/258, 95% CI: 57-69) of non-adherence prescriptions were associated with normal vaginal delivery.

Figure 21: Percentage of antimicrobial prescriptions fully adherent to prescribing guidelines among inpatients by cluster and sequence of intervention implementation before and after guideline implementation (%; 95% CI)



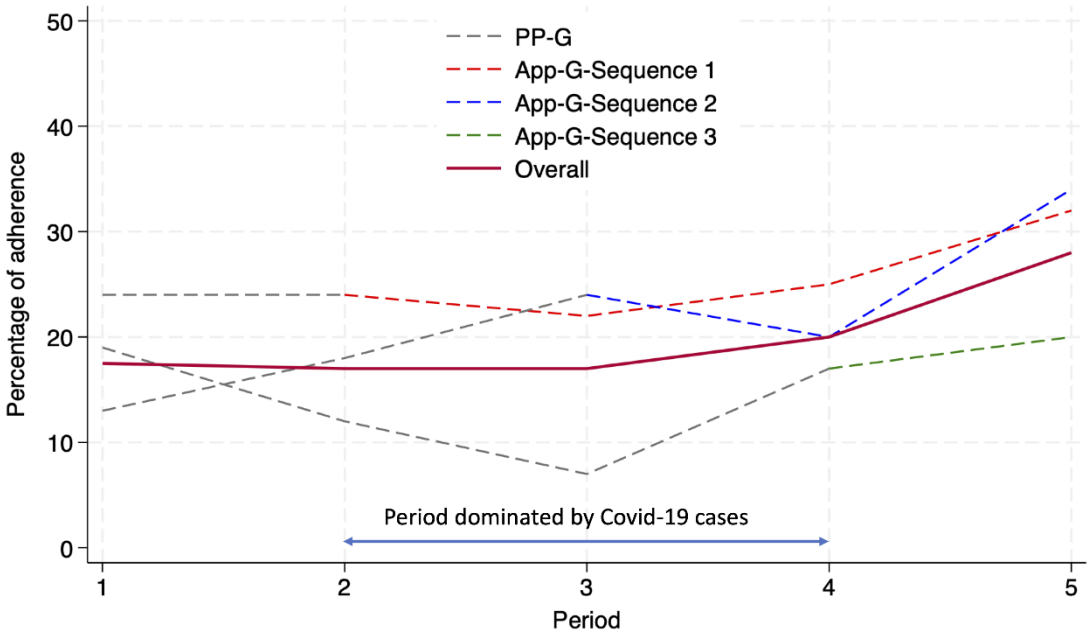
Note: **white area**=group with no antimicrobial prescribing guidelines, **green area**=group with paper-based version of prescribing guidelines (PP-G), **blue area**=group with application-based version of prescribing guidelines and antimicrobial stewardship training (App-G), **Period 1**=Pre-guideline, **Period 2**=Month-6 after PP-G implementation (all hospitals), **Period 3**=First survey after App-G implementation in XK&LNT or month-11 after PP-G introduction, **Period 4**=Second survey post-App-G for XK&LNT, first survey post-App-G for SV & SVK, or month-17 after PP-G introduction, **Period 5**=final survey after all clusters had App-G access or month-22 after PP-G introduction, **(a)**=guideline adherence by groups (pre-guideline, PP-G and App-G), **(b)**=guideline adherence by hospital in each survey, **(c)**=guideline adherence by survey, regardless of hospitals, **(d)**=guideline adherence by sequence (order of intervention delivery) of intervention implementation in each group.

Figure 22: Percentage of antimicrobial prescriptions adherent to prescribing guidelines by hospitals among inpatients



Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **XK**=Xiengkhuang, **LNT**=Luang Namtha, **SV**=Salavan, **SVK**=Savannakhet, **VTP**=Vientiane Provincial, **MS**=Mahosot.

Figure 23: Percentage of antimicrobial prescriptions adherent to prescribing guidelines by hospitals among inpatients



Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **Sequence 1** (Xiengkhuang+Luang Namtha)=started at month-6 after PP-G implementation, **Sequence 2** (Salavan+Savannakhet)=started at month-11 after PP-G, **Sequence 3** (Mahosot+Vientiane Province)=started at month-17 after PP-G.

Table 20: Univariate analysis of full guideline adherence and potential confounders in inpatients post-guideline implementation

Variables		Total			PP-G			App-G		
		OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Time:	Month 6 after PP-G	1			1			-		
	Month 11-12	1	0.74-1.38	0.953	0.98	0.71-1.35	0.891	1		
	Month 16-17	1.2	0.91-1.59	0.201	1.03	0.68-1.54	0.901	0.94	(0.41-2.15)	0.885
	Month 21-22	1.89	1.47-2.43	<0.0001	-	-	-	1.35	0.61-3.03	0.453
Age:	≤ 1 year	1			1			1		
	> 1 to ≤5 years	0.57	0.35-0.95	0.030	0.76	0.33-1.75	0.518	0.46	0.24-0.87	0.017
	> 5 to ≤14 years	0.31	0.17-0.56	<0.0001	0.55	0.24-1.24	0.149	0.19	0.08-0.48	<0.0001
	≥15 years	0.46	0.35-0.61	<0.0001	0.58	0.37-0.91	0.017	0.44	0.31-0.63	<0.0001
Sex:	Male	1			1			1		
	Female	0.53	0.44-0.65	<0.0001	0.66	0.5-0.88	0.005	0.43	0.33-0.57	<0.0001
Department:	Surgery	1			1			1		
	Obstetrics and Gynaecology	0.17	0.09-0.31	<0.0001	0.19	0.09-0.44	<0.0001	0.13	0.05-0.35	<0.0001
	Medicine	2.96	2.26-3.89	<0.0001	2.83	1.95-4.12	<0.0001	2.78	1.87-4.13	<0.0001
	Paediatrics	2.05	1.47-2.87	<0.0001	1.76	1.06-2.94	0.03	1.92	1.21-3.05	0.005
	Intensive Care Unit	2.64	1.86-3.76	<0.0001	2.62	1.59-4.32	<0.0001	2.38	1.44-3.95	0.001
	Other	0.77	0.5-1.17	0.222	1.05	0.58-1.89	0.871	0.51	0.28-0.94	0.031
Prescribing indication	Prophylaxis	1			1			1		
	Treatment	5.44	4.11-7.2	<0.0001	4.22	2.89-6.15	<0.0001	6.95	4.55-10.61	<0.0001
Type of prescriptions	Empiric	1			1			1		
	Targeted	22.49	13.23-38.26	<0.0001	8.82	4.25-18.32	<0.0001	48.57	19.32-122.09	<0.0001
Sequence of intervention										
	Sequence 3	1								
	Sequence 2	1.86	1.54-2.75	<0.0001	-			-		
	Sequence 1	2.06	1.49-2.33	<0.0001	-			-		

Note: **OR**=Odds Ratio, **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**=group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **Other**=including VIP departments, ENT-EYE (Ear, Nose, Throat and Eyes). **Sequence 1** (Xiengkhuang+Luang Namtha)=started at month-6 after PP-G implementation, **Sequence 2** (Salavan+Savannakhet)=started at month-11 after PP-G, **Sequence 3** (Mahosot+Vientiane Province)=started at month-17 after PP-G. P-values were derived from the Wald Chi-square test.

Table 21: Antimicrobial prescriptions' adherence to prescribing guidelines between PP-G and App-G groups among inpatients

Variables	aOR (95% CI)	P-value
Guideline delivery method:		
PP-G	1	
App-G	1.27 (0.84-1.90)	0.249
Sequence of intervention		
Sequence 3 (MS+VTP)	1	
Sequence 2 (SVK+SV)	1.60 (1-2.55)	0.049
Sequence 1 (XK+LNT)	2.03 (1.20-3.43)	0.008
Age:		
≤1 year	1	
>1 to ≤5 years	0.62 (0.36-1.08)	0.094
>5 to ≤14 years	0.44 (0.23-0.85)	0.014
≥15 years	0.78 (0.46-1.31)	0.343
Sex:		
Male	1	
Female	0.74 (0.59-0.93)	0.010
Department:		
Surgery	1	
Obstetrics and Gynaecology	0.37 (0.19-0.72)	0.004
Medicine	1.70 (1.23-2.35)	0.001
Paediatrics	1.37 (0.76-2.47)	0.293
Intensive Care Unit	1.82 (1.13-2.94)	0.014
Other	0.70 (0.44-1.12)	0.143
Prescribing indication:		
Prophylaxis	1	
Treatment	2.50 (1.78-3.53)	<0.0001
Type of prescription:		
Empiric	1	
Targeted	12.21 (6.91-21.56)	<0.0001

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**=group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **aOR**=adjusted Odds Ratio, **Other**=including VIP departments, ENT-EYE (Ear, Nose, Throat and Eyes), **XK**=Xiengkhuang, **LNT**=Luang Namtha, **SV**=Salavan, **SVK**=Savannakhet, **VTP**=Vientiane Provincial, **MS**=Mahosot**, Sequence 1** (Xiengkhuang+Luang Namtha)=started at month-6 after PP-G implementation, **Sequence 2** (Salavan+Savannakhet)=started at month-11 after PP-G, **Sequence 3** (Mahosot+Vientiane Province)=started at month-17 after PP-G. **P-values** were derived from the Wald Chi-Square test.

1.3. Comparison of full adherence to the prescribing guidelines between pre-guideline, PP-G and App-G among inpatients

After adjusting for potential confounders such as patient age, sex, department, prescribing indication, and types of prescription (empiric or targeted), no difference in guideline adherence was found between the PP-G group (17%, 95% CI: 15-19) compared to the pre-guideline group (18%, 95% CI:15-20) with aOR=0.99, 95% CI: 0.65–1.52, p=0.979. While, the App-G group (26%, 95% CI: 23-28) showed a 24% increase in the odds of adherence compared to the pre-guideline group (aOR=1.24, 95% CI: 0.81–1.90, p=0.315), though this difference was not statistically significant (Table 22).

Table 22: Antimicrobial prescriptions' adherence to prescribing guidelines between pre-guideline, PP-G and App-G groups among inpatients

Variables	aOR (95% CI)	P-value
Guideline delivery method:		
Pre-guideline	1	
PP-G	0.99 (0.65-1.52)	0.979
App-G	1.24 (0.81-1.90)	0.315
Sequence of intervention		
Sequence 3 (MS+VTP)	1	
Sequence 2 (SVK+SV)	1.34 (0.92-1.97)	0.129
Sequence 1 (XK+LNT)	1.81 (1.18-2.76)	0.006
Age:		
≤1 year	1	
>1 to ≤5 years	0.77 (0.50-1.19)	0.248
>5 to ≤14 years	0.30 (0.17-0.55)	<0.0001
≥15 years	0.65 (0.41-1.02)	0.064
Sex:		
Male	1	
Female	0.81 (0.66-0.99)	0.041
Department:		
Surgery	1	
Obstetrics and Gynaecology	0.31 (0.17-0.57)	<0.0001
Medicine	1.55 (1.16-2.06)	0.003
Paediatrics	1.54 (0.93-2.55)	0.093

Intensive Care Unit	1.71 (1.12-2.61)	0.013
Other	0.73 (0.48-1.12)	0.153
Prescribing indication:		
Prophylaxis	1	
Treatment	2.52 (1.86-3.41)	<0.0001
Type of prescription:		
Empiric	1	
Targeted	11.76 (6.95-19.90)	<0.0001

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **Other**=including VIP departments, ENT-EYE (Ear, Nose, Throat and Eyes), **aOR**= adjusted odds ratio, **XK**=Xiengkhuang, **LNT**=Luang Namtha, **SV**=Salavan, **SVK**=Savannakhet, **VTP**=Vientiane Provincial, **MS**=Mahosot**, Sequence 1** (Xiengkhuang+Luang Namtha)=started at month-6 after PP-G implementation, **Sequence 2** (Salavan+Savannakhet)= started at month-11 after PP-G, **Sequence 3** (Mahosot+Vientiane Province)=started at month-17 after PP-G. **P-values** were derived from the Wald Chi-Square test.

Partial adherence to the guidelines (using correct antimicrobial agent(s) only based on the provided antimicrobial prescribing guidelines) among inpatients was also assessed (Appendix 15.1). Pneumonia was the most common prescribing indication across all ages. The overall guideline adherence was 34% higher in the App-G group (31%, 95% CI: 23-39) than the PP-G group (17%, 95% CI: 10-25), after adjusting for patient's age and accounting for random effects (aOR=1.34, 95%CI: 0.36-4.98, p=0.666). Adherence was 97% lower in adults compared to infants (≤1 year) (aOR=0.04, 95% CI: 0.01-0.10, p<0.0001). Appendix 15.2 provides additional data on the top three prescribing indications by age group.

2. Outpatients

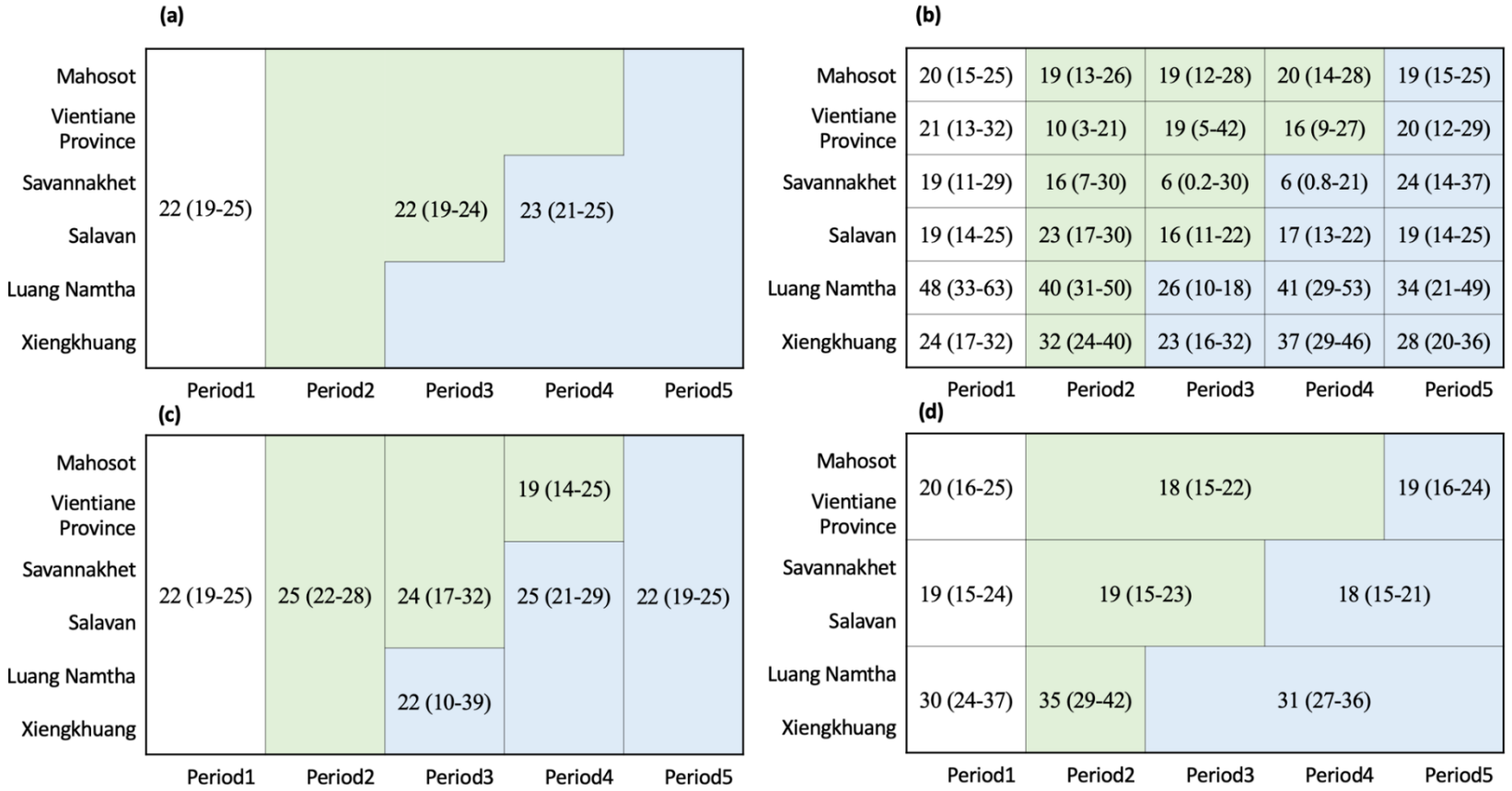
2.1. Overall percentage of antimicrobial prescriptions fully adherent to prescribing guidelines between PP-G and App-G among outpatients

Of the 3,905 OPD prescriptions, 3,568 (91%; 95% CI: 90–92) were assessable for guideline adherence. Of 337 prescriptions (9%; 95% CI: 8–10) that could not be assessed, 28% (94/337, 95% CI: 23-33) lacked clear prescribing indications, and 72% (243/337, 95% CI: 67-77) involved conditions not covered by guidelines.

Overall adherence to the guidelines among outpatients was similar in the pre-guideline, PP-G, and App-G groups, at 22% (95% CI: 19-25), 22% (95% CI: 19-24), and 23% (95% CI: 21-25), respectively (p=0.703) (Figure 24a). The percentage of guideline adherence among outpatients varied from 6% (95% CI: 0.2-30) to 48% (95% CI: 33-63) across six hospitals in five surveys. (Figure 24b, 25 and 26).

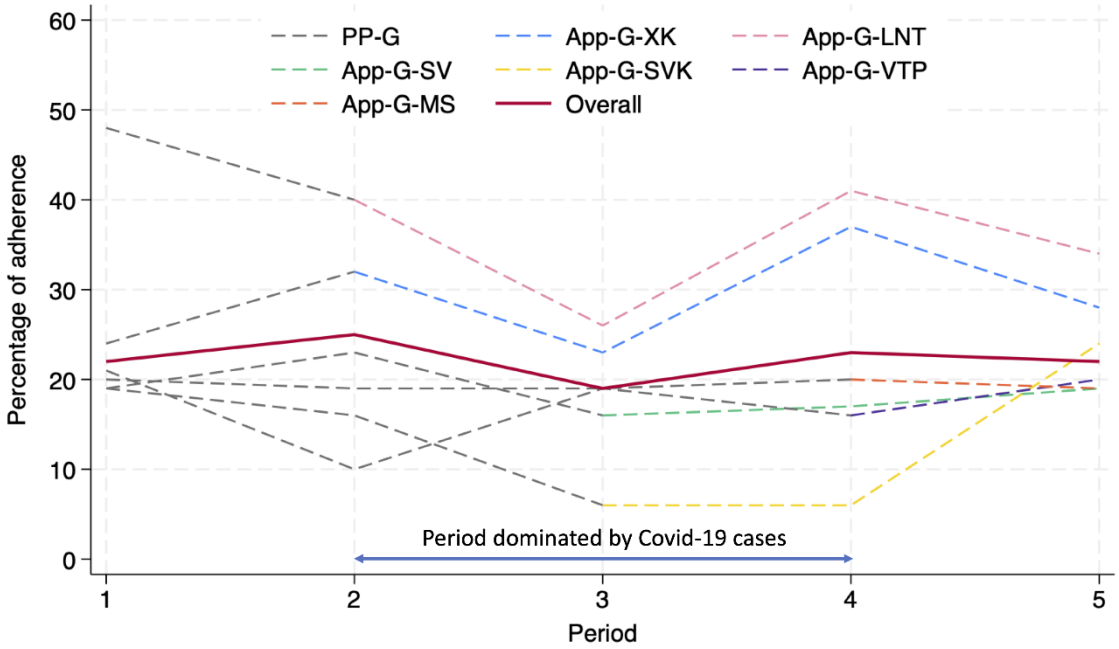
When assessing each survey (Figure 24c), adherence to the guidelines at month-6 after PP-G implementation was 25% (95% CI: 22-28). This remained at 24% (95% CI: 17-32) at month-11 and dropped to 19% (95% CI: 14-25) at month-17 of the PP-G group. Among the App-G group, the highest adherence percentage was observed at month-17 at 25% (95% CI: 21-29), decreasing to 22% (95% CI: 19-25) at month-22. The overall percentage of guideline adherence among outpatients at the end of the study when all clusters had access to both PP-G and App-G (22%; 95% CI: 19-25), was not different compared to the pre-guideline period (22%; 95% CI: 19-25), with p=0.941.

Figure 24: Percentage of antimicrobial prescriptions fully adherent to prescribing guidelines among outpatients (%; 95% CI)



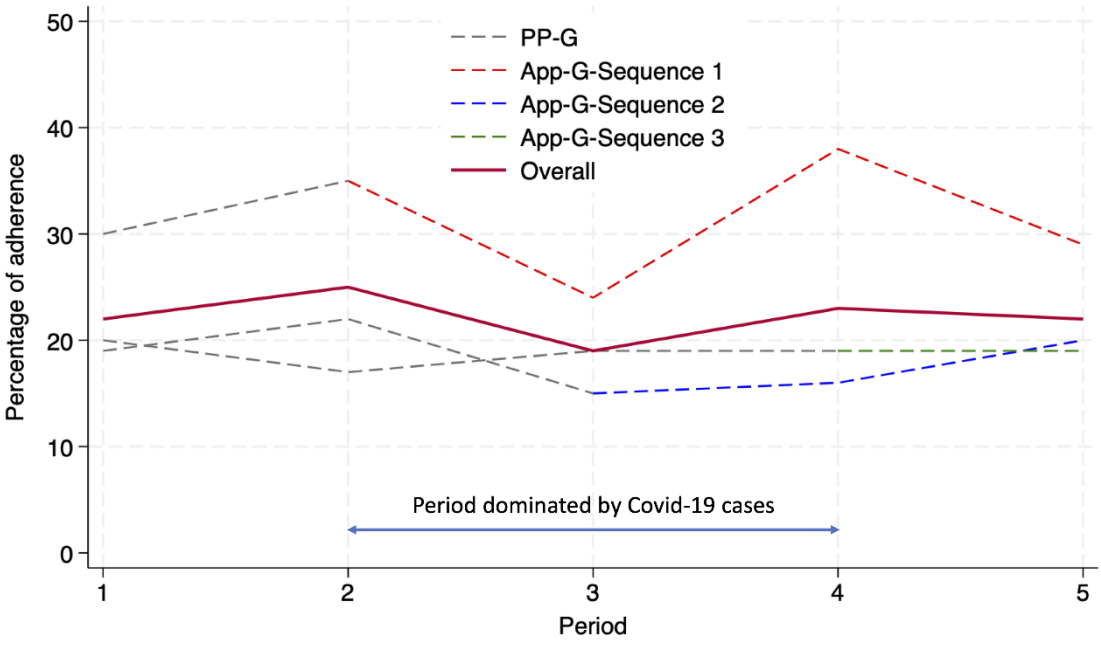
Note: **white area**=group with no antimicrobial prescribing guidelines, **green area**=group with paper-based version of prescribing guidelines (PP-G), **blue area**=group with application-based version of prescribing guidelines and antimicrobial stewardship training (App-G), **Period 1**=Pre-guideline, **Period 2**=Month-6 after PP-G implementation (all hospitals), **Period 3**=First survey after App-G implementation in XK&LNT or month-11 after PP-G introduction, **Period 4**=Second survey post-App-G for XK&LNT, first survey post-App-G for SV & SVK, or month-17 after PP-G introduction, **Period 5**=final survey after all clusters had App-G access or month-22 after PP-G introduction, **(a)**=guideline adherence by groups (pre-guideline, PP-G and App-G), **(b)**=guideline adherence by hospital in each survey, **(c)**=guideline adherence by survey, regardless of hospitals, **(d)**=guideline adherence by sequence (order of intervention delivery) of intervention implementation in each group.

Figure 25: Percentage of antimicrobial prescriptions adherent to prescribing guidelines by cluster among outpatients



Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **XK**=Xiengkhuang, **LNT**=Luang Namtha, **SV**=Salavan, **SVK**=Savannakhet, **VTP**=Vientiane Provincial, **MS**=Mahosot.

Figure 26: Percentage of antimicrobial prescriptions adherent to prescribing guidelines by sequence of intervention implementation among outpatients



Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**=group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **Sequence 1** (Xiengkhuang+Luang Namtha)=started at month-6 after PP-G implementation, **Sequence 2** (Salavan+Savannakhet)=started at month-11 after PP-G, **Sequence 3** (Mahosot+Vientiane Province)=started at month-17 after PP-G.

2.2. Comparison of full adherence to the prescribing guidelines between PP-G and App-G among outpatients

Adherence to guidelines in the PP-G group (22% adherence to guideline, 95% CI: 19-24) did not differ from the App-G group (23% adherence to guideline, 95% CI: 21-25) among outpatients, with an unadjusted OR=1.08 (95% CI: 0.9-1.29, p=0.434). After accounting for random effects (time and cluster) and adjusting for patient's age and sequence of intervention introduction as potential confounders, the adherence in the App-G group remained similar to the PP-G group (aOR=0.90, 95% CI: 0.74-1.09, p=0.299).

However, guideline adherence in the first paired hospitals with access to App-G (31%, 95% CI: 27-36) was double that of the last paired hospitals (19%, 95% CI: 16-24) with an aOR of 2.01, 95% CI: 1.59-2.54, p<0.0001. No difference in adherence was observed between the second and last paired hospitals.

Older children aged >5 to ≤14 years showed higher odds of adherence compared to infant aged ≤1 year (aOR=1.52 (95% CI: 1.01-2.27, p=0.043). No significant difference in adherence was observed for other age groups compared to infants (Table 23).

Table 23: Antimicrobial prescriptions adherence to prescribing guidelines between PP-G and App-G groups among outpatients

Characteristics	aOR (95% CI)	P-value
Guideline delivery method:		
PP-G	1	
App-G	0.90 (0.74-1.09)	0.299
Sequence of intervention		
Sequence 3 (MS+VTP)		
Sequence 2 (SVK+SV)	0.86 (0.69-1.09)	0.224
Sequence 1 (XK+LNT)	2.01 (1.59-2.54)	<0.0001
Age:		
≤1 year	1	
>1 to ≤5 years	1.23 (0.84-1.82)	0.288
>5 to ≤14 years	1.52 (1.01-2.27)	0.043
≥15 years	0.73 (0.51-1.05)	0.092

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **aOR**=adjusted odds ratio, **XK**=Xiengkhuang, **LNT**=Luang Namtha, **SV**=Salavan, **SVK**=Savannakhet, **VTP**=Vientiane Provincial, **MS**=Mahosot**, Sequence 1** (Xiengkhuang+Luang Namtha)=started at month-6 after PP-G implementation, **Sequence 2** (Salavan+Savannakhet)=started at month-11 after PP-G, **Sequence 3** (Mahosot+Vientiane Province)=started at month-17 after PP-G*,* **P-values** were derived from the Wald Chi-Square test.

2.3. Comparison of Full adherence to the prescribing guidelines between pre-guideline, PP-G and App-G among outpatients

Compared to the pre-guideline group, no significant difference in adherence was observed in either the PP-G or App-G groups, with aOR=1.04 (95% CI: 0.83-1.30, p=0.726) and 0.96 (95% CI: 0.78-1.20, p=0.737), respectively. Adherence in the first paired hospitals receiving App-G was 92% higher than in the last paired hospitals, with an aOR of 1.92 (95% CI: 1.54-2.38, p<0.0001). Older children aged >5 to <15 years had 40% higher odds of adherence compared to infants aged ≤1 year (OR=1.40, 95% CI: 1.00-1.98, p=0.050), though the significance was borderline (Table 24).

Table 24: Antimicrobial prescriptions adherence to prescribing guidelines between pre-guideline, PP-G and App-G groups among outpatients

Characteristics	aOR (95% CI)	p-value
Guideline delivery method:		
Pre-guideline	1	
PP-G	1.04 (0.83-1.30)	0.726
App-G	0.96 (0.78-1.20)	0.737
Sequence of intervention		
Sequence 3 (MS+VTP)	1	
Sequence 2 (SVK+SV)	0.86 (0.69-1.06)	0.157
Sequence 1 (XK+LNT)	1.92 (1.54-2.38)	<0.0001
Age:		
≤1 year	1	
>1 to ≤5 years	1.08 (0.77-1.49)	0.662
>5 to ≤14 years	1.40 (1.00-1.98)	0.050
≥15 years	0.75 (0.55-1.01)	0.059

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **aOR**= adjusted odds ratio, **XK**=Xiengkhuang, **LNT**=Luang Namtha, **SV**=Salavan, **SVK**=Savannakhet, **VTP**=Vientiane Provincial, **MS**=Mahosot**, Sequence 1** (Xiengkhuang+Luang Namtha)= started at month-6 after PP-G implementation, **Sequence 2** (Salavan+Savannakhet)= started at month-11 after PP-G, **Sequence 3** (Mahosot+Vientiane Province)= started at month-17 after PP-G*,* **P-values** were derived from the Wald Chi-Square test.

Partial adherence among outpatients is shown in Appendix 15.1. Most prescribing indications in OPD patients were for treating infections, with 27% (791/2,918, 95% CI: 25–29) adhering to guidelines. Non-infectious or unknown indications accounted for 23% (637/2,773, 95% CI: 21–24) of non-adherence. Tonsillopharyngitis was the most common indication, with higher adherence in the App-G group than the PP-G group (aOR=1.42, 95% CI: 0.07-2.88, p=0.324), though not significant. Adults had 64% lower adherence compared to infants (aOR=0.36, 95% CI: 0.19–0.69, p=0.002) (Appendix 15.2).

Part II: Secondary Endpoints

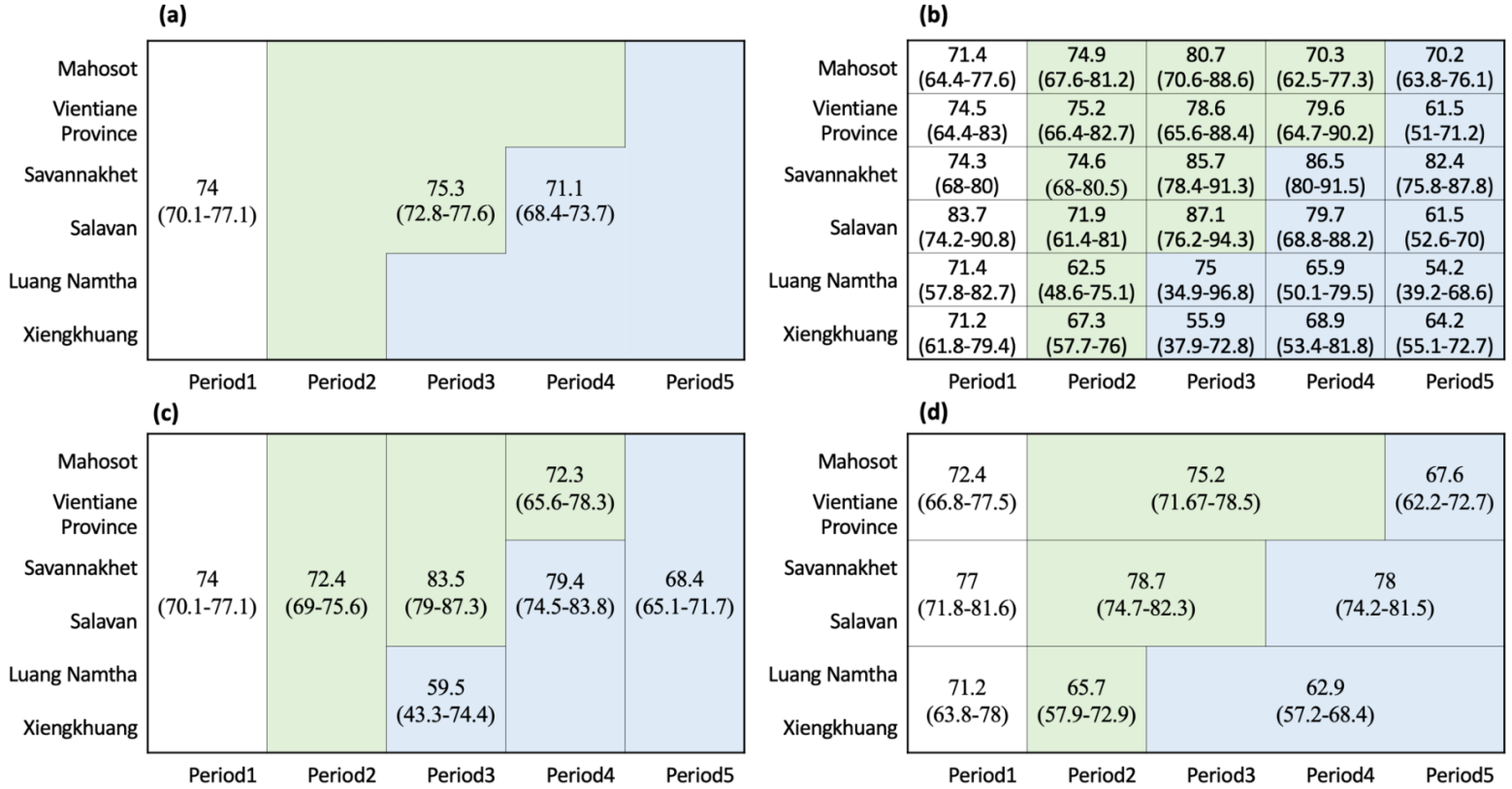
Secondary Endpoint 1: Percentage of antimicrobial prescriptions before and after guidelines implementation

1.1. Hospitalised patients

The overall antimicrobial prescriptions among inpatients was 74% (95% CI: 70.1-77.1) in the pre-guideline group, ranging from 71.2% at XK to 83.7% at SV. In the PP-G group, overall use was 75.3% (95% CI: 72.8-77.6), ranging from 62.5% (95% CI: 48.6-75.1) at LNT in period-2 (month-6 after PP-G introduction) to 87.1% (95% CI: 76.2-94.3) in period-3 (month-11). Following the App-G, overall antimicrobial use dropped to 71.1% (95% CI: 68.4-73.7), with prescriptions, varying from 54.2% (95% CI: 39.2-68.6) at LNT in period-5 (month-22) to 86.5% (95% CI: 80-91.5) at SVK at in period-4 (month-17) (Figure 27a & b).

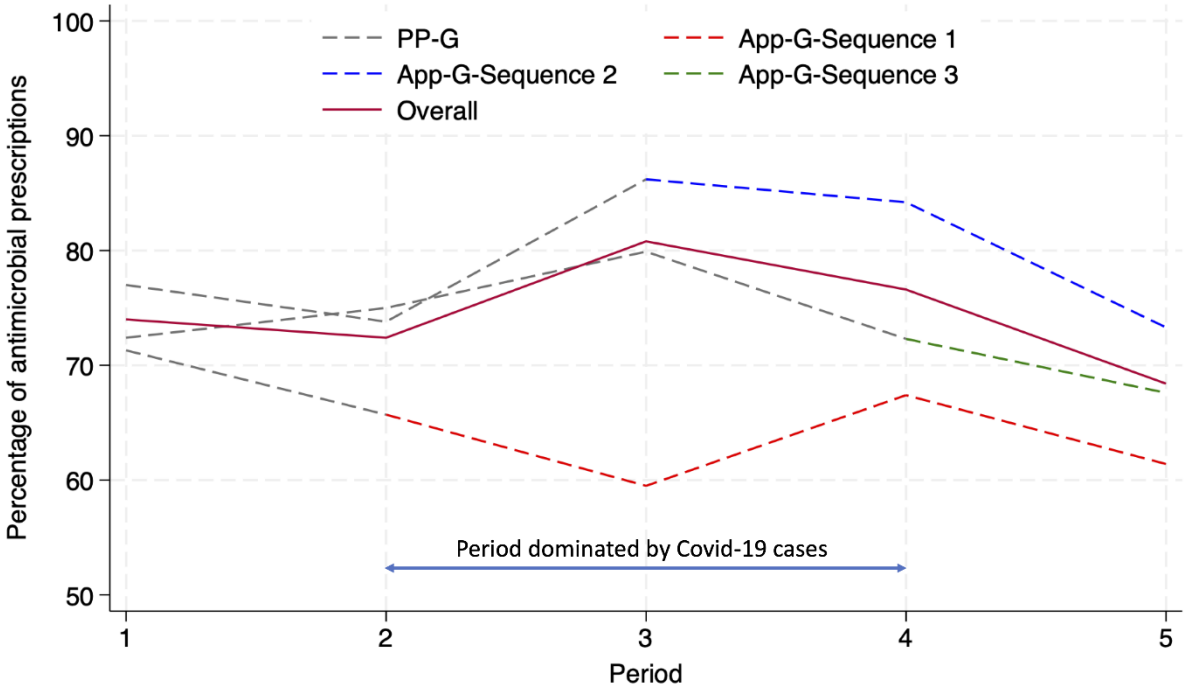
Figure 27c and Figure 28 shows the prescriptions by survey round; antimicrobial use was similar between the pre-guideline group 74% (95% CI: 70.1-77.1) and month-6 after PP-G implementation (72%; 95% CI: 69-75.6). Antimicrobial prescriptions in both PP-G and App-G fluctuated during the study periods. By month-22, the overall use of antimicrobials was 68.4% (95% CI: 65.1-71.7).

Figure 27: Percentage of antimicrobial prescriptions among inpatients before and after antimicrobial prescribing guidelines implementation (%, 95% CI)



Note: **white area**=group with no antimicrobial prescribing guidelines, **green area**=group with paper-based version of prescribing guidelines (PP-G), **blue area**=group with application-based version of prescribing guidelines and antimicrobial stewardship training (App-G), **Period 1**=Pre-guideline, **Period 2**=Month-6 after PP-G implementation (all hospitals), **Period 3**=First survey after App-G implementation in XK&LNT or month-11 after PP-G introduction, **Period 4**=Second survey post-App-G for XK&LNT, first survey post-App-G for SV & SVK, or month-17 after PP-G introduction, **Period 5**=final survey after all clusters had App-G access or month-22 after PP-G introduction, **(a)**=Antimicrobial prescriptions by groups (pre-guideline, PP-G and App-G), **(b)**= Antimicrobial prescriptions by hospital in each survey, **(c)**= Antimicrobial prescriptions by survey, regardless of hospitals, **(d)**= Antimicrobial prescriptions by sequence (order of intervention delivery) of intervention implementation in each group.

Figure 28: Trends of antimicrobial prescriptions among hospitalized patients by sequence of the intervention implementation



Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**=group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **Sequence 1** (Xiengkhuang+Luang Namtha)=started at month-6 after PP-G implementation, **Sequence 2** (Salavan+Savannakhet)=started at month-11 after PP-G, **Sequence 3** (Mahosot+Vientiane Province)=started at month-17 after PP-G.

The unadjusted OR for antimicrobial use between PP-G and App-G showed that antimicrobial use in the App-G group was 19% lower than in the PP-G group (OR=0.81, 95% CI: 0.67-0.97, p=0.021). After adjusting for patient departments, intervention sequence, and accounting for random effects, the reduction in antimicrobial use in the App-G group compared to the PP-G group was no longer significant (aOR=0.82, 95% CI: 0.59-1.13, p=0.224). Non-surgical wards had remarkably lower antimicrobial prescriptions compared to surgical wards (Table 25). Compared to the pre-guideline group, there was no significant difference in antimicrobial use in the PP-G group (aOR=1.03, 95% CI: 0.73-1.43, p=0.877) or the App-G group (aOR=0.83, 95% CI: 0.59-1.16, p=0.281) (Table 26).

Table 25: Comparison of antimicrobial use between PP-G and App-G groups among inpatients

Variables		aOR (95% CI)	P-value
Guideline delivery method:	PP-G	1	
	App-G	0.82 (0.61-1.12)	0.222
Sequence of intervention:			
	Sequence 3 (Mahosot+Vientiane Province)	1	
	Sequence 2 (Savannakhet+Salavan)	1.91 (1.34-2.73)	<0.0001
	Sequence 1 (Xiengkhouang+Luang Namtha)	0.69 (0.47-1.01)	0.060
Department:	Surgery	1	
	Obstetrics and Gynaecology	0.28 (0.19-0.43)	<0.0001
	Medicine	0.11 (0.08-0.16)	<0.0001
	Paediatrics	0.22 (0.14-0.33)	<0.0001
	Intensive Care Unit	0.36 (0.22-0.57)	<0.0001
	Other	0.17 (0.11-0.26)	<0.0001

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **Other**=including VIP departments, ENT-EYE (Ear, Nose, Throat and Eyes), **aOR**= adjusted odds ratio, **Sequence 1**=started at month-6 after PP-G implementation, **Sequence 2**=started at month-11 after PP-G, **Sequence 3**=started at month-17 after PP-G, **P-values** were derived from the Wald Chi-Square test.

Table 26: Comparison of antimicrobial use between pre-guideline, PP-G and App-G groups among inpatients

Variables		aOR (95% CI)	P-value
Guideline delivery method:	Pre-guideline	1	
	PP-G	1.03 (0.73-1.43)	0.877
	App-G	0.83 (0.59-1.16)	0.281
Sequence of intervention			
	Sequence 3 (Mahosot+Vientiane Province)	1	
	Sequence 2 (Savannakhet+Salavan)	1.80 (1.33-1.43)	<0.0001
	Sequence 1 (Xiengkhouang+Luang Namtha)	0.73 (0.63-1.01)	0.061
Department:	Surgery	1	
	Obstetrics and Gynaecology	0.36 (0.26-0.52)	<0.0001
	Medicine	0.13 (0.10-0.17)	<0.0001
	Paediatrics	0.30 (0.21-0.43)	<0.0001
	Intensive Care Unit	0.44 (0.29-0.65)	<0.0001
	Other	0.20 (0.13-0.29)	<0.0001

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **Other**=including VIP departments, ENT-EYE (Ear, Nose, Throat and Eyes), **aOR**= adjusted odds ratio, **Sequence 1**=started at month-6 after PP-G implementation, **Sequence 2**=started at month-11 after PP-G, **Sequence 3**=started at month-17 after PP-G, **P-values** were derived from the Wald Chi-Square test.

1.2. Outpatients

Antimicrobial prescriptions among outpatients at individual hospitals ranged from 7.8% (95% CI: 4.3-12.8) at SVK in period-3 to 72.4% (95% CI: 67.8-76.7) at SV in period-4. The overall use of antimicrobials in the pre-guideline group was 27.3% (95% CI: 25.8-29), ranging from 11.2% (95% CI: 9-13.7) at VTP to 58.2% (95% CI: 46.6-69.2) at SV. The overall use in the PP-G group was 21.2% (95% CI: 20.1-22.3), ranging from 7.8% (95% CI: 4.3-12.8) at SVK in period-3 to 49.7% (95% CI: 44.6-54.9) at SV in the same period. The percentage of antimicrobial use then peaked at 29% (95% CI: 27.8-30.2) in the App-G group, ranging from 10.4% (95% CI: 6.8-15.1) at SVK in period-4 to 72.4% (95% CI: 67.8-76.7) at SV in the same period (Figure 29a & b).

At month-6 after PP-G introduction, the overall use of antimicrobials in outpatient settings dropped from 27.3% (95% CI: 25.8-29) in the pre-guideline group to 21.3% (95% CI: 19.9-22.8). The use of antimicrobials in the PP-G and App-G groups fluctuated throughout the study periods. By period-5, when all clusters had access to the intervention, the overall use of antimicrobials was 23.8% (95% CI: 22.4-25.4) (Figure 29c).

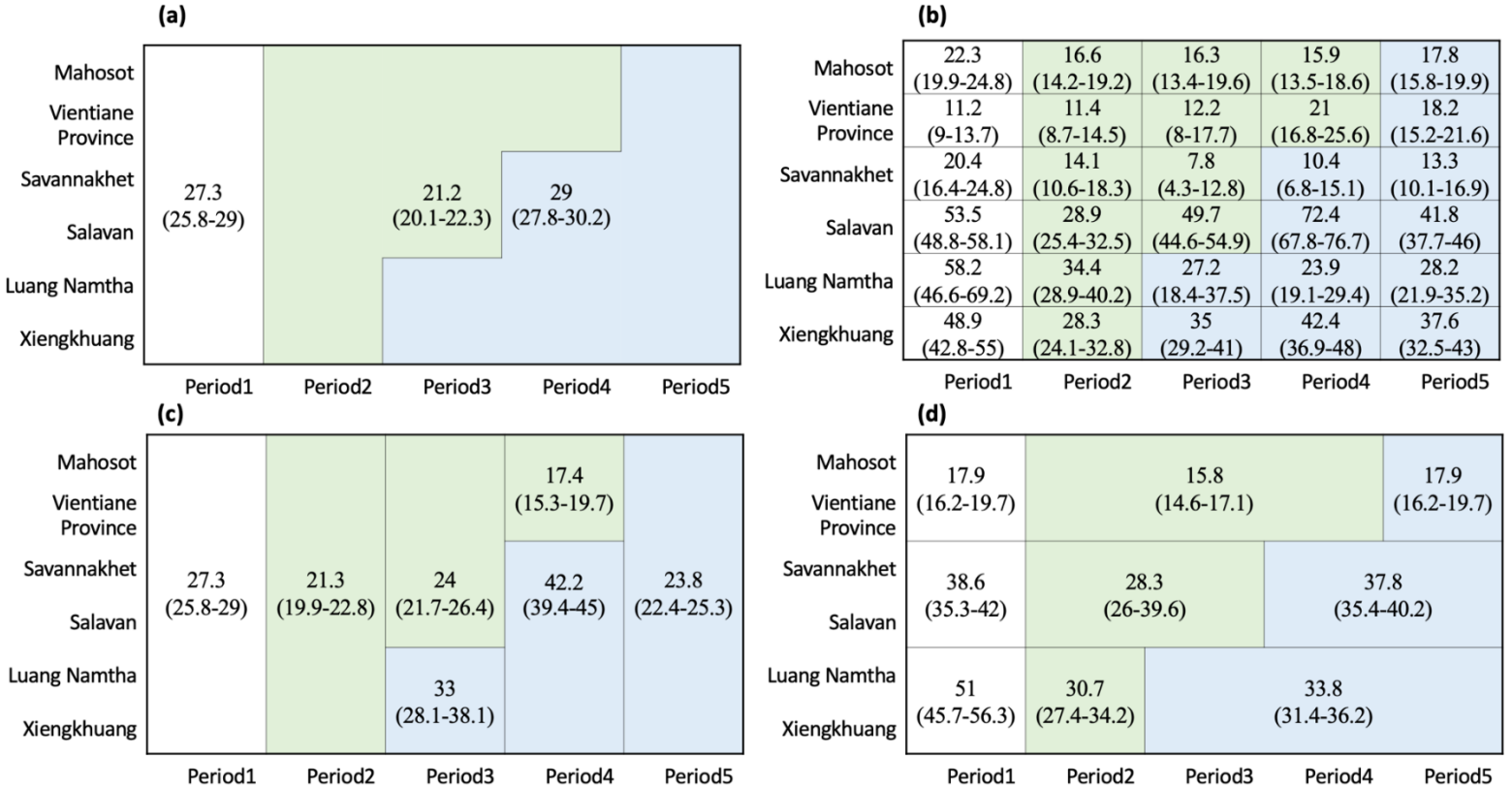
Focusing on the sequence of intervention implementation, antimicrobial use in the first sequence (XK and LNT) decreased in the PP-G group, then went up in the App-G group. A similar trend was observed in sequences-2 (SV and SVK) and sequence-3 (VTP and MS), where antimicrobial use decreased in the PP-G group and increased again by the end of the study (Figure 29d & Figure 30).

The unadjusted OR for antimicrobial use between PP-G and App-G among outpatients showed that antimicrobial use in the App-G group (29%, 95% CI: 27.8-30.2) was 52% higher than in the PP-G group (21.2%, 95% CI: 20.1-22.3), with an

OR of 1.52, 95% CI: 1.39-1.66, p<0.0001. After adjusting for intervention sequence and random effects, antimicrobial use in the App-G group was 28% higher than in the PP-G group (aOR=1.28, 95% CI: 0.72-2.29, p=0.411).

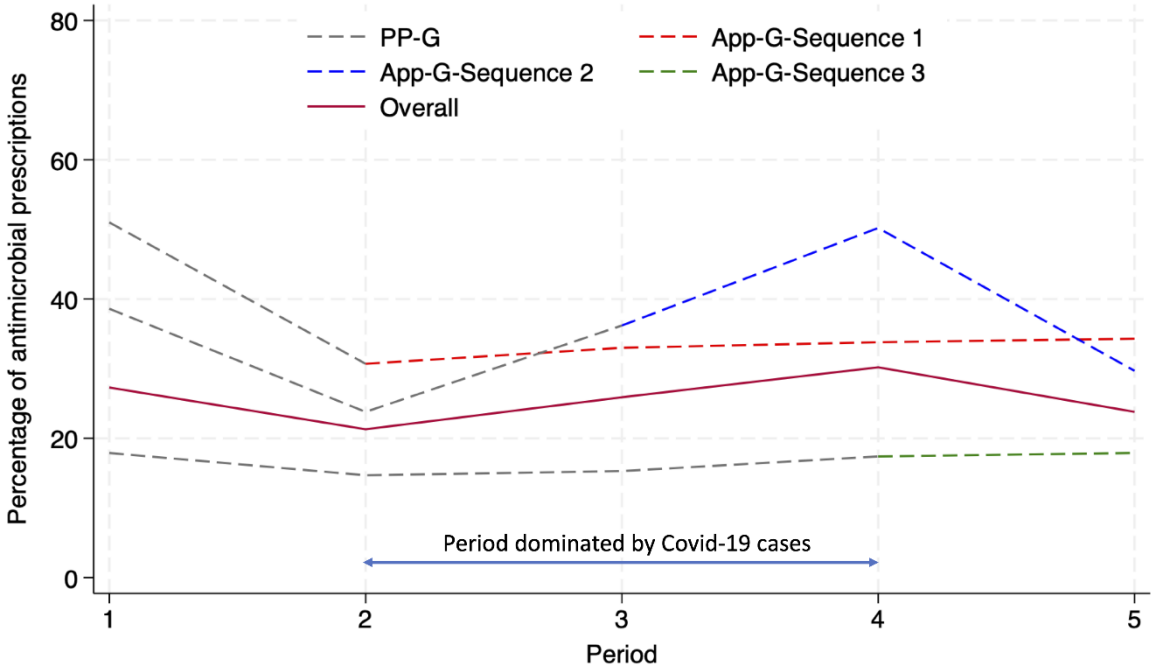
Compared to the pre-guideline group (27.3%, 95% CI: 25.8-29), antimicrobial use was 41% lower in the PP-G group (aOR=0.59, 95% CI: 0.31–1.14, p=0.117) and 30% in the App-G group (aOR=0.74, 95% CI: 0.36–1.35, p=0.290). Antimicrobial use in the first paired hospitals with App-G access was more than double that of the last paired hospitals (aOR=2.76, 95% CI: 1.48-5.12, p=0.001) and 97% higher in the second paired hospitals (aOR=1.97, 95% CI: 1.09-3.54, p=0.024).

Figure 29: Percentage of antimicrobial prescriptions among outpatients before and after antimicrobial prescribing guidelines implementation (%, 95% CI)



Note: **white area**=group with no antimicrobial prescribing guidelines, **green area**=group with paper-based version of prescribing guidelines (PP-G), **blue area**=group with application-based version of prescribing guidelines and antimicrobial stewardship training (App-G), **Period 1**=Pre-guideline, **Period 2**=Month-6 after PP-G implementation (all hospitals), **Period 3**=First survey after App-G implementation in XK&LNT or month-11 after PP-G introduction, **Period 4**=Second survey post-App-G for XK&LNT, first survey post-App-G for SV & SVK, or month-17 after PP-G introduction, **Period 5**=final survey after all clusters had App-G access or month-22 after PP-G introduction, **(a)**=guideline adherence by groups (pre-guideline, PP-G and App-G), **(b)**=guideline adherence by hospital in each survey, **(c)**=guideline adherence by survey, regardless hospitals, **(d)**=guideline adherence by sequence of intervention implementation in each group.

Figure 30: Trends of antimicrobial prescriptions among outpatients in six clusters over 22 months by sequence of intervention implementation



Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**=group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **Sequence 1** (Xiengkhuang+Luang Namtha)=started at month-6 after PP-G implementation, **Sequence 2** (Salavan+Savannakhet)=started at month-11 after PP-G, **Sequence 3** (Mahosot+Vientiane Province)=started at month-17 after PP-G.

Part II: Secondary Endpoint 2 - Antibiotic Defined Daily Doses (DDD) before and after antimicrobial prescribing guidelines implementation

2.1. Hospitalised patients

2.1.1. Adult patients

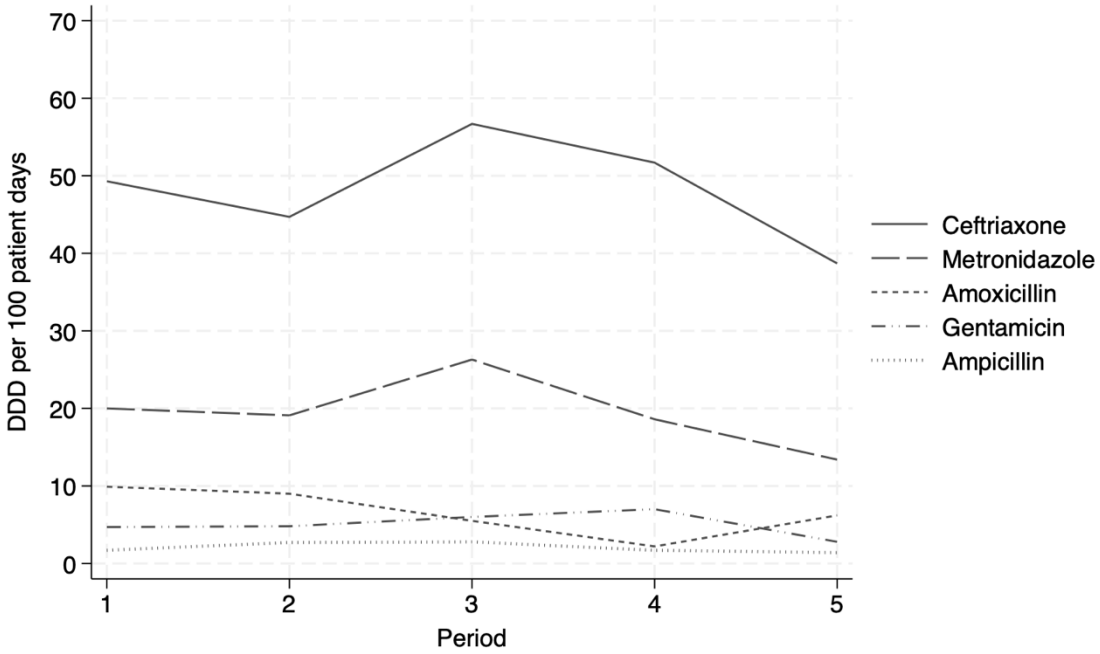
The overall use of antibiotics, measured in Defined Daily Doses (DDD) per 100 patient days, was calculated for patients in adult wards. Some hospitals have a few wards, such as ICUs in Luang Namtha, Salavan, and Savannakhet, that admit both paediatric and adult patients. It was not possible to determine the age of 85/3,167 (3%) inpatients during the study period. VIP wards also admit adults and children; 273/3,167 (9%) patients in this study were from these wards. Adult surgical wards occasionally serve pediatric patients, and 49 paediatric patients on adult surgical wards received antimicrobials in this study. For the DDD calculation, to simplify the analysis mixed age wards were classified as adult wards and 49 pediatric patients known to have received antimicrobials from surgical wards were excluded. The overall defined daily doses (DDD) per 100 patient-days among adult inpatients was 105.3. DDD varied between hospitals and over time (Table 27). In the pre-guideline group, DDD was 103.4 per 100 patient-days, compared to 113 in the PP-G group and 97.3 in the App-G group (Table 27). The most commonly prescribed antibiotic among adult inpatients was ceftriaxone (24%, 95% CI: 23-25.7), contributing 49.3 DDD per 100 patient-days in the pre-guideline group, 50.5 DDD in the PP-G group, and 41.4 DDD in the App-G group. Figure 31 illustrates the DDD of five commonly prescribed antibiotics at each time point.

Table 27: Overall antibiotic defined daily doses (DDD) per 100 patient days in adult inpatients in six hospitals before and after antimicrobial prescribing guidelines implementation

Mahosot	97.9	98.2	136.5	92.7	102.7	**102.2**
Vientiane Province	122.0	135.3	139.3	127.6	90.1	**122.6**
Savannakhet	100.7	107.2	128.1	133.0	107.2	**113.3**
Salavan	114.5	95.0	131.5	101.9	80.2	**101.6**
Luang Namtha	100.6	86.8	233.4	98.0	77.8	**94.9**
Xiengkhuang	93.3	111.2	74.1	75.6	59.8	**84.9**
Total	**103.4**	**107.4**	**129.3**	**107.3**	**91.0**	**105.3**
	Period 1	Period 2	Period 3	Period 4	Period 5	Total

Note: **white area**=group with no antimicrobial prescribing guidelines, **green area**=group with paper-based version of prescribing guidelines (PP-G), **blue area**=group with application-based version of prescribing guidelines and antimicrobial stewardship training (App-G). **Period 1**=Pre-guideline, **Period 2**=Month-6 after PP-G implementation (all hospitals), **Period 3**=First survey after App-G implementation in XK&LNT or month-11 after PP-G introduction, **Period 4**=Second survey post-App-G for XK&LNT, first survey post-App-G for SV & SVK, or month-17 after PP-G introduction, **Period 5**=final survey after all clusters had App-G access or month-22 after PP-G introduction.

Figure 31: Antibiotic defined daily doses (DDD) per 100 patient days for 5 commonly prescribed antibiotics in adult inpatients

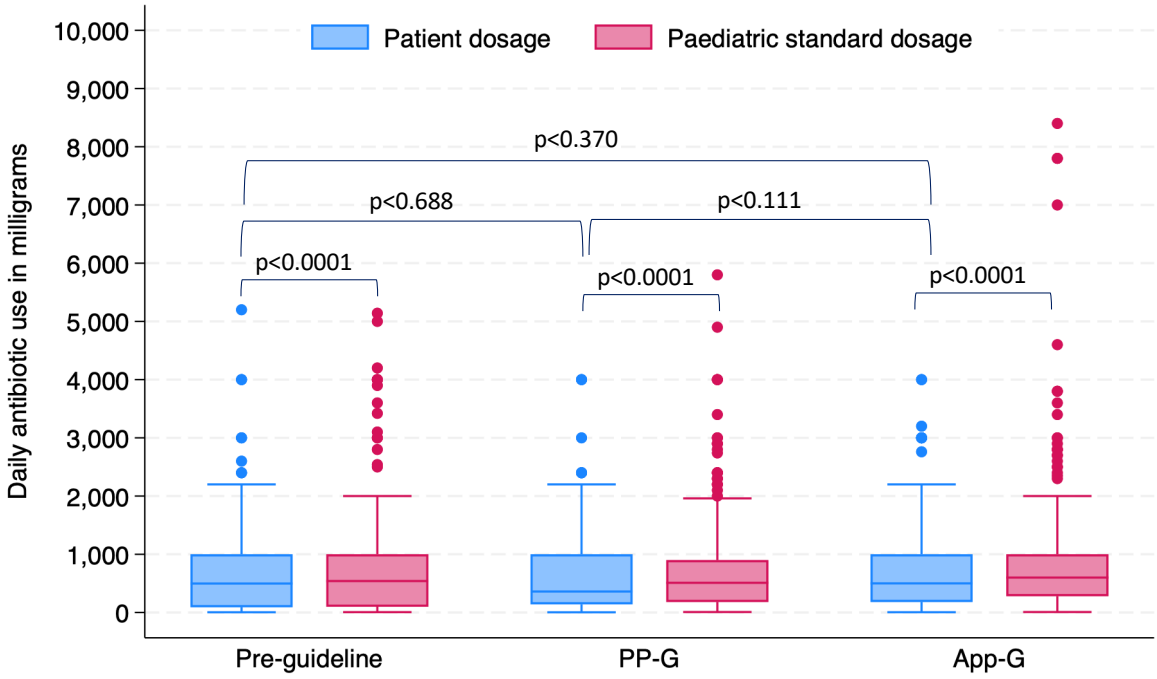


Note: **Period 1**=Pre-guideline, **Period 2**=Month-6 after PP-G implementation (all hospitals), **Period 3**=First survey after App-G implementation in XK&LNT or month-11 after PP-G introduction, **Period 4**=Second survey post-App-G for XK&LNT, first survey post-App-G for SV & SVK, or month-17 after PP-G introduction, **Period 5**=final survey after all clusters had App-G access or month-22 after PP-G introduction.

2.1.2. Paediatric patients

DDDs were not estimated for hospitalized children in this chapter because the DDD system is primarily designed for adult populations. Instead, for the hospitalized children in this study, the actual daily antibiotic dose for each child was assessed and compared with paediatric standard dosages as specified in current antimicrobial prescribing guidelines and international recommendations based on patient's age or weight. When comparing the actual use of antibiotics among hospitalized children to the standard dosages (Wilcoxon Signed-Rank Test), the standard recommended doses were higher than the overall actual use of antibiotics in hospitalized patients in these settings. In the pre-guideline group, median use was 497.5 mg (IQR: 90-1,000) compared to the recommended 540 mg (IQR: 98-1000), $p<0.0001$. In the PP-G group, the median use was 360 mg (IQR: 140-1,000) compared to the recommended 510 mg (IQR: 180-900), $p<0.0001$. Similarly, in the App-G group, the median use was 500 mg (IQR: 180-1,000) compared to the recommended 600 mg (IQR: 280-1,000), $p<0.0001$ (Figure 32).

Figure 32: The median dose of antibiotics among hospitalized children in six clusters over 22 months during paper-based phase and app-based phase



Note: Pre-guideline=group with no antimicrobial prescribing guidelines, **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training.

2.2. Outpatients

2.2.1. Adult outpatients

The overall use of antibiotics in DDD per patient day among adult outpatients varied by hospital and over time (Table 28). The coefficient for DDD in the App-G group when taking into account the time, clusters and sequence of intervention implementation, was -0.04 (95%CI: -0.19–0.11, p=0.593) when compared to the PP-G. The model revealed that the intervention did not significantly affect the DDD among adult outpatients.

Table 28: Overall antibiotic defined daily dose (DDD) among adult outpatients insix hospitals before and after antimicrobial prescribing guidelines implementation

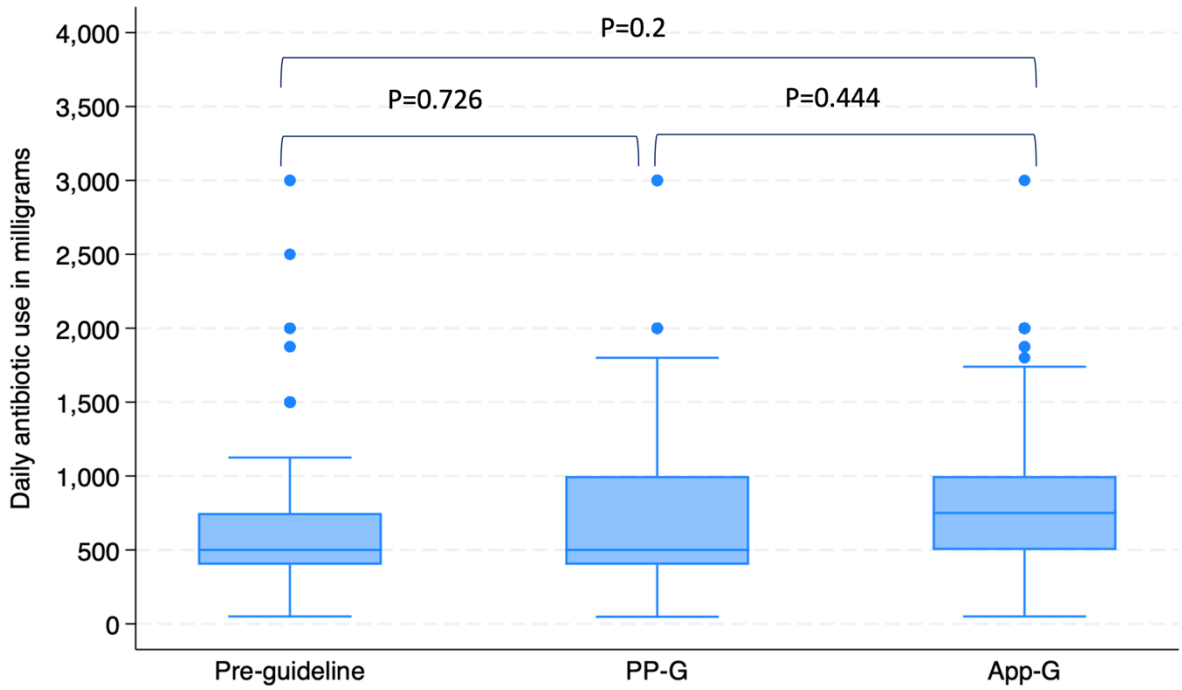
	Period 1	Period 2	Period 3	Period 4	Period 5
Mahosot	268.57	144.75	140.67	155.13	127.6
Vientiane Province	86.4	80	29.33	100.46	85
Savannakhet	62.5	54.12	16.83	27.58	18.25
Salavan	86.28	118.43	139.14	142.45	150.83
Luang Namtha	52.5	56.23	20.17	76.83	56.33
Xiengkhuang	100.24	181.69	145.85	74.42	95.29

Note: white area=group with no antimicrobial prescribing guidelines, **green area**=group with paper-based version of prescribing guidelines (PP-G), **blue area**=group with application-based version of prescribing guidelines and antimicrobial stewardship training (App-G), **Period 1**=Pre-guideline, **Period 2**=Month-6 after PP-G implementation (all hospitals), **Period 3**=First survey after App-G implementation in XK&LNT or month-11 after PP-G introduction, **Period 4**=Second survey post-App-G for XK&LNT, first survey post-App-G for SV & SVK, or month-17 after PP-G introduction, **Period 5**=final survey after all clusters had App-G access or month-22 after PP-G introduction.

2.2.2. Paediatric patients

Among 1,284 antibiotic prescriptions for paediatric outpatients, the most commonly prescribed antibiotics were amoxicillin, with 407 (31.7%) prescriptions, followed by cefalexin with 393 (30.6%), azithromycin with 109 (8.5%), penicillin V with 71 (5.5%), and cloxacillin with 67 (5.2%). The standard antibiotic dose for paediatric outpatients was not estimated because the weights of 92% of the children at OPD were unavailable. The overall median of antibiotic dose for paediatric outpatient in the pre-guideline group was 500mg (IQR: 400-750). In the PP-G group, the median dose was 500 mg (IQR: 500-1,000), and in the App-G group, it was 750 mg (IQR: 500-1,000), with no difference between groups (Figure 33).

Figure 33: Median dose of antibiotics among hospitalized children in six clusters over 22 months during paper-based phase and app-based phase



Note: Pre-guideline=group with no antimicrobial prescribing guidelines, **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training.

Secondary Endpoint 3: Percentage of inpatients receiving antimicrobials via the intravenous (IV) route before and after guidelines implementation

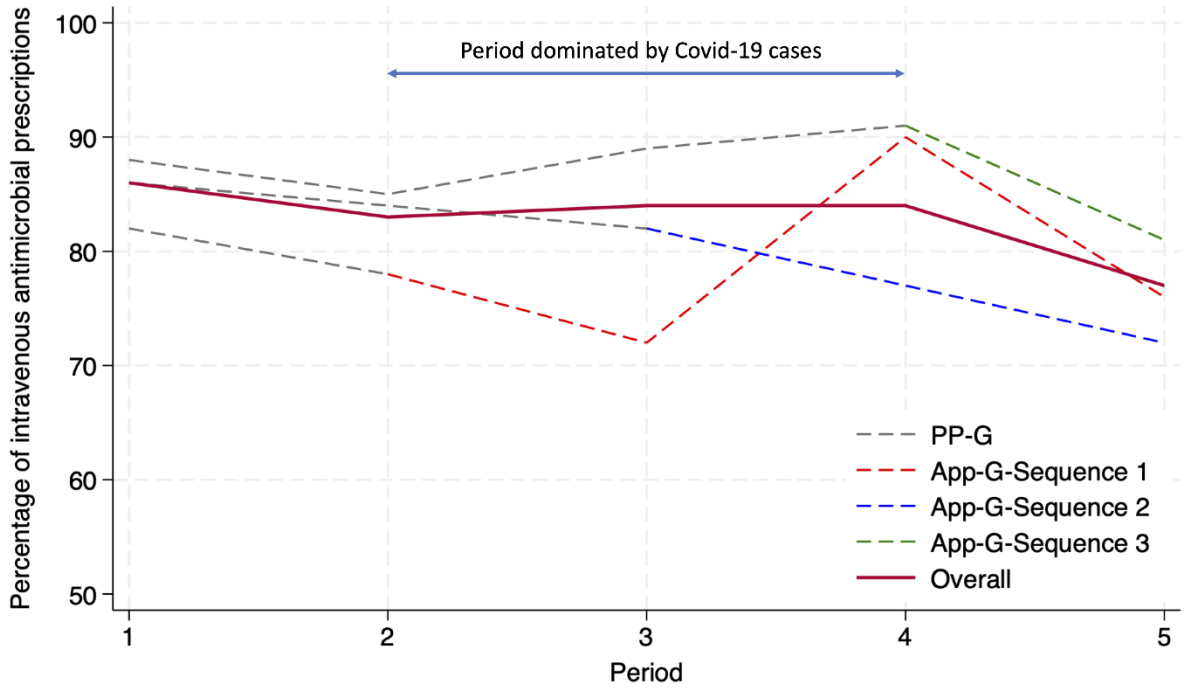
Overall, intravenous antimicrobial use among hospitalized patients accounted for 2,943/3,561 (83%; 95% CI: 81.4-83.9) prescriptions. In the pre-guideline group, 733/852 (86%; 95% CI: 83.5-88.3) received IV antimicrobials. While the use in the PP-G group was 1,267/1,492 (85%, 95% CI: 83-86.7), and in the App-G group was 943/1,217 (77%; 95% CI: 75-79.8). Table 29 and Figure 34 provide an overview of intravenous antimicrobial use across different periods.

Table 29: Percentage of intravenous antimicrobial prescriptions before and after prescribing guidelines implementation among hospitalized patients in six hospitals over 22 months

	Period 1	Period 2	Period 3	Period 4	Period 5
Mahosot	84	83	88	90	79
Vientiane Province	95	87	91	94	85
Savannakhet	85	86	82	76	67
Salavan	88	78	81	80	85
Luang Namtha	82	89	77	94	66
Xiengkhuang	82	73	69	86	80

Note: **white area**=group with no antimicrobial prescribing guidelines, **green area**=group with paper-based version of prescribing guidelines (PP-G), **blue area**=group with application-based version of prescribing guidelines and antimicrobial stewardship training (App-G), **Period 1**=Pre-guideline, **Period 2**=Month-6 after PP-G implementation (all hospitals), **Period 3**=First survey after App-G implementation in XK&LNT or month-11 after PP-G introduction, **Period 4**=Second survey post-App-G for XK&LNT, first survey post-App-G for SV & SVK, or month-17 after PP-G introduction, **Period 5**=final survey after all clusters had App-G access or month-22 after PP-G introduction.

Figure 34: Trends in the use of intravenous antimicrobials before and after prescribing guidelines implementation among hospitalized patients in six clusters over 22 months



Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**=group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **Sequence 1** (Xiengkhuang+Luang Namtha)=started at six months after PP-G implementation, **Sequence 2** (Salavan+Savannakhet)=started at 11-12 months after PP-G, **Sequence 3** (Mahosot+Vientiane Province)=started at 16-17 months after PP-G.

The unadjusted OR showed that IV antimicrobial use in the App-G group (77%; 95% CI: 75-79.8) was 39% lower than in the PP-G group (85%, 95% CI: 83-86.7) with an OR=0.61, 95% CI: 0.50-0.74, p<0.0001). After adjusting for sequence of intervention introduction, patient's age, and department, the odds of IV antimicrobial use in the App-G group were 31% lower than the PP-G group (aOR=0.69, 95% CI: 0.50-0.95, p=0.024). IV antimicrobial use was significantly lower in older children and adults compared to infants, and in non-surgical wards compared to surgical wards. IV antimicrobial use was 49% lower in the first paired hospitals with access to App-G, and 27% lower in the second paired hospitals compared to the third pair,

with aORs of 0.51 (95% CI: 0.33-0.79, p=0.002) and 0.73 (95% CI: 0.51-1.05, p=0.088), respectively (Table 30).

Table 30: Comparing the use of intravenous antimicrobials between PP-G and App-G groups among hospitalized patients

Characteristics	aOR (95% CI)	p-value
Guideline delivery method:		
PP-G	1	
App-G	0.69 (0.50-0.95)	0.024
Sequence of intervention		
Sequence 3	1	
Sequence 2	0.73 (0.51-1.05)	0.088
Sequence 1	0.51 (0.33-0.79)	0.002
Age:		
≤1 year	1	
>1 to ≤5 years	0.28 (0.12-0.65)	0.003
>5 to ≤14 years	0.31 (0.12-0.79)	0.015
≥15 years	0.19 (0.07-0.43)	<0.0001
Department:		
Surgery	1	
Obstetrics and Gynaecology	0.19 (0.13-0.27)	<0.0001
Medicine	0.13 (0.09-0.19)	<0.0001
Paediatrics	0.37 (0.16-0.87)	0.023
Intensive Care Unit	0.61 (0.33-1.13)	0.116
Other	0.42 (0.26-0.66)	<0.0001

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**=group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **Other**=including VIP departments, ENT-EYE (Ear, Nose, Throat and Eyes), **aOR**= adjusted odds ratio, **XK**=Xiengkhuang, **LNT**=Luang Namtha, **SV**=Salavan, **SVK**= Savannakhet, **VTP**=Vientiane Provincial, **MS**=Mahosot**, Sequence 1** (Xiengkhuang+Luang Namtha)=started at month-6 after PP-G implementation, **Sequence 2** (Salavan+Savannakhet)= started at month-11 after PP-G, **Sequence 3** (Mahosot+Vientiane Province)= started at month-17 after PP-G*,* **P-values** were derived from the Wald Chi-Square test.

Part III: General description of antimicrobial prescriptions in Laos

3.1. Hospitalised patients

3.1.1. Patterns of antimicrobial use in six hospitals in five surveys

A total of 3,561 antimicrobials prescriptions were made for inpatients, covering 49 agents. Antibiotics accounted for 3,433 (96.4%, 95% CI: 95.7-97) of prescriptions, followed by antituberculosis agents for 77 (2.2%, 95% CI: 1.7-2.7), antifungals for 24 (0.7%, 95% CI: 0.04-1), antiparasitics for 14 (0.4%, 95% CI: 0.2-0.7), antivirals for 6 (0.2%, 95% CI: 0.08-0.4), and antiretrovirals for 6 (0.2%, 95% CI: 0.06-0.4). The most frequently prescribed antimicrobials were cephalosporins, with 1,629/3,561 (45.7%, 95% CI: 44.1-47.4), followed by nitroimidazoles (metronidazole) with 656/3,561 prescriptions (18.4%, 95% CI: 17.2-19.7), penicillins with 479/3,561 (13.5%, 95% CI: 12.4-14.6), aminoglycosides with 323/3,561 (9.1%; 95% CI: 8.2-10.1) of which amikacin accounted for 5/323 (1.6%, 95% CI: 0.5-3.6) and gentamicin for 318/323 (98.4%, 95% CI: 96.4-99.5) and fluoroquinolones with 90 (2.5%; 95% CI: 2-3.1) (Table 31 and Figure 35).

Third-generation cephalosporins (3rdGC) were the most commonly observed among cephalosporins, accounting for 1,556/1,629 (95.5%, 95% CI: 94.4-96.5). Of 1,556 3rdGC prescriptions. Ceftriaxone accounted for 1,426 (91.6%, 95% CI: 90.2-93), followed by ceftazidime with 70 (4.5%, 95% CI: 3.5-5.7) and cefotaxime with 53 (3.4%, 95% CI: 2.6-4.4). 2ndGC were rarely found, appearing only in survey-5, with 2/1,629 (0.1%, 95% CI: 0.01-0.4). Oral antibiotics were infrequently prescribed, with 493/3,433 (14.4%, 95% CI: 13.2-15.6). Vancomycin was rarely prescribed; with 0.2% (2/798, 95% CI: 0.03-0.9) prescriptions (Table 31).

Table 31: List of antimicrobial prescriptions in six hospitals in each survey period

Antimicrobial class	Antimicrobial agent	Survey 1		Survey 2		Survey 3		Survey 4		Survey 5		Total	
		IPD (n=852)	OPD (n=926)	IPD (n=808)	OPD (n=748)	IPD (n=496)	OPD (n=515)	IPD (n=607)	OPD (n=809)	IPD (n=798)	OPD (n=907)	IPD (n=3,561)	OPD (n=3,905)
Antibiotics		842 (98.8)	826 (89.2)	786 (97.3)	646 (86.4)	475 (95.8)	476 (92.4)	584 (96.2)	731 (90.4)	746 (93.5)	847 (93.4)	3,433 (96.4)	3,526 (90.3)
WHO AWaRe													
Access		423 (50.2)	561 (68)	401 (51)	431 (67)	222 (46.7)	287 (60)	256 (44)	496 (68)	326 (44)	559 (66)	1,628 (47.4)	2,334 (66)
Watch		416 (49.4)	265 (32)	384 (48.8)	215 (33)	252 (53)	189 (40)	328 (56)	235 (32)	420 (56)	288 (34)	1,800 (52.4)	1,192 (34)
Reserve		0	0	0	0	0	0	0	0	0	0	0	0
Not recommended		3 (0.4)	0	1 (0.1)	0	1 (0.2)	0	0	0	0	0	5 (0.2)	0
Aminoglyco-sides		85 (10)	0	70 (8.7)	0	39 (7.9)	0	68 (11.2)	0	61 (7.6)	1 (0.1)	323 (9.1)	1 (0.03)
	Amikacin	1 (0.1)	0	1 (0.1)	0	0	0	0	0	3 (0.4)	0	5 (0.1)	0
	Gentamicin	84 (10)	0	69 (8)	0	39 (8)	0	68 (11)	0	58 (7)	1 (0.1)	318 (9)	1 (0.03)
BL/BLIs		4 (0.5)	33 (3.6)	8 (1)	48 (6.4)	6 (1.2)	25 (4.9)	3 (0.5)	30 (3.7)	15 (1.9)	44 (4.9)	36 (1)	180 (4.6)
	Amoxicillin/ clavulanic acid	1 (0.1)	33 (4)	7 (1)	48 (6)	5 (1)	25 (5)	3 (0.5)	30 (4)	15 (2)	44 (5)	31 (1)	180 (5)
	Ceftriaxone/ sulbactam	3 (0.3)	0	1 (0.1)	0	1 (0.2)	0	0	0	0	0	5 (0.1)	0
Carbapenems	Meropenem	10 (1.2)	0	19 (2)	0	10 (2)	0	13 (2)	0	21 (3)	0	73 (2)	0
Cephalospo-rins		388 (45.5)	242 (26.1)	357 (44.2)	139 (18.6)	224 (45.2)	103 (20)	304 (50.1)	211 (26.1)	356 (44.6)	228 (25.1)	1,629 (45.8)	923 (23.6)
1stGC	Cefalexin	15 (2)	189 (20)	21 (3)	109 (15)	4 (1)	72 (14)	15 (2)	180 (22)	16 (2)	184 (20)	71 (2)	734 (19)
2ndGC	Cefuroxime	0	0	0	0	0	0	0	0	2 (0.2)	0	2 (0.06)	0
3rdGC	Cefixime	0	53 (6)	3 (0.4)	28 (4)	0	31 (6)	3 (0.5)	31 (4)	1 (0.1)	42 (5)	7 (0.2)	185 (5)
	Cefotaxime	14 (1.6)	0	9 (1)	0	7 (1)	0	12 (2)	0	11 (1)	0	53 (1)	0
	Ceftazidime	8 (1)	0	12 (1)	0	13 (3)	0	13 (2)	0	24 (3)	0	70 (2)	0
	Ceftriaxone	354 (41)	0	312 (39)	2 (0.3)	200 (40)	0	261 (43)	0	302 (38)	2 (0.2)	1,426 (40)	4 (0.1)

Fluoroquino-lones		17 (2)	80 (8.6)	15 (1.9)	84 (11.2)	8 (1.6)	63 (12.2)	16 (2.6)	82 (10.1)	34 (4.3)	86 (9.5)	90 (2.5)	395 (10.1)
	Ciprofloxacin	8 (1)	8 (1)	8 (1)	22 (3)	6 (1)	11 (2)	9 (1)	21 (3)	16 (2)	20 (2)	47 (1)	82 (2)
	Levofloxacin	2 (0.2)	0	0	1 (0.1)	0	0	3 (0.5)	0	9 91)	0	14 (0.4)	1 (0.03)
	Norfloxacin	2 (0.2)	30 (3)	2 (0.2)	19 (2)	1 (0.2)	29 (6)	1 (0.2)	20 (2)	5 (1)	31 (3)	11 (0.3)	129 (3)
	Ofloxacin	5 (0.6)	42 (4)	5 (0.6)	42 (6)	1 (0.2)	23 (4)	3 (0.5)	41 (5)	4 (0.5)	35 (4)	18 (0.5)	183 (5)
Glycopeptide	Vancomycin	0	0	0	0	0	0	0	0	2 (0.2)	0	2 (0.06)	0
Lincosamides		1 (0.1)	1 (0.1)	0	3 (0.4)	0	0	0	0	0	0	1 (0.03)	4 (0.1)
	Clindamycin	1 (0.1)	0	0	0	0	0	0	0	0	0	1 (0.03)	0
	Lincomycin	0	1 (0.1)	0	3 (0.4)	0	0	0	0	0	0	0	4 (0.1)
Macrolides		16 (1.9)	131 (14.2)	14 (1.7)	99 (13.2)	14 (2.8)	95 (18.5)	10 (1.7)	121 (15)	23 (2.9)	158 (17.4)	77 (2.2)	604 (15.5)
	Azithromycin	11 (1)	97 (10)	13 (2)	73 (10)	12 (2)	71 (14)	8 (1)	86 (11)	20 (2)	122 (13)	64 (2)	449 (11)
	Clarithromycin	1 (0.1)	5 (0.5)	1 (0.1)	4 (0.5)	2 (0.4)	5 (1)	1 (0.2)	7 (1)	1 (0.1)	11 (1)	6 (0.2)	32 (1)
	Erythromycin	4 (0.5)	26 (3)	0	21 (3)	0	18 (3)	1 (0.2)	28 (3)	2 (0.2)	24 (3)	7 (0.2)	117 (3)
	Roxythromycin	0	3 (0.3)	0	1 (0.1)	0	1 (0.2)	0	0	0	1 (0.1)	0	6 (0.1)
Nitroimidazole	Metronidazole	164 (19)	52 (6)	167 (21)	53 (7)	113 (23)	37 (7)	105 (17)	47 (6)	107 (13)	40 (4)	656 (18)	229 (6)
Penicillins		141 (16.6)	251 (27.1)	124 (15.4)	187 (25)	50 (10.1)	133 (25.8)	53 (8.7)	214 (26.5)	111 (13.9)	236 (26)	479 (13.5)	1,021 (26.2)
	Amoxicillin	58 (7)	143 (15)	44 (5)	92 (12)	16 (3)	69 (13)	14 (2)	137 (17)	43 (5)	190 (21)	175 (5)	631 916)
	Ampicillin	58 (7)	22 (2)	53 (6)	21 (3)	22 (4)	21 (4)	32 (5)	30 (4)	49 (6)	4 (0.4)	214 (6)	98 (2)
	Cloxacillin	19 (2)	36 (4)	22 93)	52 (7)	12 (2)	32 (6)	7 (1)	28 (3)	18 (2)	26 (3)	78 (2)	174 (4)
	Penicillin G	4 (0.5)	0	4 (0.5)	0	0	0	0	0	0	4 (0.4)	8 (0.2)	4 (0.1)
	Penicillin V	2 (0.2)	50 (5)	1 (0.1)	22 (3)	0	11 (2)	0	19 (2)	1 (0.1)	12 (1)	4 (0.1)	114 (3)
Sulfonamides	Co-trimoxazole	7 (0.8)	6 (1)	5 (1)	8 (1)	5 (1)	4 (1)	3 (0.5)	5 (1)	8 91)	6 (0.7)	28 (1)	29 (1)
Tetracyclines	Doxycycline	9 (1.1)	30 (3)	7 (1)	25 (3)	6 (1)	16 (3)	9 (1)	21 (3)	8 (1)	48 (5)	39 (1)	140 (3)
Antifungals		3 (0.4)	12 (1.3)	2 (0.3)	18 (2.4)	9 (1.8)	4 (0.8)	2 (0.3)	16 (2)	8 (1)	11 (1.2)	24 (0.7)	61 (1.6)
	Amphotericin B	0	0	0	0	1 (0.2)	0	1 (0.2)	0	1 (0.1)	0	3 (0.08)	0
	Fluconazole	3 (0.3)	0	1 (0.1)	0	7 (1)	0	1 (0.2)	2 (0.3)	7 (1)	2 (0.2)	19 (0.5)	4 (0.1)
	Ketoconazole	0	9 (1)	0	14 (2)	0	2 (0.4)	0	5 (1)	0	5 (0.5)	0	35 (1)
	Nystatin	0	3 (0.3)	1 (0.1)	4 (0.5)	1 (0.2)	2 (0.4)	0	9 (1)	0	4 (0.4)	2 (0.06)	22 (0.5)

Antiparasitics		2 (0.2)	84 (9.1)	7 (0.9)	83 (11.1)	0	31 (6)	1 (0.2)	60 (7.4)	4 (0.5)	42 (4.6)	14 (0.4)	300 (7.7)
	Albendazole	1 (0.1)	79 (9)	4 (0.5)	63 (8)	0	29 (6)	1 (0.2)	55 (7)	4 (0.5)	36 (4)	10 (0.3)	262 (7)
	Mebendazole	1 (0.1)	3 (0.3)	3 (0.4)	18 (2)	0	1 (0.2)	0	4 (0.5)	0	5 (0.5)	4 (0.1)	31 (1)
	Praziquantel	0	2 (0.2)	0	2 (0.3)	0	1 (0.2)	0	1 (0.1)	0	1 (0.1)	0	7 (0.2)
Antiretrovirals		0	0	3 (0.4)	0	2 (0.4)	0	1 (0.2)	0	0	1 (0.1)	6 (0.2)	1 (0.03)
	ABC and 3TC	0	0	0	0	0	0	1 (0.2)	0	0	0	1 (0.03)	0
	ABC	0	0	0	0	1	0	0	0	0	1 (0.1)	1 (0.03)	1 (0.03)
	DTG	0	0	1 (0.1)	0	0	0	1 (0.2)	0	0	0	2 (0.06)	0
	3TC and AZT	0	0	1 (0.1)	0	0	0	0	0	0	0	1 (0.03)	0
	TDF, 3TC and DTG	0	0	1 (0.1)	0	1 (0.2)	0	0	0	0	0	2 (0.06)	0
Antivirals		0	4 (0.4)	2 (0.3)	1 (0.1)	0	4 (0.8)	1 (0.3)	2 (0.3)	3 (0.4)	6 (0.7)	6 (0.2)	17 (0.4)
	Aciclovir	0	4 (0.4)	2 (0.2)	1 (0.1)	0	4 (1)	1 (0.2)	2 (0.3)	2 (0.5)	5 (0.5)	5 (0.14)	16 (0.4)
	Molnupiravir	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.03)	0
	Ombitasvir, Paritaprevir and Ritonavir	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.03)
Antitubercu-losis		5 (0.6)	0	8 (1)	0	10 (2)	0	17 (2.8)	0	37 (4.6)	0	77 (2.2)	0
	Bedaquiline	0	0	0	0	0	0	2 (0.3)	0	8 (1)	0	10 (0.3)	0
	Clofazimine	0	0	0	0	0	0	3 (0.5)	0	8 (1)	0	11 (0.3)	0
	Ethambutol	0	0	0	0	0	0	1 (0.2)	0	0	0	1 (0.03)	0
	Linezolid	0	0	0	0	0	0	2 (0.3)	0	4 (0.5)	0	6 (0.2)	0
	Pyrazinamide	0	0	0	0	0	0	3 (0.5)	0	8 (1)	0	11 (0.3)	0
	Rifampicin	0	0	1 (0.1)	0	2 (0.4)	0	1 (0.2)	0	0	0	4 (0.1)	0
	Rifampicin, isoniazid	2 (0.2)	0	0	0	0	0	0	0	1 (0.1)	0	3 (0.08)	0
	4FDC	3 (0.3)	0	7 (1)	0	8 (2)	0	5 (1)	0	8 (1)	0	31 (1)	0

Note: **IPD**=Inpatients, **OPD**=Outpatient Department, **BL/BLIs**=Beta-lactam/Beta-lactamase inhibitors, **GC**=Generation Cephalosporin, **ABC**=Abacavir, **DTG**=Dolutegravir, **3TC**=Lamivudine, **AZT**=Zidovudine, **TDF**=Tenofovir Disoproxil fumarate, **4FDC** (fixed-dose combination)=Rifampicin, pyrazinamide, ethambutol, isoniazid.

Figure 35: Distribution of antimicrobial prescriptions by Pre-guidelines, PP-G and App-G groups among inpatients



Note: **Pre-guideline**=group with no antimicrobial prescribing guidelines, **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**=group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **BL/BLIs**= Beta-lactam/Beta-lactamase inhibitors.

3.1.2. Antimicrobial prescriptions categorised by WHO AWaRe antibiotics

The use of Access group antibiotics among inpatients was 47.4% (1,628/3,433, 95% CI: 45.7-49.1), 52.4% (1,800/3,433, 95% CI: 50.8-54.1) of Watch group and 0.2% (5/3,433, 95% CI: 0.05-0.3) of Not recommended group. In the App-G group, Access use was 44.6% (511/1,145, 95% CI: 41.7-47.6) and in the PP-G group, it was 48% (694/1,446, 95% CI: 45.4-50.6) both lower than in the pre-guideline group at 50.2% (423/842, 95% CI: 46.8-53.7), p=0.040. Watch group use increased from 49.4% (416/842, 95% CI: 46-52.8) in pre-guideline to 51.9% (750/1,446, 95% CI: 49.3-54.5) in PP-G and to 55.4% (634/1,145, 95% CI: 53.4-58.3) in App-G group, p=0.027 (Table 32).

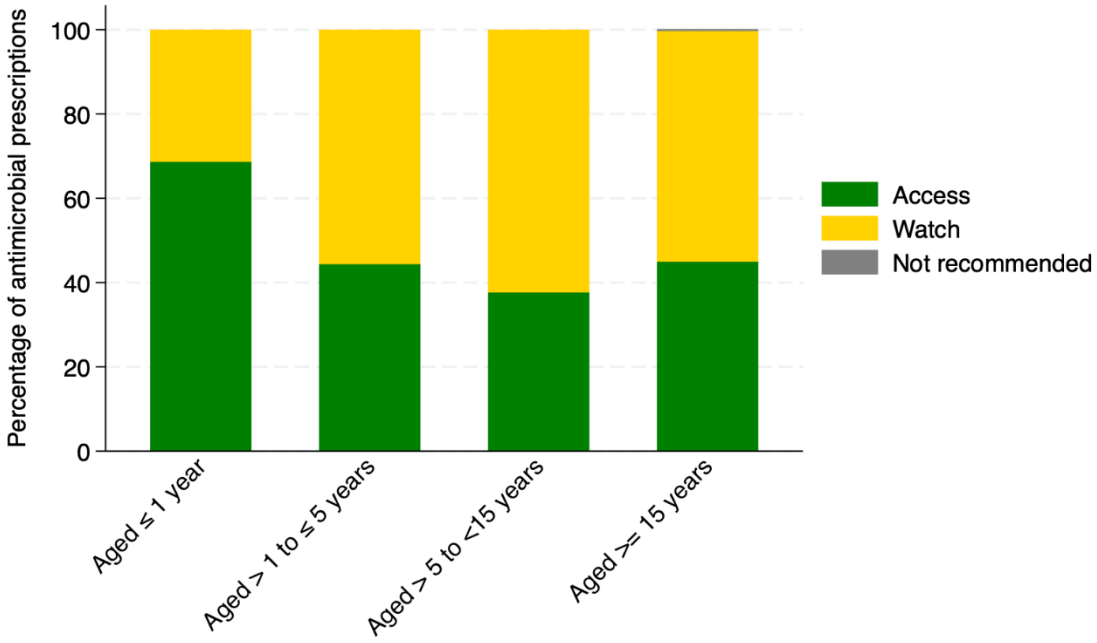
Access antibiotics were used more in children aged <15years (56.6% (415/733), 95% CI: 52.9-60.2) than in adults aged ≥15years (45%, 1,213/2,700, 95% CI: 43-46.8), p<0.0001; and even more in younger children aged ≤1year (68.7%, 281/409, 95% CI: 64-73.2) compared to older children aged >1-14 years (41.2%, 134/324, 95% CI: 36-47), p<0.0001 (Figure 36).

Table 32: Antimicrobial prescription distributing by WHO AWaRe antibiotics among hospitalized patients

Antibiotics	Pre-guideline; n (%)	PP-G, n (%)	App-G; n (%)
Access	423 (50.2)	694 (48)	511 (44.6)
Metronidazole	164 (38.8)	314 (45.2)	178 (34.8)
Gentamicin	84 (19.9)	133 (19.2)	101 (19.8)
Amoxicillin	58 (13.7)	84 (12.1)	61 (11.9)
Ampicillin	58 (13.7)	56 (8.1)	72 (14.1)
Cloxacillin	19 (4.5)	33 (4.8)	26 (5.1)
Cefalexin	15 (3.6)	28 (4)	28 (5.5)
Doxycycline	9 (2.1)	14 (2)	16 (3.1)
Co-trimoxazole	7 (1.7)	11 (1.6)	10 (2)
Penicillin G	4 (5)	4 (0.6)	0
Penicillin V	2 (0.5)	1 (0.1)	1 (0.2)
Amikacin	1 (0.2)	1 (0.1)	3 (0.6)
Amoxicillin/clavulanic acid	1 (0.2)	15 (2.2)	15 (2.9)
Clindamycin	1 (0.2)	0	0
Watch	416 (49.4)	750 (51.9)	634 (55.4)
Ceftriaxone	351 (84.4)	610 (81.3)	465 (73.3)
Cefotaxime	14 (3.4)	21 (2.8)	18 (2.8)
Azithromycin	11 (2.6)	28 (3.7)	25 (3.9)
Meropenem	10 (2.4)	33 (4.4)	30 (4.7)
Ceftazidime	8 (1.9)	27 (3.6)	35 (5.5)
Ciprofloxacin	8 (1.9)	13 (1.7)	26 (4.1)
Ofloxacin	5 (1.2)	8 (1.1)	5 (0.8)
Erythromycin	4 (1)	0	3 (0.5)
Levofloxacin	2 (0.5)	0	12 (1.9)
Norfloxacin	2 (0.5)	3 (0.4)	6 (0.9)
Clarithromycin	2 (0.5)	2 (0.3)	3 (0.5)
Cefixime	0	5 (0.7)	2 (0.3)
Cefuroxime	0	0	2 (0.3)
Vancomycin	0	0	2 (0.3)
Not-recommended	3 (0.4)	2 (0.1)	0
Ceftriaxone/sulbactam	3 (100)	2 (100)	0

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training.

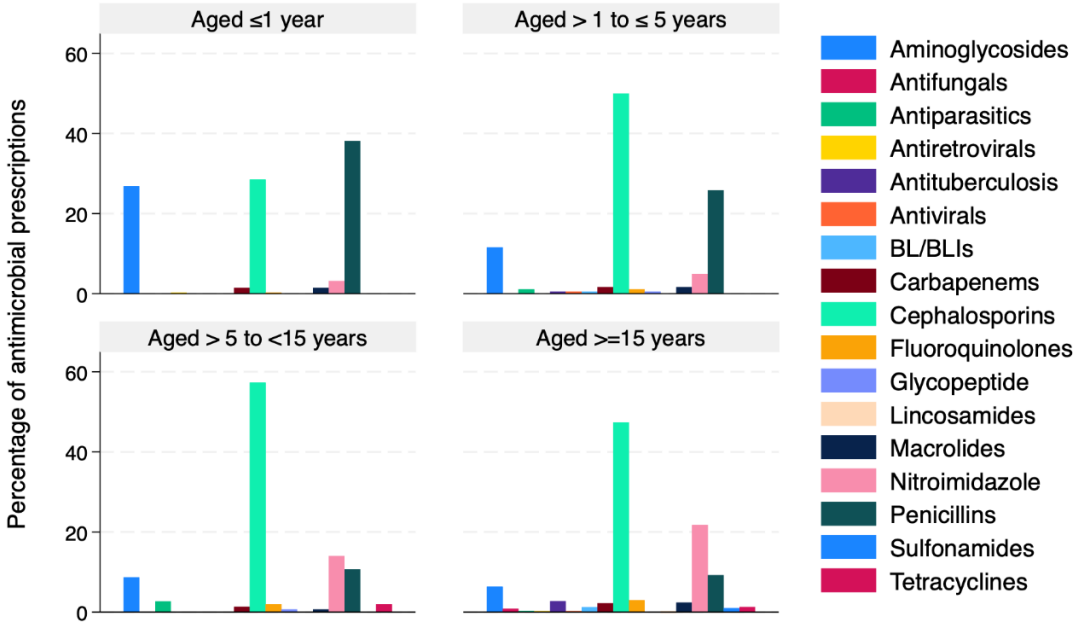
Figure 36: WHO AWaRe group use by age category among hospitalized patients



3.1.3. Antimicrobial prescription distributed by age and prescribing indications among inpatients

Penicillins were most commonly used among infants ≤1 year, accounting for 321/737 (43.5%; 95% CI: 39.9-47.2) prescriptions, followed by cephalosporins at 30.1% (222/737; 95% CI: 26.8-33.6) and aminoglycosides at 14.9% (110/737; 95% CI: 12.4-17.7). For children >1 to ≤5 years, cephalosporins were most frequently prescribed at 38% (319/840; 95% CI: 34.7-41.4). This usage continued for children >5 to <15 years at 32% (198/619; 95% CI: 28.3-35.8) and for adults ≥15 years at 34.4% (1,813/5,270; 95% CI: 33.1-35.7). Antituberculosis medications, antifungals, and antivirals were not prescribed to infants ≤1 year. BL/BLIs were rarely prescribed to children <15 years, with only 1/742 (0.1%) prescription. The variety of antimicrobials used in children was less compared to adults (Figure 37).

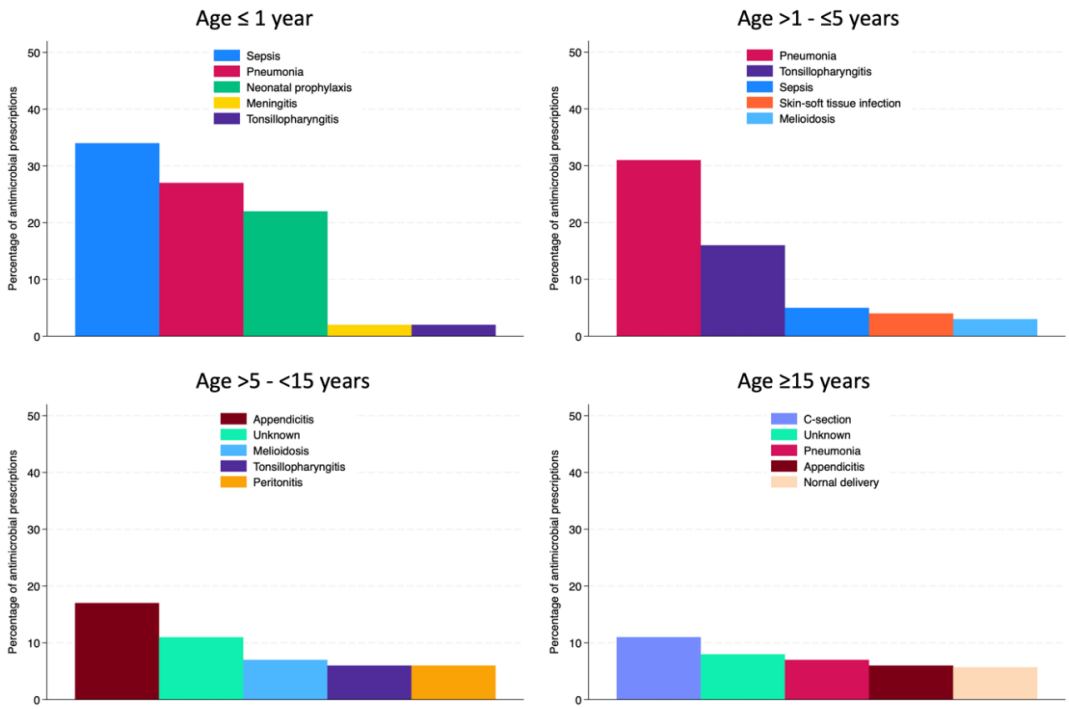
Figure 37: Antimicrobial prescriptions distributed by age group among inpatients



Note: BL/BLIs= Beta-lactam/Beta-lactamase inhibitors.

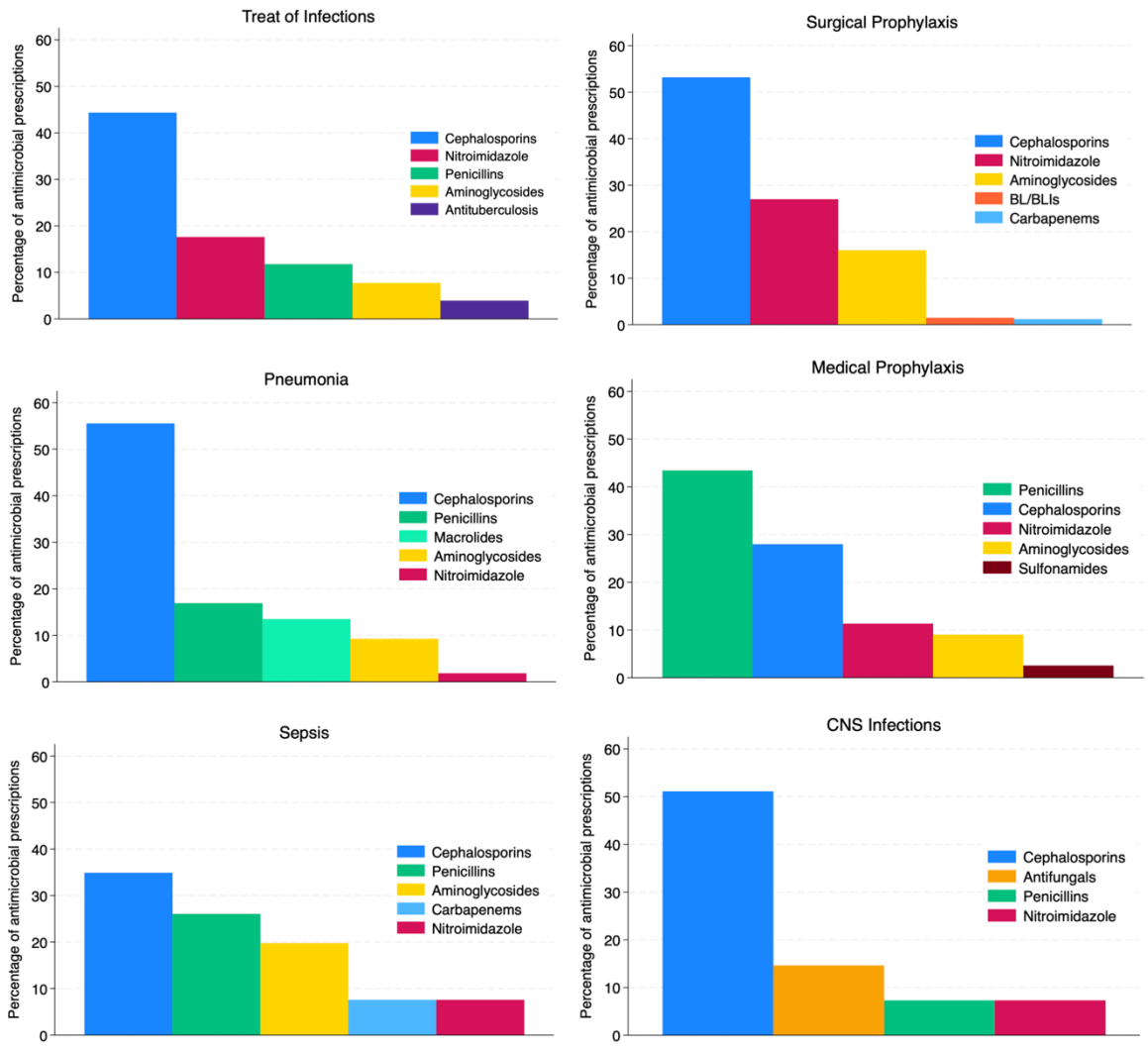
The most common prescribing indications, regardless of the patient's age, were pneumonia with (10.6% (378/3,561), 95%CI: 9.6-11.7), Caesarean section (9% (322/3,561), 95%CI: 8.4-10.4), unknown indications (without a written diagnosis or with a diagnosis unrelated to infection treatment or prophylaxis) at 7% (248/3,561, 95%CI:6.2-7.9), sepsis (6.7% (238/3,561), 95%CI: 5.9-7.6), and appendicitis (5.7% (204/3,561), 95%CI: 5-6.5) (Figure 38). However, when focusing solely on the treatment of infections, the main indications were pneumonia (19.2% (378/1,971), 95% CI: 17.5-21), sepsis (12.1% (238/1,971), 95% CI: 10.7-13.6), appendicitis (10.4% (204/1,971), 95% CI: 9-11.8), peritonitis (7.6% (150/1,971), 95% CI: 6.5-8.9), and skin/soft tissue infections (7.5% (148/1,971), 95% CI: 6.4-8.8) (Figure 39).

Figure 38: Five most common prescribing indications among inpatients, by age group



Note: Unknown=without a written diagnosis or with a diagnosis unrelated to infection treatment or prophylaxis.

Figure 39: Antimicrobial prescriptions by selected indications among inpatients

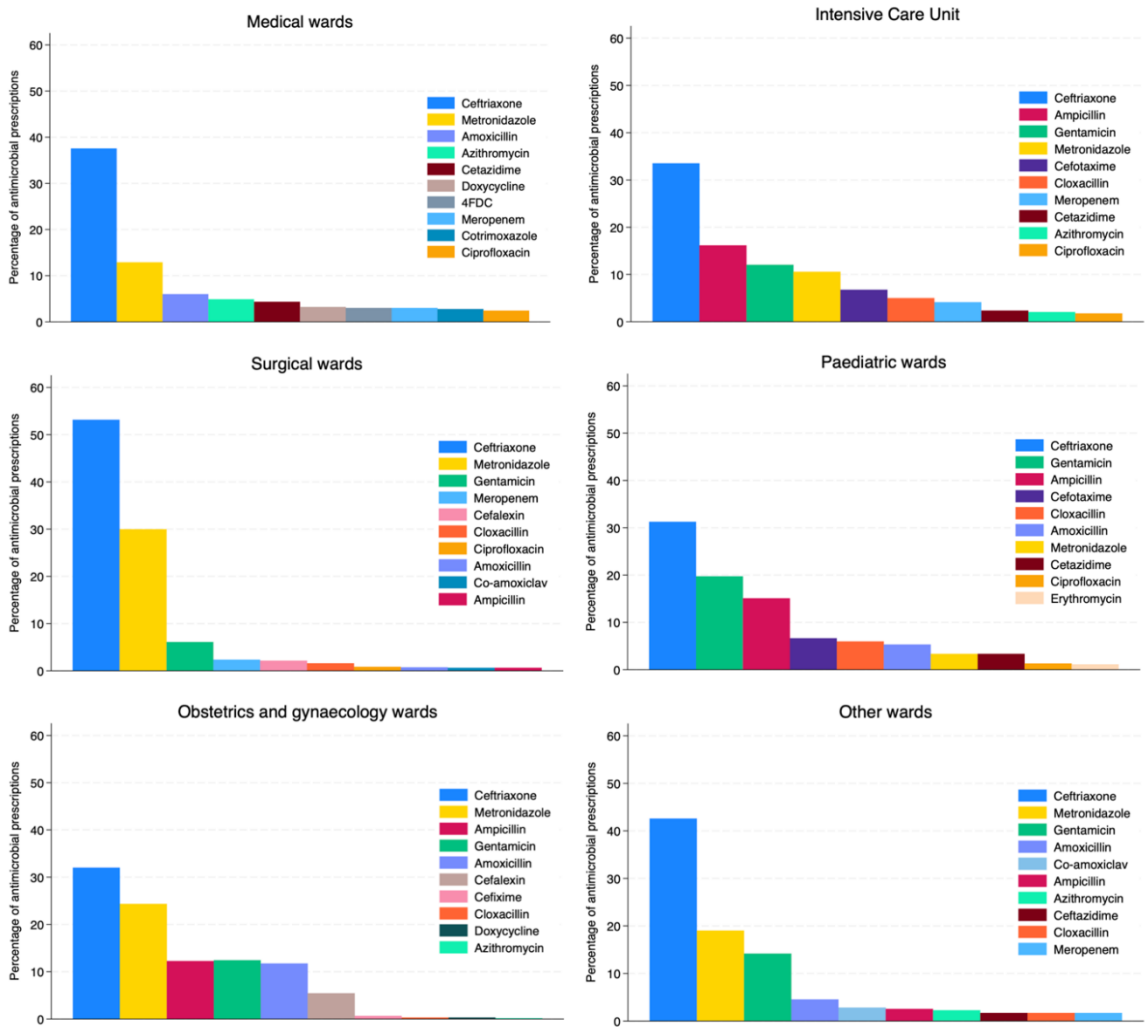


Note: **BL/BLIs**= Beta-lactam/Beta-lactamase inhibitors.

3.1.4. Antimicrobial prescriptions distributed by departments (wards)

The use of antimicrobials was similar across all departments. Ceftriaxone remained the most common antimicrobial prescribed on all wards. Azithromycin (44/900; 4.9%; 95%CI: 3.6-6.5) was found more in medicine wards, while meropenem was the 4th ranked most common prescribed antimicrobial in surgical wards (22/931; 2.4%; 95%CI: 1.5-3.6). Cefotaxime (30/451; 6.7%; 95%CI: 4.5-9.4) and cloxacillin (27/451; 6%; 95%CI: 4-8.6) were more commonly prescribed in paediatric wards than other wards (Figure 40).

Figure 40: Ten most commonly prescribed antimicrobial agents, by wards



Note: Other wards=including VIP departments, ENT-EYE (Ear, Nose, Throat and Eyes).

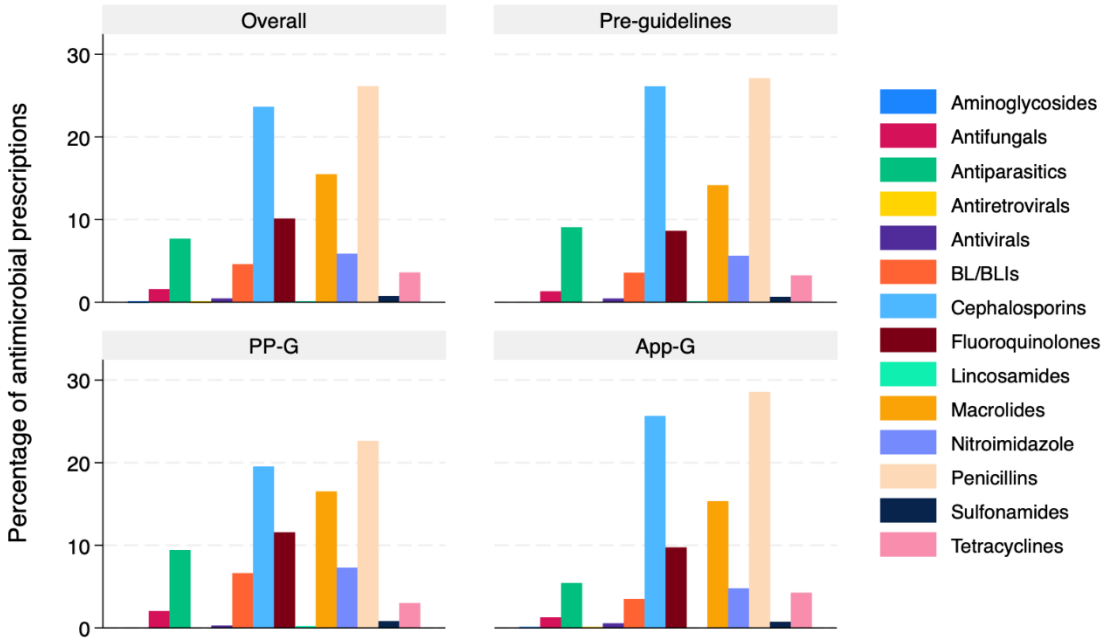
3.2. Outpatients

3.2.1. Patterns of antimicrobial use among outpatients in six hospitals in five surveys

The most frequently prescribed antimicrobials in these OPD settings were penicillins, accounting for 1,021/3,905 (26.2%; 95% CI: 24.8-27.6) prescriptions. This was followed by cephalosporins with 923/3,905 (23.6%; 95% CI: 22.3-25), macrolides with 604/3,905 (15.5%; 95% CI: 14.4-16.6), fluoroquinolones with 395/3,905 (10.1%; 95% CI: 9.2-11.1) and anti-parasitics with 300/3,905 (7.7%; 95% CI: 6.9-8.6). Antimicrobial usage remained consistent across the five surveys (Table 31).

In the pre-guidelines group, penicillins were the most frequently used antimicrobials, with 251/926 (27.1%; 95% CI: 24.3-30.1) prescriptions, followed by cephalosporins with 242 (26.1%; 95% CI: 23.3-29.1) and macrolides with 131 (14.2%; 95%CI: 12-26.6). This pattern persisted in the PP-G and App-G groups. Penicillins accounted for 307/1,357 prescriptions (22.6%; 95% CI: 20.4-24.9) in the PP-G group and 463/1,622 prescriptions (28.6%; 95% CI: 26.4-30.8) in the App-G group. Cephalosporins were prescribed at 265/1,357 (19.5%; 95% CI: 17.5-21.7) in the PP-G group and 4161,622 (25.6%; 95% CI: 23.5-27.9) in the App-G group. Macrolides were prescribed 224/1,357 (16.5%; 95% CI: 14.6-18.6) in the PP-G group and 249/1,622 (15.4%; 95% CI: 13.6-17.2) in the App-G group (Figure 41).

Figure 41: Distribution of antimicrobial prescriptions by Pre-guidelines, PP-G and App-G groups among outpatients



Note: Pre-guideline=group with no antimicrobial prescribing guidelines, **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **BL/BLIs**= Beta-lactam/Beta-lactamase inhibitors**.**

3.2.2. Antimicrobial prescription categorised by WHO AWaRe antibiotics among outpatients

Access antibiotics were used more frequently in outpatients than inpatients, accounting for 68% (561/826; 95% CI: 64.6-71.1) in the pre-guideline group, 62% (743/1,197; 95%CI: 59.3-64.8) in the PP-G group, and 69% (1,030/1,503; 95%CI: 66.1-70.9) in the App-G group. Reserve and Not Recommended antibiotics were not used among OPD patients. The use of Access antibiotics in outpatients was above the WHO target of 60% across all three groups, with 67.9% (561/826; 95% CI: 64.6-71.1) in the pre-guideline group, 62.1% (743/1,197; 95% CI: 59.3-64.8) in the PP-G group and 68.5% (1,030/1,503; 95% CI: 66.1-70.9) in the App-G group (Table 33).

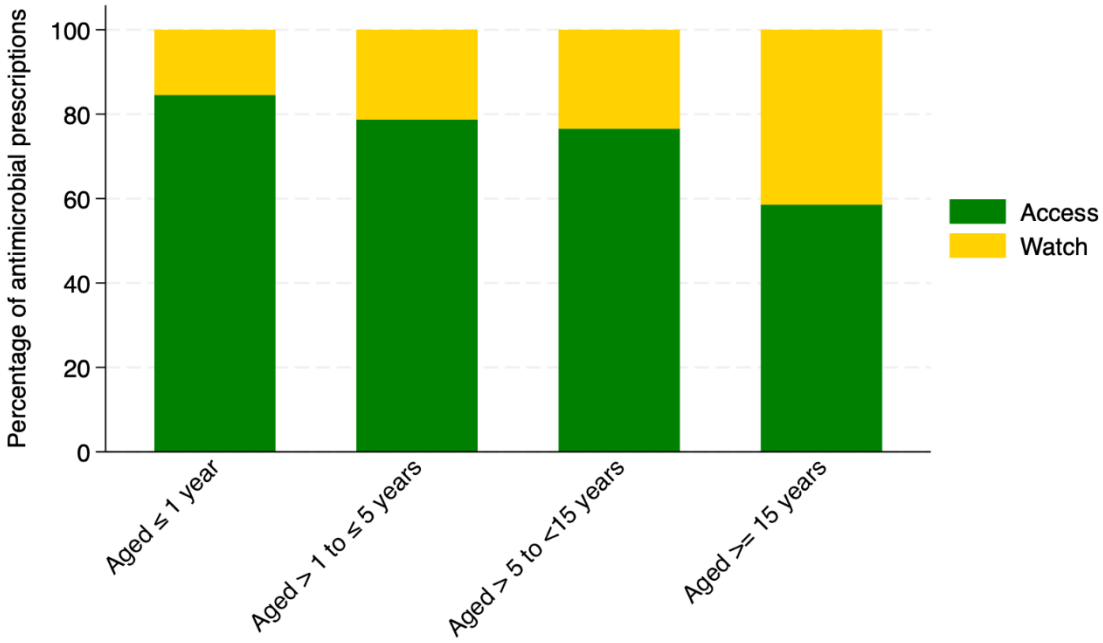
By age group, Access antibiotics were use more frequently in children aged <15years with 79.5% (1,021/1,284, 95% CI: 77.2-81.7) than aged ≥15years, with 58.6% (1,313/2,242, 95% CI: 56.5-60.6), p<0.0001 (Figure 42).

Table 33: Antimicrobial prescription distributing by WHO AWaRe categorization among outpatients

Antibiotics	Pre-guideline; n (%)	PP-G, n (%)	App-G, n (%)
Access	561 (67.9)	743 (62.1)	1,030 (68.5)
Cefalexin	189 (33.7)	195 (26.2)	350 (34)
Amoxicillin	143 (25.5)	161 (21.7)	327 (31.8)
Metronidazole	52 (9.3)	99 (13.3)	78 (7.6)
Penicillin V	50 (8.9)	26 (3.5)	38 (3.7)
Cloxacillin	36 (6.4)	81 (10.9)	57 (5.5)
Amoxicillin/clavulanic acid	33 (5.9)	90 (12.1)	57 (5.5)
Doxycycline	30 (5.4)	41 (5.5)	69 (6.7)
Ampicillin	22 (3.9)	39 (5.3)	37 (3.6)
Co-trimoxazole	6 (1.1)	11 (1.5)	12 (1.2)
Penicillin G	0	0	4 (0.4)
Gentamicin	0	0	1 (0.1)
Watch	265 (32.1)	454 (37.9)	473 (31.5)
Azithromycin	97 (36.6)	171 (37.7)	181 (38.3)
Cefixime	53 (20)	68 (15)	64 (13.5)
Ofloxacin	42 (15.9)	79 (17.4)	62 (13.1)
Norfloxacin	30 (11.3)	37 (8.2)	62 (13.1)
Erythromycin	26 (9.8)	38 (8.4)	53 (11.2)
Ciprofloxacin	8 (3)	40 (8.8)	34 (7.2)
Clarithromycin	5 (1.9)	13 (2.9)	14 (3)
Roxythromycin	3 (1.1)	2 (0.4)	1 (0.2)
Lincomycin	1 (0.4)	3 (0.7)	0
Levofloxacin	0	1 (0.2)	0
Ceftriaxone	0	2 (0.4)	2 (0.4)

Note: Pre-guideline=group with no antimicrobial prescribing guidelines, **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training.

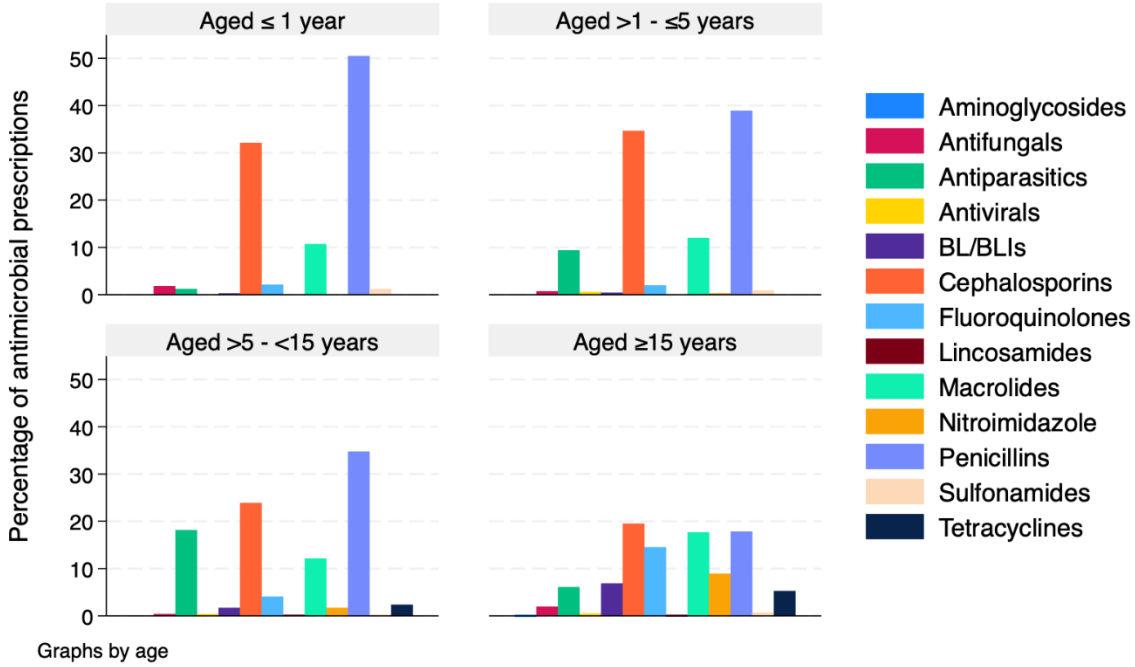
Figure 42: WHO AWaRe group use by age category among outpatients



3.2.3. Antimicrobial prescription distribution by age and prescribing indication among outpatients

Antimicrobial use across all age groups is presented in Figure 43. Overall, penicillins, cephalosporins, and macrolides were the most commonly used antibiotics in both children and adults

Figure 43: Antimicrobial prescriptions distribution by age group among hospitalised patients



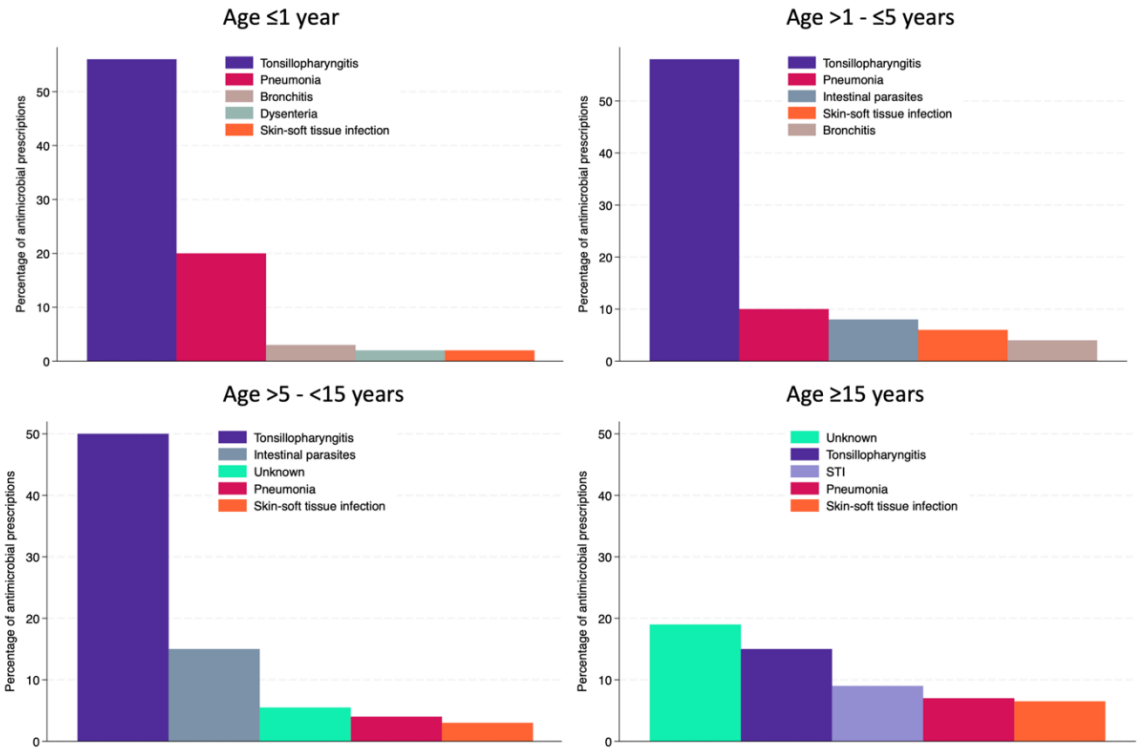
Note: BL/BLIs= Beta-lactam/Beta-lactamase inhibitors

The majority of prescribing indications for those who consulted the OPD across all ages during these surveys were as follows: tonsillopharyngitis accounted for 1,157/3,905 (29.6%; 95% CI: 28.2-31.1) prescriptions, unknown indications (without a written diagnosis or with a diagnosis unrelated to infection treatment or prophylaxis) for 508/3,905 (13%; 95% CI: 12-14.1), pneumonia for 313/3,905 (8%; 95%CI: 7.2-8.9), sexually transmitted infections (STIs) for 226/3,905 (5.8%; 95%

CI: 5.1-6.6), and skin and soft tissue (SST) infections for 224/3,905 prescriptions (5.7%; 95% CI: 5-6.5) (Figure 44).

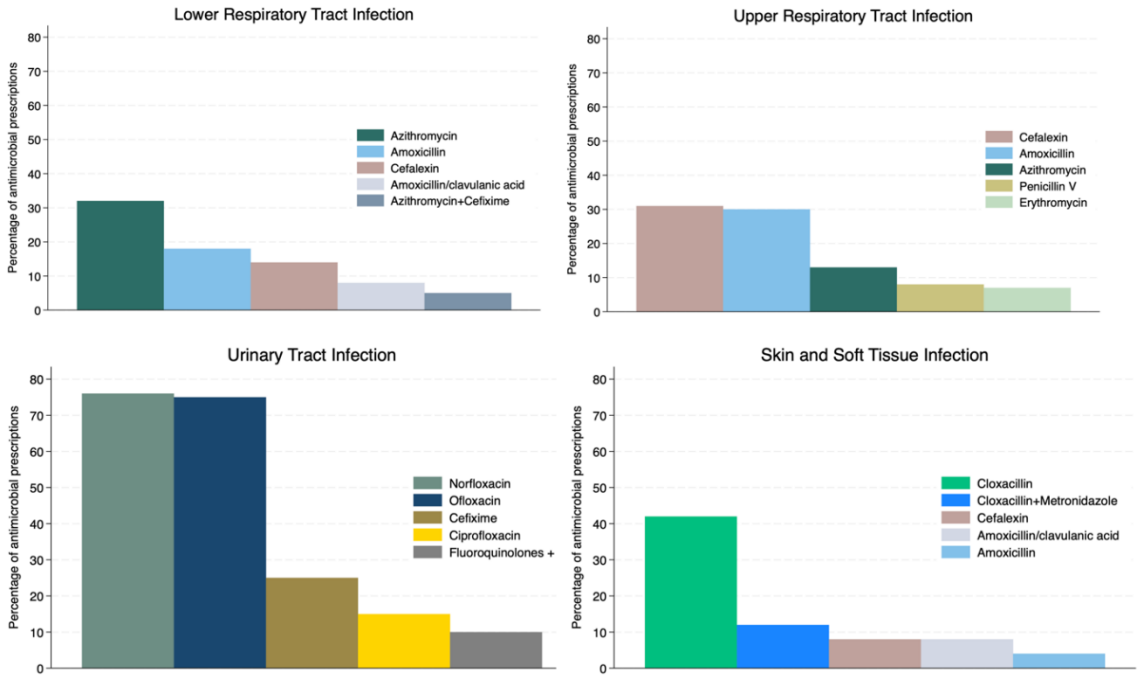
For upper respiratory infections (e.g., tonsillopharyngitis (98.5%), sinusitis, laryngitis), cefalexin was most prescribed, accounting for 31% (362/1,167; 95% CI: 28.4-33.8). For lower respiratory infections (e.g., pneumonia (68%), bronchitis, chronic obstructive pulmonary disease (COPD)), azithromycin was most common at 32% (153/485; 95% CI: 27.4-36). Fluoroquinolones were frequently prescribed for urinary tract infections in 75% (127/169; 95% CI: 68-81). For skin and soft tissue infections, cloxacillin alone (41%; 95% CI: 34-48) or with metronidazole (12%; 95% CI: 8-17) was common (Figure 45).

Figure 44: Five most common prescribing indications among outpatients, by age group



Note: Unknown= without a written diagnosis or with a diagnosis unrelated to infection treatment or prophylaxis; **STI**= sexually transmitted infection.

Figure 45: Five most common antimicrobials used in four selected prescribing indications



Note: Fluoroquinolones +=fluoroquinolones with any other antibiotic.

Discussion

This study is the first to document the development and implementation of local antimicrobial prescribing guidelines in Laos. While previous studies have evaluated adherence to antimicrobial prescribing guidelines delivered via mobile phone applications, this stepped wedge cluster randomized controlled trial in Laos compared adherence to newly released local antimicrobial prescribing guidelines delivered in both paper-based and mobile app formats and provides a comprehensive view of the process from guideline creation through to implementation and testing changes in adherence.

Guideline adherence in hospitalised patients and outpatients

1. **Hospitalised patients**

Full adherence to antimicrobial prescribing guidelines was observed in 18% (95% CI: 15-20) in the pre-guideline group, 17% (95% CI: 15-19) in the PP-G group, and 26% (95% CI: 23-28) in the App-G group. Generally, these adherence percentages were much lower than those reported in other LMICs (31.9% in Myanmar (177), 52.2% in Indonesia (178), 54.5% in Uganda (180), 69.2% in Vietnam (171), 77.4% in India (182), 84% in Tanzania (234) and 85.8% in high-income countries like North America (166) and 83.6% in Canada (235). The majority of these studies classified guideline adherence based only on the correct choice of antimicrobial agents or it was not clear how guideline adherence was defined. Full adherence to prescribing guidelines in this study was classified as correct antimicrobial agent and dose based on provided local antimicrobial prescribing guidelines, except for surgical prophylaxis which included duration of prophylaxis. We also assessed partial adherence (only correct agent) to the prescribing guidelines. Even by this measure, overall adherence in our study (pre-guideline: 29.2% (95% CI: 26-32.6), PP-G:

39.6% (95% CI: 28.2-33.1), and App-G: 34.6% (95% CI: 31.8-37.8)) remained lower compared to studies from other countries. It is essential to establish standardized criteria and definitions for adherence to prescribing guidelines to ensure data comparability.

The key finding of this study is that guideline adherence among inpatients in the App-G group was 27% higher than the PP-G group but statistical significance was not observed (aOR=1.27; 95% CI: 0.84-1.90, p=0.249). It is possible that the study was underpowered to detect a difference, due to the small number of clusters (six hospitals), or slightly lower percentage of prescribers with access to the App-G (76%) compared to the PP-G (82.3%). Adherence in the PP-G group did not improve compared to the pre-guideline group, while adherence in the App-G group was 24% higher. Although this increase was not statistically significant, the small increase in adherence after guidelines introduction is encouraging and highlights the positive impact of structured antimicrobial prescribing guidelines. We also observed that hospitals exposed to the intervention earlier demonstrated better adherence to the guidelines compared to those that gained access later. This improvement highlights the need for ongoing efforts to implement and strengthen adherence to the guidelines. Previous studies have reported improvements in adherence to antimicrobial prescribing guidelines after implementing mobile phone applications. Most of these studies converted existing prescribing guidelines in their settings into a mobile phone application format (223, 224, 226, 229, 230), and focused on specific infectious diseases, for example: pyelonephritis (222), diarrhoeal disease (224), CAP and UTI (229, 230), or in specific situations such as paediatric patients (226, 227) or surgery procedures (225).

2. Outpatients

In our outpatient settings, we did not observe a difference in guideline adherence between PP-G and App-G (aOR=0.90, 95%CI: 0.74-1.09; p=0.299); and there was no difference in guideline adherence when comparing App-G (aOR=0.96, 95% CI: 0.78-1.20, p=0.737) and PP-G aOR=1.04, 95% CI: 0.83-1.30, p=726) to the pre-guideline groups. This low adherence was consistent with previously reported studies. Several interventional studies related to improving appropriate use of antimicrobials in outpatient settings have been reported. The majority of them were bundle interventions, including infectious disease training sessions, audit, feedback (236). However, there was a cluster randomized controlled trial by Rambaud-Althaus et al. (2017) which compared a new clinical algorithm for managing childhood illness among outpatient departments, delivered via paper-based and a mobile phone application. The study showed a significant decrease in antibiotic prescriptions in both the paper-based (26%, OR=0.4, 95%CI: 0.2-0.6, p<0.001) and mobile phone application groups (25%, OR=0.3, 95%CI: 0.2-0.5, p<0.001) compared to standard practice (70%, range: 60-85%) but there was no difference between the paper and mobile phone application methods (OR=1.1, 95%CI: 0.6-1.6, p=0.825). Antibiotic prescription adherence to guidelines was not assessed in this study. It was noted that among children who needed antibiotics, only 28.6% in the paper-based group were actually prescribed antibiotics compared to 48% in the app group (227).

Inappropriate use of antimicrobials among outpatients is commonly described. Ardrillon et al. (2023) reported 76.5% (95% CI: 75.1-77.9) of outpatients in their study populations from three LMICs received antibiotics when it was not necessary

(237). A large OPD national survey from China from 2017 to 2019, also showed that 70.5% (147,758/209,662; 95% CI: 70.3-70.7) had inappropriate antibiotics during their OPD consultations (238). Highly inappropriate use was also described when focusing on some specific prescribing indications such as UTI, pneumonia or upper respiratory infections. For example, among UTI patients in USA from 2013 to 2018, using Optum and Premier Healthcare Database data, appropriateness was reported as 47% (2,762/5,870; 95% CI: 45.8-48.3) (239). Of 42,452 paediatric CAP consultations at OPD between 2014 and 2018 in British Columbia, 44% prescriptions were assessed to be inappropriate (240).

3. Possible explanations for modest adherence to prescribing guidelines

While the pocketbook is the traditional way to share guidelines in LMICs, the mobile app offers a modern, innovative approach, highlighting the move towards digital solutions in healthcare. This study showed the impact on guideline adherence of the two methods in both hospitalized patients and outpatients. A small increase in guideline adherence was observed following the implementation of local antimicrobial prescribing guidelines in Laos. However, the evidence was insufficient to determine whether the app-based guideline and antimicrobial stewardship training had more impact than the paper-based version. In Laos, when new treatment guidelines become available, it is difficult to ensure that all hospital prescribers have access. Typically, only a few copies are provided per ward, which prescribers must share. In this study, the paper-based and App-based guidelines were distributed to all prescribers in participating hospitals. Although, even with full availability of new guidelines, if prescribers were not fully aware of the importance of adhering to them, their prescribing behaviour might not change much. Chapter 5

provides a more detailed exploration of the factors influencing antimicrobial prescribing practices among Lao doctors and the uptake of the guidelines.

Low adherence to guidelines in the surgical and obstetrics and gynaecology departments likely contributed to the overall low adherence observed in this study. A possible explanation for this could be concerns about hospital-acquired infections, leading to extended durations of antimicrobial prophylaxis or the unnecessary combination of antibiotics, even for routine procedures like normal vaginal deliveries, where prophylaxis is not required. These prescribing patterns were also observed in Chapter 2, with similar trends seen over a longer study period (2017–2020). Prescriptions for unknown conditions, such as antibiotics used for high blood pressure, intestinal parasite infections, or anaemia, accounted for nearly a quarter of non-guideline adherence among outpatients. Addressing this issue requires improving clinical knowledge, closely monitoring prescribing practices, and implementing decision support systems for prescribers.

Another possible contributor to low adherence could be the Covid-19 pandemic. The intervention was implemented between June 2021 and April 2022, during the peak of Covid-19 in Laos. This disrupted the distribution of the App-G, as most doctors were focused on managing Covid-19 cases and working in Covid centres, making them unavailable for training sessions. Hospital patient numbers also dropped, to as low as only eight patients for the whole hospital at one survey in Luang Namtha. Additionally, some wards were reserved for Covid-19 case management. This unexpected situation could affect the prescribing patterns and guidelines uptake. Unfortunately, antimicrobial prescription data for Covid-19

patients were not available, with only two positive cases recorded: one received molnupiravir with ceftriaxone, and the other azithromycin alone.

Additionally, the App and AMS training was conducted only once per hospital, which may have resulted in insufficient understanding and confidence in using the app effectively. In some regions of Laos, healthcare providers may not have full digital literacy. Even among those who do, there may be a reluctance to adopt new technology due to unfamiliarity or complexity. This digital divide can result in lower utilization of App-based guidelines; therefore, the prescribers might have continued using the traditional paper-based version rather than switching to App-based version.

In many healthcare settings, long-standing habits can also influence prescribing behaviours. These deeply entrenched practices can be resistant to change, even with new guidelines which fit to their local situation. Workload could also make it challenging for healthcare providers to consistently adhere to new guidelines. Another possible reason is the lack of feedback and reinforcement by senior staff or higher levels (241).

To maintain the study's pragmatic nature, we did not have an active contact with prescribers in our study unless they had questions about using the guidelines. As a result, encouragement and reinforcement of guideline use were not systematically applied across all study sites. In the absence of these mechanisms, guideline adherence improvement may not be highly successful, and the impact of the guidelines may remain limited.

Healthcare facilities in Laos could also play an important role in promoting prescribing guideline adherence. Though five of our study sites can perform cultures in their laboratories (one site is the reference Microbiology Laboratory for the country), only 3.1% (110/3,561; 5% CI: 2.5-3.7) prescriptions were prescribed based on laboratory/microbiological results among hospitalized patients. Among those prescriptions with known pathogens/confirmed laboratory results, the guideline adherence in the App-G group was 11.16 (95% CI: 6.34-19.62; p<0.0001) higher than the PP-G group. Compared to high-income settings, where recommended antimicrobial treatments are mostly available alongside efficient infectious disease diagnostic tools, the guideline adherence was much higher.

Some studies have described that guideline uptake could be influenced by the acceptance of the prescribers and how they perceived the guidelines (242) (198). In our study, both paper-based and App-based guidelines were well accepted by Lao prescribers based on the results of the guideline satisfaction surveys. Detailed survey results and the factors influencing guidelines uptake are presented in Chapter 5.

Improving guideline adherence is difficult, but ensuring it is sustained is even more challenging. Given the limited number of studies on sustainability of guideline adherence following the implementation of mobile phone applications (223, 226, 230), it is challenging to pinpoint the exact factors influencing these changes and to provide concrete evidence on how to enhance adherence. To gain a clearer understanding, more mixed method research (quantitative and qualitative) with extended monitoring periods would be useful.

Other key insights from study findings

This study also revealed a high percentage of overall antimicrobial prescriptions among hospitalized patients both before (74%) and after the implementation of local prescribing guidelines (PP-G at 75.3% and App-G at 71.1%). These percentages were similar to those reported in a previous study conducted in the same settings from 2017 to 2020, which found a 71% inpatients were prescribed antimicrobials (152). However, by the end of the study, when all participating hospitals had access to the local prescribing guidelines (regardless PP-G or App-G), the overall percentage of antimicrobial prescriptions was 68.4% (95% CI: 65.1-71.1). The significant difference in antimicrobial use among inpatients was not observed before and after the implementation of the PP-G (aOR=1.03, 95% CI: 0.73-1.43, p=0.877) and App-G (OR=0.83, 95% CI: 0.59-1.16, p=0.281) guidelines.

Among hospitalized patients, the most commonly prescribed antimicrobials were ceftriaxone (40%, 95% CI: 39.4-42.7), metronidazole (18%, 95% CI: 17.2-19.7), and gentamicin (9%, 95% CI: 8-9.9) across all age groups. This prescribing pattern is consistent with other LMICs (167, 171, 178, 180, 182, 183, 234). Change in diversity of the antimicrobial use in this study was not observed over time. One possible explanation for this limited diversity could be restricted access to antimicrobials in the country or behavioural practice (241). According to the latest registration by the Food and Drug Department, Ministry of Health in Laos, only 29 antibiotic agents were on the registered list as of 2019 (192). The use of non-registered antibiotics has also been reported, predominantly in the capital city, Vientiane (152). The local antimicrobial prescribing guidelines include two non-registered antibiotics based on local antimicrobial susceptibility data: nitrofurantoin for suspected ESBL-producing

bacteria causing uncomplicated UTIs and vancomycin for suspected MRSA bacteremia. However, we did not observe the use of nitrofurantoin and noted only a few prescriptions for vancomycin.

This is the first report of systematic antimicrobial use data collection among provincial and central hospital outpatients in Laos. The findings from this study showed percentage of antimicrobial use among outpatients, with 27.3% (95% CI: 25.8-29) in the pre-guideline group, 21.2% (95% CI: 20.1-22.3) and 29% (95% CI: 27.8-30.2) in the PP-G and App-G groups, respectively. Comparatively, a report by Holloway et al. (2017) on antibiotic prescriptions for outpatients in selected Southeast Asian countries found a range from 12% (95% CI: 11-14) to 62% (95% CI: 53-67) (243). A more recent study across three LMICs reported that 29.3% of 3,448/11,762 (95% CI: 28.5-30.1) outpatient consultations in Cambodia, Madagascar, and Senegal involved antibiotic prescriptions during their OPD visits (237). These studies demonstrate that the percentage of antimicrobial use among outpatients is fairly consistent across many LMICs.

Upper respiratory infections were the most commonly prescribed indication in the OPD settings in this study and 98.5% of them were tonsillopharyngitis. Cefalexin and azithromycin were frequently prescribed in all study sites and periods, despite not being recommended in the antimicrobial prescribing guidelines. This practice contributed to a high percentage of inappropriate use of antimicrobials in OPD settings in Laos. There is an urgent need for an antimicrobial stewardship programme to improve this situation. Qualitative research would help understand the reasons behind this practice. Cloxacillin was commonly used for skin and soft infections. However, an increase of MRSA in non-blood specimens in Laos from

16% in 2020 to 44% in 2023 was observed [LOMWRU, unpublished data]. This suggests switching to co-trimoxazole as the first choice of empiric treatment for skin and soft tissue infections in Laos should be considered, since most *S. aureus* isolates are susceptible.

Strengths and Limitations

The stepped wedge cluster randomized design ensured all participating hospitals received the first comprehensive antimicrobial prescribing guidelines in Laos. Starting with no guidelines, the study progressed through paper-based to app-based formats, enabling a clear comparison of prescribing practices. This study provided all prescribers in participating hospitals easy access to prescribing guidelines, accompanied by training of the use, which is not typically done in Laos when introducing new guidelines. It also offered insights into guideline implementation from the ground up, highlighting challenges and establishing a framework for future antimicrobial stewardship efforts, with findings applicable to other LMICs.

There are several limitations to this trial:

1. it was conducted during the Covid-19 pandemic. This delayed intervention implementation and outcome measurements. The original plan was to collect the outcomes every four months over a 16-month study period. However, due to travel restriction, and Covid-19 priority for most prescribers, the time interval between each intervention implementation had to be expanded to every five to six months. In addition, the majority of prescribers in the participating hospitals were focused on Covid-19 management, with many of

them working at Covid-19 centres for at least 2 weeks at a time. As a result, some prescribers did not participate to the study.

2. Having only six sites (three clusters of two hospitals and three steps) could lead to low statistical power to estimate guideline adherence in some specific infectious diseases/conditions accurately due to limited number of cases. In addition, some clusters had smaller size than others which might not have enough information to detect the true differences.
3. We did not gather data on the overall microbiological culture requirements for the entire prescription population. Having this information could allow us to understand whether adherence to the guidelines was influenced by the limitations of microbiological capacity.
4. We collected data on the total number of patients without antimicrobials in each survey but we did not collect details on patient's age of those who did not receive antimicrobials to identify children and adults. In provincial hospitals several wards admit patients of all ages. As a result, we were unable to fully calculate DDD/100 patient days in caomparison with other studies.
5. We were unable to measure individual prescriber behaviour changes after the intervention implementation. Data were collected from patients' documents, which did not specify which prescribers were responsible for each prescription. Furthermore, the movement of prescribers in and out of some hospitals made it difficult to identify individual prescribers accurately.
6. Full adherence to guidelines among hospitalized patients in this study did not include duration of antimicrobial treatment, except for surgical prophylaxis.

We have observed the significant reduction of IV antimicrobial use but data on oral switch were not available, due to the nature of PPS methodology.

Conclusion

This study has shown that technology to deliver antimicrobial prescribing guidelines can be successfully implemented in a low-resource setting, such as Laos. This shows promise to enhance the quality of healthcare in the long term. However overall guideline adherence was low and there was insufficient evidence to conclude that using a mobile phone application to deliver prescribing guidelines had a greater impact on adherence compared to the paper-based guidelines. Nevertheless, paper-based guidelines present significant challenges, such as difficulties in nationwide dissemination, delays in updating, and the costs associated with printing, especially when compared to app-based guidelines. The urgent priority is to tackle the broader, multifaceted challenges that affect guideline implementation. This includes providing ongoing support to increase guideline awareness and ensure that all healthcare providers have the necessary technology and skills to use it effectively. Additionally, it is important to address human resource limitations and improve healthcare services. Providing regular feedback and encouragement from senior hospital staff and the Ministry of Health is also crucial. These approaches must be continuous and sustainable to ensure that deeply ingrained inappropriate prescribing behaviours can be improved over time. These efforts can also create an environment where healthcare providers consistently follow guidelines, leading to better patient outcomes.

Chapter 5: Understanding hospital antimicrobial prescribing decisions and determinants of uptake of new local antimicrobial prescribing guidelines in Lao PDR

Abstract

Background: Antimicrobial use in Laos is among the highest in Southeast Asia. The first Lao comprehensive antimicrobial prescribing guidelines have been available since 2021. This chapter explored the determinants of antibiotic prescribing decisions and how the new prescribing guidelines were being used.

Methods: In August 2022, in-depth interviews were conducted with 16 Lao prescribers from two hospitals. Participants were questioned about their prescribing behaviours, attitudes to guidelines, how they learned about the guidelines and factors influencing their uptake. The interviews were audio-recorded, transcribed, and translated into English. Thematic analysis of the transcripts was conducted. Additionally, this chapter describes the antimicrobial stewardship knowledge survey and feedback on the newly released prescribing guidelines from Chapter 3.

Results: Lao prescribers considered multiple factors before deciding to prescribe antibiotics to their patients. The most common factor was based on their clinical judgement. Lack of certain antibiotics and turnaround times of laboratory results were the main challenges to prescribing antibiotics appropriately. The majority of participants were satisfied with both paper-based and app-based guidelines, regarding them as comprehensive, simple and convenient. However, most participants admitted that they did not access the guidelines very often. The main reason was that they could remember the treatment recommendations because

they treat similar diseases on a daily basis. Improving antibiotic use knowledge was the most common recommendation in order to improve the appropriate use of antibiotics. Raising awareness of the guidelines and promoting their use should also be considered. In addition, heads of the wards, and policy and implementation leaders, should support, monitor and feedback their use to encourage all prescribers to access the guidelines.

Conclusion: Several factors could contribute to enhancing appropriate antibiotic prescription. Key factors for improving antibiotic prescription include enhancing prescribers' clinical knowledge, ensuring access to essential antibiotics, and updating guidelines regularly. Health leaders must get involved to promote their use.

Background

Antimicrobial use (AMU) is one of the key drivers of antimicrobial resistance (AMR) (244). The use of antimicrobials in the human healthcare sector has been shown to be influenced by several factors including previous clinical experience, physicians' knowledge and attitudes (e.g. ignorance, complacency), fear of harming patients, lack of autonomy (i.e. following the decision of seniors), demands of patients and families, other patient-related factors, healthcare-related factors, the influence of pharmaceutical companies, and the cost of medications (245-247). The appropriateness of AMU in hospitals could be improved with comprehensive and up-to-date antibiotic use guidelines. Maina et al. described that the prevalence of appropriate use of antibiotics in settings with treatment guidelines was higher than where guidelines were absent (14% *vs* 33%) (186). However, previous reports have emphasized that guidelines alone might not be enough to assure the appropriate use of antimicrobials. Combined approaches such as explicit and appropriate guideline implementation strategies, engagement with prescribers, antimicrobial stewardship programmes including restrictive policies, such as not allowing certain prescriptions to be dispensed without consultation with specialists or evidence of an infection requiring that agent, or prescribers not getting paid for their services if they did not follow the guideline recommendations (248) have been proposed to reduce the inappropriate use of antimicrobials (185, 186, 248, 249).

Laos began participation in global point prevalence surveys (PPS) of hospital antimicrobial use in 2017, with baseline data of hospital antimicrobial use as high as 71% between 2017 and 2020 among six general hospitals across the country (152). This percentage was higher than other low- and middle-income countries and high-income countries globally (166, 184). Laos has had treatment guidelines

available for some specific diseases such as malaria, tuberculosis, and sexually transmitted infections for some years. The latest national standard treatment guidelines (STG) were released in 2012. These contained information on clinical characteristics of diseases, diagnoses and treatment recommendations. Infectious diseases were a part of the STG but the antibiotic treatment recommendations were only available for some diseases (141). A qualitative study to understand factors influencing uptake of the WHO pocketbook of hospital care for children in Laos, published in 2017 showed that there were several key factors affecting uptake of those guidelines, including the completeness of the guideline, unclear Lao translation for some sections, the fact that guidelines were not always physically available, lack of training in their use, and lack of trust (198). The first comprehensive Lao antimicrobial prescribing guidelines for adults and children were introduced in January 2021 (134, 135). These guidelines were developed specifically to fill the gaps mentioned above. The guidelines were developed based on the epidemiology of infectious diseases in Laos and local antimicrobial susceptibility patterns, as well as international recommendations. They were made available for all prescribers in six general hospitals across Laos following a workshop on how to use them, as a part of a stepped wedge cluster randomized controlled trial to evaluate the impact of guidelines delivered via a mobile phone application versus pocket book (NCT04914793) (Chapters 3 and 4). The baseline antimicrobial prescription proportion in six hospitals before introduction of the guidelines was 73% (95% CI, 70%-76.5%) among inpatients and 27% (95% CI, 25.8%-28.9%) among outpatients in the first survey round of 2021. Antimicrobial prescribing increased to 79.6% (95% CI, 75.7%-83%; p=0.02), and 30% (95% CI, 28.4%-32.2%; p=0.01) among in- and outpatients, respectively, one year (the first

survey round of 2022) after the introduction of the guidelines (https://laoamr.net). One probable reason could be due to the peak of the Covid-19 pandemic in Laos during 2021 and 2022. Such an increase in antibiotic use was described in many countries during the Covid-19 pandemic (250). Therefore, this study aimed to explore the determinants of antibiotic prescribing decisions and how these new Lao antimicrobial prescribing guidelines were being used.

Methods

Prescriber survey section

This section covers the prescriber behaviour survey conducted before the implementation of antimicrobial prescribing guidelines, feedback on both the paper-based and app-based versions, and the antimicrobial stewardship (AMS) knowledge survey before and after guideline implementation. The methodology is detailed in Chapter 3.

Qualitative section

Study design and settings

This qualitative study was designed to evaluate prescribers' perceptions of the new guidelines and factors influencing their use at the sites participating in the stepped wedge cluster randomised trial outlined in Chapter 3. In-depth interviews were conducted in two general hospitals (one central hospital (450-beds) and one provincial hospital (70-beds)). These two hospitals were purposively selected as representative of a central referral hospital and a rural hospital in Laos. Prescribers in both hospitals had access to the new local antimicrobial prescribing guidelines in both pocketbook and mobile phone application versions and participated in the workshop of how to use these guidelines.

Participants

Participants in this study were purposively selected based on seniority and their specialties (prescribing antibiotics, from infectious disease departments or intensive care units, paediatric *vs* adult). We focused on prescribers who prescribed antibiotics at least three times a week on average and who had access to the local antimicrobial prescribing guidelines, either pocketbook or mobile phone application versions or both, and were willing to give written informed consent to participate. The possible target prescribers were listed based on the above-mentioned criteria before the invitations were distributed. The purposive selection allowed us to capture a range of different perspectives.

The eligible participants were invited to join the in-depth interviews, including senior doctors and juniors/residents in a 1:1 ratio. There is no formal definition of junior and senior physicians in Laos. In general, doctors who are aged less than 40 years old, are classified as early career, 40-50 years old as mid-career and >50 years old as late career. It is more complex when it comes to “senior *vs* junior”. In this study, junior was defined as doctors/prescribers aged <40 years old or with medical experience of 10 years or less. Senior was defined as doctors/prescribers aged ≥40 years old and with medical experience of more than 10 years.

Study procedures and data collection

Invitation letters were sent to those who met the inclusion criteria. Written informed consent was obtained if the prescriber agreed to participate. Additional invitations were sent to new target interviewees in the list if the previous one declined the invitation. Two in-depth interviews a day were performed in August 2022, taking a maximum of one hour and a half per interviewee. Interviews were led by Vilada

Chansamouth in the Lao language and conducted based on the discussion guide (Appendix 16).

Vilada Chansamouth and a trained co-investigator conducted face-to-face interviews in a quiet, private room. Participants' demographic information (age, sex, title, and specialty) was collected. The interviews (Appendix 16) focused on the antimicrobial prescribing experience and use of new local guidelines of the participants, covering behaviours, attitudes, guideline awareness, and factors influencing uptake. Interviews were audio-recorded, then transcribed and translated into English by a professional translation company.

Data analysis

Three investigators reviewed the transcripts for accuracy and completeness and discussed the content. Thematic analysis of the transcripts was conducted. Both inductive and deductive approaches were used to analyse the data. NVIVO software (version 14) was used to assist in coding and handling data. Codes were added, then discussed and modified among the investigators. Themes were generated after agreement was reached for the codes. Main themes and sub-themes were identified based on the richest codes. Those themes with less supportive codes were combined as one theme.

Ethics and consent

Ethics approval was obtained from both the University of Health Sciences Ethics Committee, Ministry of Health, Lao PDR (reference number: 318/REC, date 22 April 2022) and the Oxford Tropical Research Ethics Committee (OxTREC), University of Oxford, United Kingdom (reference number: 510-22, date: 02 April 2022). Written informed consent was obtained from all participants.

Results

The results are presented in three parts: the prescriber behaviour survey before guideline implementation, and feedback surveys on the guidelines, followed by the AMS knowledge survey, and then the in-depth interviews.

Part I: Prescriber behaviour survey and feedback survey on paper-based (PP-G) and app-based guidelines (App-G)

1.1. Pre-guideline survey on antimicrobial prescribing behaviour

Among 508 prescribers from six participating hospitals, 418 (82.3%; 95%CI: 78.7-85.8) participated in the prescribing assessment surveys and training for the use of PP-G. High participation was found in Xiengkhuang and Vientiane Province with 100% at each hospital, while the largest hospital, Mahosot, had the lowest participation at 76.2%.

Of the 418 prescribers who participated in the guideline enrollement session, 415 (99.3%, 95% CI: 97.9-99.8) completed the prescriber behaviour survey. Most, 228/384 (59.4%; 95% CI: 54.3-64.3), had graduated within the past 10 years, particularly in SV, where 29/36 (80.6%; 95% CI: 64-91.8) had graduated ≤10 years earlier. More than one-third (150/380; 36%; 95% CI: 31.6-41.1) were from medical wards. Nearly all (375/415, 90%; 95% CI: 87.1-93) reported prescribing antimicrobials nearly or every day, 274/415 (66%; 95% CI: 61.3-70.6) accessed guidelines weekly or less. Smartphone ownership was high (92%; 95% CI: 88.5-94.1), with 43% (162/379; 95% CI: 37.7-47.9) having an antimicrobial app, half using it daily (Table 34).

Table 34: Characteristics of prescribers in the pre-guidelines survey

Characteristics	XK, n= 52	LNT, n= 27	SV, n= 39	SVK, n= 69	VTP, n=39	MS, n= 189	Total, n= 415
Years since medical school graduation, median (IQR)	8 (4-11)	10 (2-14)	5 (3-8)	12 (7-24)	11 (8-21)	8 (5-17)	8.5 (5-16)
Years since medical school graduation, n (%)							
≤5 years	15 (33)	8 (31)	19 (53)	6 (11)	4 (10)	47 (25)	99 (24)
>5 to ≤10 years	15 (33)	6 (23)	10 (28)	17 (32)	14 (36)	67 (36)	129 (31)
>10 to ≤20 years	14 (31)	9 (35)	1 (3)	13 (25)	11 (28)	32 (17)	80 (19)
>20 years	1 (2)	3 (12)	6 (17)	17 (32)	10 (26)	39 (21)	76 (18)
Prescribers' departments, n= 414 (%)							
Medicine	19 (37)	9 (33)	12 (31)	34 (49)	8 (21)	68 (36)	150 (36)
Intensive Care Unit – Emergency Room	13 (25)	5 (18)	10 (26)	10 (14)	9 (23)	37 (20)	84 (20)
Obstetrics and Gynaecology	6 (12)	5 (18)	5 (13)	4 (6)	8 (21)	29 (15)	57 (14)
Surgery	8 (15)	3 (11)	8 (21)	7 (10)	4 (10)	35 (19)	63 (15)
Paediatrics	6 (12)	4 (15)	3 (8)	11 (16)	4 (10)	16 (9)	46 (11)
OPD	-	1 (4)	1 (3)	3 (4)	6 (15)	3 (2)	14 (3)
Prescribing frequency, n= 415 (%)							
Nearly or every day	42 (81)	25 (93)	37 (95)	67 (97)	36 (92)	168 (89)	375 (90)
Weekly or less often	20 (19)	2 (7)	2 (5)	2 (3)	3 (8)	21 (11)	40 (10)
Frequency of access any prescribing guidelines, n= 415 (%)							
Nearly or every day	18 (35)	13 (48)	11 (28)	23 (33)	11 (28)	65 (34)	141 (34)
Weekly or less often	34 (65)	14 (52)	28 (72)	46 (67)	28 (72)	124 (66)	274 (66)
Having smartphone at work, n= 415 (%)	51 (98)	24 (89)	33 (84)	58 (84)	37 (95)	177 (94)	380 (92)
Having antimicrobial use application on smartphone, n= 379 (%)	22 (43)	10 (42)	11 (33)	19 (33)	12 (32)	88 (50)	162 (43)
Frequency of any antimicrobial use application usage, n= 162 (%)							
Nearly or every day	12 (55)	5 (50)	5 (45)	13 (68)	7 (58)	45 (51)	87 (54)
Weekly or less often	10 (45)	5 (50)	6 (55)	6 (32)	5 (42)	43 (49)	75 (46)

1.2. Prescriber satisfaction with the antimicrobial prescribing guidelines

Out of 418 prescribers who had access to the PP-G at the beginning of the study (Table 35), only 281 (67.7%; 95%CI: 62.5-71.2) participated in the PP-G feedback survey, with 273/281 (97.2%; 95%CI: 94.5-98.8) actually using the PP-G. In the App-G survey, 260/370 (70.3%; 95%CI: 65.3-74.9) participated, and 251/260 (96.5%; 95%CI: 93.5-98.4) used the App-G (Table 36). Among PP-G respondents, 89% (239/269; 95%CI: 84.5-92.3) reported that they prescribed antimicrobials nearly or every day, similar to 84% (206/245; 95%CI: 78.9-88.4) of App-G users. Over half, 53% (128/243; 95%CI: 46.2-59.1) used the App-G weekly or less, compared to 63% (165/261; 95%CI: 57.1-69.1) in the PP-G group.

Table 35: Total number of prescribers who had access to paper-based and app-based version of antimicrobial prescribing guidelines

Hospital	Prescribers with access to PP-G, n (%; 95% CI)	Prescribers with access to App-G, n (%; 95%CI)
Xiengkhuang	53/53 (100)	49/64 (76.6; 64.3-86.3)
Luang Namtha	27/35 (77; 59.9-89.6)	32/33 (97; 84-99.9)
Salavan	39/49 (79.6; 65.7-89.8)	36/44 (81.8; 67.3-91.8)
Savannakhet	70/83 (84.3; 74.7-91.4)	85/96 (88.5; 80.4-94.1)
Vientiane Province	40/40 (100)	28/36 (77.8; 60.8-89.9)
Mahosot	189/248 (76.2; 70.4-81.4)	140/213 (67.7; 58.9-72.1)
Total	418/508 (82.3; 78.7-85.5)	370/486 (76; 72.1-79.9)

Note: PP-G=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training.

Table 36: Prescriber Characteristics in Satisfaction Surveys of Paper-Based and App-Based Guidelines

Characteristics	Prescribers with PP-G	Prescribers with App-G
Number of respondents, n (%)	281/415 (67.7)	260/370 (70.3)
Xiengkhuang	52/52 (100)	35/49 (71.4)
Luang Namtha	24/27 (88.9)	32/32 (97)
Salavan	29/39 (74.4)	29/36 (80.6)
Savannakhet	54/69 (78.3)	58/85 (68.2)
Vientiane Province	27/39 (69.2)	17/28 (60.7)
Mahosot	95/189 (50.3)	89/140 (63.6)
Prescribers ever used prescribing guidelines; n (%)	273/281 (97.2)	251/260 (96.5)
Number of years on medical career, median (IQR)	10 (6-20)	11 (7-20)
Number of years on medical career, n (%)	273	251
≤5 years	54 (19.8)	46 (18.3)
>5 - ≤10 years	80 (29.3)	73 (29.1)
>10 - ≤20 years	56 (20.5)	69 (27.5)
>20 years	83 (30.4)	63 (25.1)
Prescribers' departments, n (%)	273	251
Medicine	64 (23.4)	62 (24.7)
Intensive Care Unit – Emergency Room	39 (14.3)	33 (13.1)
Obstetrics and Gynaecology	37 (13.5)	24 (9.6)
Surgery	39 (14.3)	42 (16.7)
Paediatrics	32 (11.7)	33 (13.1)
Other	46 (16.8)	41 (16.3)
OPD	16 (5.9)	16 (6.4)
Prescriber's position, n (%)	266	251
Hospital staff	253 (95)	249 (99)
Resident	13 (5)	2 (1)
Frequency of antimicrobial prescription after having access to guidelines	269	245
Nearly or every day	239 (89)	206 (84)
Weekly or less often	30 (11)	39 (16)
Frequency of use of the antimicrobial prescribing guidelines	261/273 (95.6)	243/251 (96.8)
Nearly or every day	96 (37)	115 (47)
Weekly or less often	165 (63)	128 (53)

Note: PP-G=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **IQR**=interquartile range, **ICU-ER**=Intensive Care Unit – Emergency Room, **OBGY**=Obstetrics and Gynaecology, **OPD**=Outpatient Department, **Other**=Including Ear, Nose, Throat (ENT), ophthalmology, dermatology, radiology (prescribed), dental care, administration (prescribers).

The PP-G feedback survey (Table 37) and App-G survey (Table 38) showed generally positive opinions. Most respondents felt the guidelines were well-named (97.4%), user-friendly (91.1%), linguistically appropriate (91.1%), and easy to follow for prescribing (91.5%). However, 39.8% found the physical guidelines bulky, while 28.2% were neutral on this issue. Most respondents agreed the guidelines covered relevant infectious disease topics (87.7%), with 88.9% noting the recommended antimicrobials were available in their hospitals, and 94.1% appreciating the prophylaxis section. However, 60.3% felt the guidelines somewhat restricted their antibiotic choices. The guidelines encouraged better documentation practices, with 92.6% and 91.2% feeling prompted to note indications and duration of antimicrobial use. The AMS section was found useful by 96.3%, and 97.4% agreed the guidelines increased their knowledge of antimicrobial stewardship.

Table 37: Prescriber satisfaction with the newly released antimicrobial prescribing paper-based guidelines

Prescriber's opinions	**Strongly agree (5)**	**Agree (4)**	**Neutral (3)**	**Disagree (2)**	**Strongly disagree (1)**	**No opinion (0)**	**Median score[a] (IQR)**
Physical characteristics and internal structure							
Appropriate name of guidelines; n= 268 (%)	121 (45.2)	140 (52.2)	6 (2.2)	0	0	1 (0.4)	4 (4-5)
Structure and design are intuitive and user-friendly; n= 272 (%)	82 (30.1)	166 (61)	23 (8.5)	0	0	1 (0.4)	4 (4-5)
Appropriate language used; n= 260 (%)	88 (33.8)	149 (57.3)	14 (5.4)	0	0	9 (3.5)	4 (4-5)
Prescribing instructions (antibiotic of choice, dose and duration) are easy to follow; n= 269 (%)	89 (33.1)	157 (58.4)	21 (7.8)	0	0	2 (0.7)	4 (4-5)
Bulky guidelines and inconvenient to carry, n= 269 (%)	42 (15.6)	65 (24.2)	76 (28.2)	61 (22.7)	18 (6.7)	7 (2.6)	3 (2-4)
Contents of the guidelines							
Covered relevant topics to routine practice; n= 269 (%)	87 (32.3)	149 (55.4)	28 (10.4)	2 (0.7)	0	3 (1.2)	4 (4-5)
Recommended antimicrobials are available in my hospital; n= 269 (%)	78 (29)	161 (59.9)	25 (9.3)	2 (0.7)	1 (0.4)	2 (0.7)	4 (4-5)
Guidelines restrict my choice of antibiotics, n=263 (%)	49 (18.6)	115 (43.7)	69 (26.2)	25 (9.5)	2 (0.8)	3 (1.2)	4 (3-4)
Useful prophylaxis section, n= 270 (%)	125 (46.3)	129 (47.8)	9 (3.3)	3 (1.1)	1 (0.4)	3 (1.1)	4 (4-5)
Useful extra information, n= 272 (%)	105 (38.6)	147 (54)	18 (6.6)	1 (0.4)	0	1 (0.4)	4 (4-5)
Learning/improving knowledge or behaviour							
Able to search for information easily; n= 272 (%)	84 (30.9)	154 (56.6)	29 (10.7)	2 (0.7)	0	3 (1.1)	4 (4-5)
Able to access information using references, n=269 (%)	77 (28.6)	155 (57.6)	31 (11.5)	3 (1.1)	0	3 (1.1)	4 (4-5)

Guidelines encourage me to document the indication for antimicrobial on hospital charts, n= 269 (%)	94 (35)	155 (57.6)	17 (6.3)	1 (0.4)	0	2 (0.7)	4 (4-5)
Guidelines encourage me to document the duration for antimicrobial on hospital charts, n= 271 (%)	97 (35.8)	150 (55.4)	21 (7.7)	2 (0.7)	0	1 (0.4)	4 (4-5)
Useful antimicrobial stewardship (AMS) section, n= 271 (%)	131 (48.3)	130 (48)	9 (3.3)		0	1 (0.4)	4 (4-5)
Guidelines increased my knowledge of AMS, n= 271 (%)	144 (53.1)	120 (44.3)	6 (2.2)	0	0	1 (0.4)	5 (4-5)

Note: IQR= interquartile range.

Table 38: Prescriber satisfaction with the newly released antimicrobial prescribing App-based guidelines

Prescriber's opinions	**Strongly agree (5)**	**Agree (4)**	**Neutral (3)**	**Disagree (2)**	**Strongly disagree (1)**	**No opinion (0)**	**Median score[a] (IQR)**
Intuitive structure/design and user-friendly, n=251 (%)	112 (45)	130 (52)	9 (3)	0	0	0	4 (4-5)
Offline mode makes it easy for me to access the guidelines anywhere, n=250 (%)	108 (43)	131 (52)	11 (4)	0	0	0	4 (4-5)
Language font size and colour are easy to read, n=248 (%)	85 (34)	146 (59)	17 (7)	0	0	0	4 (4-5)
I can find information which I look for more easily than from paper-based guidelines, n=251 (%)	105 (42)	132 (53)	14 (5)	0	0	0	4 (4-5)
Prescribing instructions (antibiotic of choice, dose and duration) are easy to follow, n=247 (%)	88 (36)	140 (57)	19 (8)	0	0	0	4 (4-5)
Links to extra information (data on antibiotic susceptibility pattern, causes of infections in Laos, international recommendation) are useful, n=250 (%)	90 (36)	146 (58)	14 (6)	0	0	0	4 (4-5)
App guideline encourages me to document the indication for antimicrobial on hospital charts, n=251 (%)	90 (35.8)	139 (55.4)	21 (8.4)	1 (0.4)	0	0	4 (4-5)
App guideline encourages me to document the duration of antimicrobial on hospital charts, n=250 (%)	94 (37.6)	140 (56)	15 (6)	1 (0.4)	0	0	4 (4-5)
App guideline has increased my knowledge of Antimicrobial Stewardship (AMS), n=250 (%)	117 (47)	127 (51)	6 (2)	0	0	0	4 (4-5)
AMS training increased my knowledge of AMS, n=251 (%)	123 (49)	121 (48)	7 (3)	0	0	0	4 (4-5)

The App-G feedback survey showed highly positive results, with most categories scoring a median of 4 (IQR: 4-5), indicating strong satisfaction. Most respondents (97%) found the app intuitive and user-friendly, while 95% valued the offline mode for easy access. Visual accessibility was rated highly, with 93% finding the font size and colour easy to read. Information retrieval was improved, with 95% saying it was easier than using the PP-G, and 93% found the prescribing instructions clear and easy to follow.

The app's links to local antibiotic susceptibility patterns, infection causes in Laos, and international recommendations were useful to 94% of respondents. It also promoted better documentation, with 91% prompted to note indications and 94% to document durations. A notable 98% said the app increased their AMS knowledge, and 97% confirmed that the embedded AMS training further enhanced this (Table 38).

Regardless of years since graduation, 89% of respondents of the PP-G group, and over 80% of the App-G group, reported prescribing antimicrobials nearly every day or more. This ranged from 77% in XK to 93% in SV for PP-G, and from 79% in LNT and SVK to 100% in VTP for App-G. Among surgery ward prescribers, 97% prescribed antimicrobials daily in the PP-G group, and 90% in the App-G group. Notably, 97% of paediatricians and 91% of ICU-ER prescribers reported daily antimicrobial prescribing in the App-G group (Table 39).

The majority of respondents reported accessing the PP-G weekly or less frequently, irrespective of their medical experience (63%) or work location (by hospital: 59%-77%, by department: 47%-79%). In contrast, prescribers from XK and SVK indicated they accessed the App-G nearly every day or more often. This frequent

usage was also reported by doctors from ICU-ER and paediatrics wards, with 65% and 63% respectively accessing the App-G almost daily.

Above data were based on self-reported data, where prescribers provided insights into their own prescribing practices. MicroGuide provided the cumulative access data to the App-G. Hits peaked between 8am and 10am, with the highest usage at 9am, reaching 899 times. Activity surged again around 1pm to 2pm, coinciding with typical patient consultation times (Figure 46). The App-G was opened a total of 6,239 times over 22 months, averaging about 24.8 times per prescriber (6,239/251 prescribers), or approximately once per month per prescriber. Among the most frequently searched topics in the App-G, melioidosis led with 181/527 (34%) searches, followed by pneumonia with 108/527 (20.5%) searches, and antimicrobial agents with 82/527 (15.6%) searches throughout the study period (Figure 47).

Table 39: Frequency of antimicrobial prescriptions and the use of prescribing guidelines after guideline implementation

Characteristics	Prescriptions after PP-G		Use of PP-G		Prescriptions after App-G		Use of App-G	
	Nearly or every day, n (%, 95% CI)	Weekly or less, n (%, 95% CI)	Nearly or every day, n (%, 95% CI)	Weekly or less, n (%, 95% CI)	Nearly or every day, n (%, 95% CI)	Weekly or less, n (%, 95% CI)	Nearly or every day, n (%, 95% CI)	Weekly or less, n (%, 95% CI)
Years since medical graduation								
≤10 years	116/131 (89; 82-93)	15/131 (11; 7-18)	47/128 (37; 28-46)	81/128 (63; 54-72)	94/114 (82; 74-89)	20/114 (18; 11-26)	49/115 (43; 33-52)	66/115 (57; 48-67)
>10 years	123/138 (89; 83-94)	15/138 (11; 6-17)	49/133 (37; 29-46)	84/133 (63; 54-71)	112/131 (86; 78-91)	19/131 (14; 9-22)	66/128 (52; 43-60)	62/128 (48; 40-57)
Hospital								
Xiengkhuang	40/52 (77; 63-87)	12/52 (23; 13-37)	18/51 (35; 22-50)	33/51 (65; 50-78)	27/32 (84; 67-94)	5/32 (16; 5-33)	19/33 (58; 39-75)	14/33 (42; 25-61)
Luang Namtha	21/23 (91; 72-99)	2/23 (9; 1-28)	7/21 (33; 15-57)	14/21 (67; 43-85)	23/29 (79; 60-92)	6/29 (21; 8-40)	10/29 (34; 18-54)	19/29 (66; 46-82)
Salavan	27/29 (93; 77-99)	2/29 (7; 0.8-23)	12/29 (41; 24-61)	17/29 (59; 39-76)	23/27 (85; 66-96)	4/27 (15; 4-34)	8/25 (32; 15-54)	17/25 (68; 47-85)
Savannakhet	44/49 (90; 78-97)	5/49 (10; 3-22)	19/47 (40; 26-56)	28/47 (60; 44-74)	46/58 (79; 67-89)	12/58 (21; 11-33)	33/57 (58; 44-71)	24/57 (42; 29-56)
Vientiane Province	24/26 (92; 75-99)	2/26 (8; 0.9-25)	6/26 (23; 9-44)	20/26 (77; 56-91)	15/15 (100)	0	7/16 (44; 20-71)	9/16 (56; 30-80)
Mahosot	83/90 (92; 85-97)	7/90 (8; 3-15)	34/87 (39; 29-50)	53/87 (61; 50-81)	72/84 (86; 76-92)	12/84 (14; 8-24)	38/83 (46; 35-57)	45/83 (54; 43-65)
Department								
Medicine	51/62 (82; 70-91)	11/62 (18; 9-29)	24/60 (40; 28-53)	36/60 (60; 47-72)	49/61 (80; 68-89)	12/61 (20; 11-32)	26/58 (45; 32-58)	32/58 (55; 42-68)
ICU-ER	34/38 (89; 75-97)	4/38 (11; 3-25)	17/37 (46; 29-63)	20/37 (54; 37-71)	30/33 (91; 76-98)	3/33 (9; 2-24)	20/31 (65; 45-81)	11/31 (35; 19-55)
OBGY	34/37	3/37	9/35	26/35	19/24	5/24	8/24	16/24

	(92; 78-98)	(8; 2-22)	(26; 12-43)	(74; 57-88)	(79; 58-93)	(21; 7-42)	(33; 16-55)	(67; 45-84)
Surgery	38/39 (97; 86-100)	1/39 (3; 0.06-13)	8/39 (21; 9-36)	31/39 (79; 64-91)	37/41 (90; 77-97)	4/41 (10; 3-23)	20/42 (48; 32-64)	22/42 (52; 36-68)
Paediatrics	30/32 (94; 79-99)	2/32 (6; 0.8-21)	15/31 (48; 30-67)	16/31 (52; 33-70)	31/32 (97; 84-100)	1/32 (3; 0.08-16)	20/32 (63; 44-79)	12/32 (37; 21-56)
Other	40/46 (87; 74-95)	6/46 (13; 5-26)	15/44 (34; 20-50)	29/44 (66; 50-80)	29/40 (72; 51-85)	11/40 (28; 15-44)	18/40 (45; 29-62)	22/40 (55; 38-71)
OPD	12/15 (80; 52-96)	3/15 (20; 4-48)	8/15 (53; 27-79)	7/15 (47; 21-73)	11/14 (79; 49-95)	3/14 (21; 5-51)	3/16 (19; 4-46)	13/16 (81; 54-96)

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **ICU-ER**= Intensive care unit – emergency room, **OBGY**= obstretrics and gynaecology, **OPD**= outpatient department, **Other**= Including Ear-Nose-Throat (ENT), ophthalmology, dermatology, radiology (prescribed), dental care, administration (prescribers).

Figure 46: Frequency of antimicrobial prescribing guideline access by time of day (data from MicroGuide)

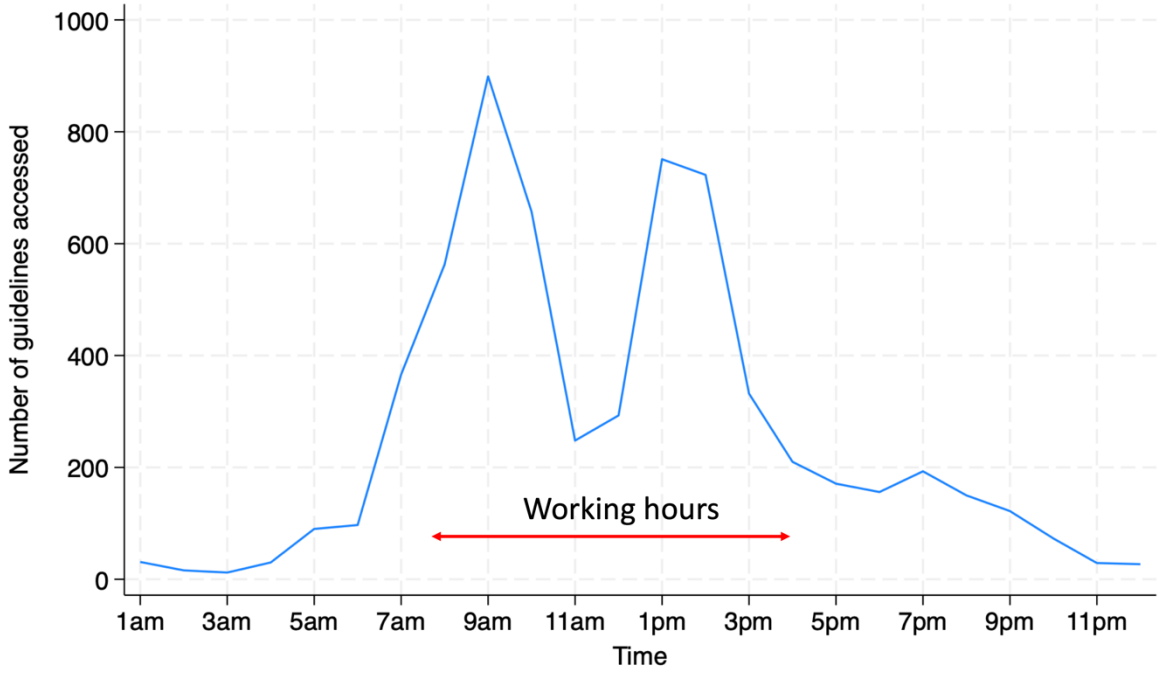
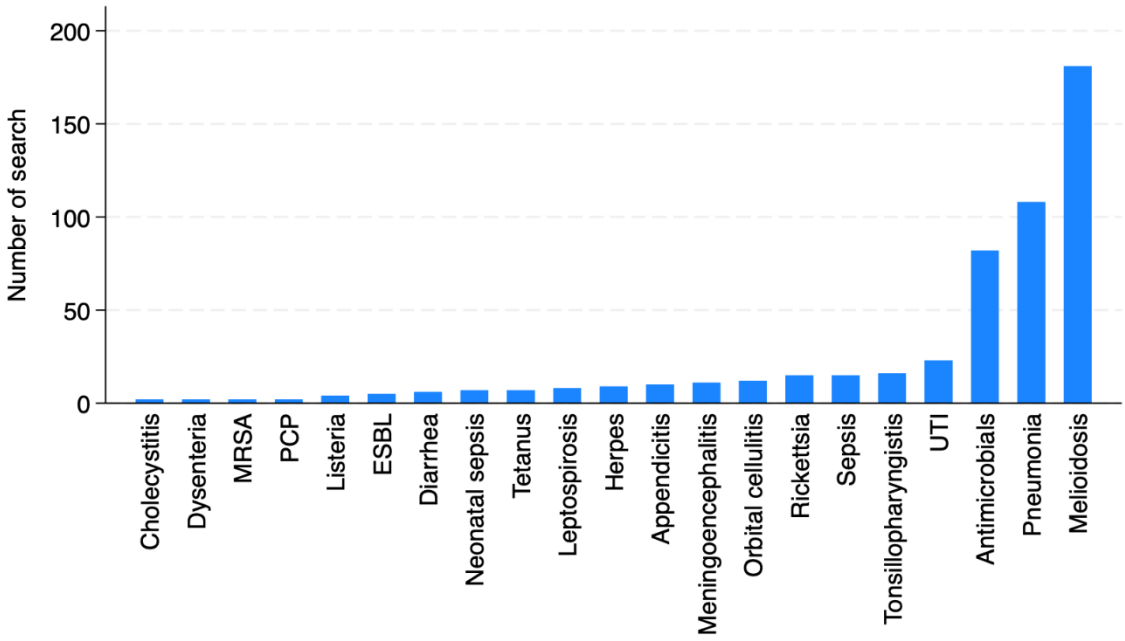


Figure 47: Guideline search patterns among prescribers (Data from MicroGuide)



Note: ESBL= Extended-Spectrum Beta-Lactamase, **MRSA**= Methicillin-Resistant Staphylococcus aureus, **PCP**= Pneumocystis Pneumonia, **UTI**= urinary tract infection.

Part II: Antimicrobial stewardship knowledge survey before and after the intervention implementation

AMS knowledge surveys (see Appendix 8 for questionnaires) were conducted five times during the study (Chapter 3): once pre-guideline, before each cluster's intervention (three times), and at the end of the study after all hospitals had used the intervention for at least four months. There were 415 respondents in the pre-guideline survey, 381 in the PP-G, and 305 in the App-G groups across six hospitals. Most respondents in the pre-guideline and PP-G groups had ≤10 years since graduation, while half of the App-G group had ≤10 years. Most prescribers were from medical departments, with general medicine comprising 50-53% of respondents (Table 40).

Eight multiple-choice questions were used in each period to assess the AMS knowledge level of prescribers. A score of four or above was considered a pass. The median correct scores during pre-guidelines, and in PP-G and App-G groups were 1 (range: 0-5), 2 (range: 0-8), and 1 (range: 0-5), respectively. In the pre-guideline period, only 16/415 (4%; 95%CI: 2-6.2) respondents passed the test. In the PP-G group, scores showed 5/80 (6%; 95%CI: 2-14) respondents passed among hospitals exposed to PP-G for six months. This increased to 27/174 (16%; 95%CI: 10.5-21.8) passing among those exposed to PP-G for 17 months. However, in the App-G group, the passing percentage dropped to 7/129 (5%; 95%CI: 2-10.9) at six months post-intervention implementation. This percentage was unchanged at 12 months and remained similar at 3% passing at 17 months post-intervention implementation (Table 41).

Table 40: Characteristics of prescribers who underwent knowledge assessment in six hospitals in different study groups

Characteristics	Pre-guideline; n (%)	PP-G; n (%)	App-G; n (%)
Total number of respondents	415 (38)	381 (35)	305 (28)
Xiengkhuang	53 (13)	55 (14)	47 (15)
Luang Namtha	27 (6)	25 (6)	17 (6)
Salavan	40 (10)	37 (10)	37 (12)
Savannakhet	64 (15)	90 (24)	75 (25)
Vientiane Province	30 (9)	28 (7)	24 (8)
Mahosot	192 (46)	146 (38)	105 (34)
Years since medical school graduation, median (IQR)	9 (6-17)	9 (6-17.5)	11 (6-21)
n	n= 393	n= 348	n= 295
≤5 years	94 (24)	84 (24)	60 (20)
>5 to ≤10 years	133 (34)	114 (33)	87 (29)
>10 to ≤20 years	84 (21)	74 (21)	71 (24)
>20 years	82 (21)	76 (22)	99 (26)
Prescribers' departments, n (%)	n= 407	n= 378	n= 304
Medicine	112 (27)	147 (39)	126 (41)
Intensive Care Unit – Emergency Room	52 (13)	62 (16)	49 (16)
Obstretrics and Gynaecology	54 (13)	49 (13)	26 (8)
Surgery	33 (8)	31 (8)	20 (7)
Paediatrics	66 (16)	38 (10)	45 (15)
OPD	90 (22)	51 (13)	38 (12)
Type of prescriber, n (%)	n= 413	n= 379	n= 304
Hospital staff	389 (94)	356 (94)	298 (98)
Resident	24 (6)	23 (6)	6 (2)

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **OPD**=outpatient department, **Other**=Including Ear, Nose, Throat (ENT), ophthalmology, dermatology, radiology (prescribed), dental care, administration (prescribers).

Table 41: Frequency of correct answers before and after implementation of the guidelines (paper-based guidelines and app-based guidelines)

Correct answers	Pre-guideline n= 415 (%)	PP-G			App-G			Post- guidelines implementation
		month-6 post PP-G; n= 80 (%)	month-12 post PP-G; n=127 (%)	month-17 post PP-G; n= 174 (%)	month-6 post App-G; n= 129 (%)	month-12 post App-G; n =112 (%)	month-17 post App-G; n= 64 (%)	Post Guidelines; n= 305 (%)
0	112 (27%)	1 (1)	8 (6)	17 (10)	37 (29)	42 (37)	16 (25)	95 (31)
1	143 (34)	32 (40)	25 (20)	56 (32)	56 (43)	53 (47)	32 (50)	141 (46)
2	102 (25)	30 (37)	58 (46)	49 (28)	22 (17)	6 (5)	11 (17)	39 (12.7)
3	42 (10)	12 (15)	26 (20)	25 (14)	7 (5)	5 (4)	3 (5)	15 (5)
4	12 (3)	3 (4)	7 (6)	15 (9)	7 (5)	6 (5)	1 (1)	14 (5)
5	4 (1)	2 (2)	2 (1)	8 (5)	0	0	1 (1)	1 (0.3)
6	0	0	1 (1)	2 (1)	0	0	0	0
7	0	0	0	1 (0.5)	0	0	0	0
8	0	0	0	1 (0.5)	0	0	0	0
<4*	399 (96)	75 (94)	117 (92)	147 (84)	122 (95)	106 (95)	62 (97)	290 (95)
≥4*	16 (4)	5 (6)	10 (8)	27 (16)	7 (5)	6 (5)	2 (3)	15 (5)

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, * Correct answers were equal or above four

Part III: In-depth Interviews on prescribing decisions and uptake of antimicrobial prescribing guidelines among Lao prescribers

The in-depth interviews were conducted in August 2022 with 16 participants, including eight from each hospital, with no refusals. Among the participants, 12 (75%) were female, the median (IQR) age was 36 (31-48) years and the median (IQR) years of medical experience was nine (6-18) years with half of them recognized as seniors. Four (25%) participants were from paediatric wards, four (25%) from adult general internal medical wards, four (25%) from intensive care units, three (19%) from infectious disease wards and one (1%) from a surgery ward (Table 42). Nearly all participants had access to both paper-based and app-based Lao antimicrobial prescribing guidelines, with only one participant having solely to the app-based guidelines.

Table 42: Demographic characteristics of study participants

Participant ID	Age range	Sex	Years [a]	Department	Hospital
1	30-39	Male	10	Medicine	Rural
2	30-39	Male	8	Paediatrics	Urban
3	30-39	Female	6	Infectious Diseases	Urban
4	50-59	Female	23	Medicine	Urban
5	30-39	Female	10	Intensive Care	Urban
6	50-59	Male	18	Infectious Diseases	Urban
7	30-39	Female	3	Infectious Diseases	Urban
8	40-49	Female	23	Intensive Care	Urban
9	20-29	Female	6	Medicine	Rural
10	20-29	Male	5	Surgery	Rural
11	40-49	Female	18	Paediatrics	Rural

12	30-39	Female	5	Intensive Care	Rural
13	50-59	Female	30	Medicine	Rural
14	40-49	Female	18	Paediatrics	Rural
15	30-39	Female	6	Intensive Care	Rural
16	30-39	Female	8	Paediatrics	Urban

Note: [a] Number of years since medical graduation.

Factors influencing antibiotic prescribing decisions

Prescribers shared their opinions about how they prescribed antibiotics in their facilities. They were asked what factors they considered before deciding to prescribe, including how they selected antibiotics, route of administration and why they might combine antibiotics (see Appendix 16 for the interview guide). The majority of participants explained that they prescribed antibiotics based on the patient's characteristics obtained from asking for the history of illness, underlying diseases, physical examination findings, and whether patients were in a severe condition. Suspected diseases and likely source of infection were also commonly mentioned as important factors for them to decide whether to start antibiotics, or which antibiotic or route of administration should be selected. Most of the time these factors influencing prescribing decisions took into account laboratory results, either complete blood count or specimen culture result (e.g., blood culture). Most of the time, participants considered multiple factors before deciding to start antibiotic therapy. These were similar between participants in central and provincial hospitals. A few interviewees mentioned that sometimes they also prescribed antibiotics based on their habit or medical experience of treating patients consulting with the same disease (e.g., pneumonia) when they already have a good idea what the causative pathogens are and what antibiotics need to be given. This was mentioned

more commonly among participants from the provincial hospital than those from the central hospital. Nearly half of the participants said that they prescribed antibiotics based on treatment/antibiotic use guidelines or textbooks, mostly to decide doses and treatment duration. Four main themes emerged from analysis of this content to describe how prescribers prescribed, including prescribing based on clinical judgement, following what has been done before, following specialist recommendations, and prescribing due to taking a precautionary approach (Table 43).

Table 43: Themes of factors influencing antibiotic prescribing from in-depth interviews with 16 prescribers in Lao hospitals

Themes/sub-themes	Quotations (participant ID)
Prescribing based on their clinical judgement: 1. Patient characteristics 2. Suspected disease/ causative pathogens/ source of infection 3. Antibiotic effects 4. Previous antibiotic use by the patient	" *It will be based on two things: first, on the clinical [symptoms/physical examination] of the patient. After 3-5 days of medicines, we recheck if the patient is getting better or not; our initial diagnosis is correct or not. Second, we rely on the lab [laboratory] results. If the medicines we initially provided is not the right one, then we'll need to change medicine based on the laboratory report* " (Participant 1, senior, medical ward, rural). *" Before we decide to prescribe antibiotics, we need to see if it is an infection. Most of the time, we search for the source of infection by information from the family. Most importantly is physical examination, because for myself and I believe for other doctors too, we need to know the source of infection before giving any antibiotic…. Above all, we cannot forget culture every single time, at least hemoculture each time "* (Participant 8, senior, intensive care unit, urban). " *If patients present with a severe condition, with anybody organ being affected badly or lightly, then the medicine will be based on the class of the antibiotics, or based on how severe the body organ is affected. These should be okay* " (Participant 7, junior, medical ward, urban). " *We also have to look into the choice of medicine. For example, for a case of pneumonia, we'll have to see which bacteria is it. We'll choose the lowest level [narrow spectrum] of medicine for the particular age group of the child, based on which bacteria is the common cause. We will not jump to a higher level [broad spectrum] of medicines* " (Participant 3, junior, paediatric ward, urban). " *Normally in my ward, we will base on the disease of the patient. For example, appendicitis, we would give ceftri [ceftriaxone]*

	before surgery, cloxacillin for abscess, and ampicillin for normal injury " (Participant 10, junior, surgical ward, rural). " *Those with respiratory issues, like a patient with previous pneumonia, comes to hospital because of breathing difficulty, we examine and find lung crepitation, then we'll immediately give antibiotics because this patient has previously received antibiotics. It's chronic* " (Participant 12, junior, intensive care unit, rural).
Prescribing based on the existing resources : 1. Following laboratory results 2. Following choice of available antibiotics in hospital	" *Patients who are admitted in our ward must have CBC tested urgently. If it shows high white blood cells, then undoubtedly, it's an infection and would first need antibiotics* " (Participant 5, senior, medical ward, urban). " *Before prescribing antibiotic for a patient, I mainly refer to the result of white blood cells of the patient. For instance, whether the level of white blood cells is high or too low in case the patient also has fever. A second criteria is the culture result, if it comes out positive. If not based on the above-mentioned reasons, then it would be mainly based on the CBC result and the condition of the patient* " (Participant 13, senior, medical ward, rural). " *The fundamental of giving antibiotics is based on the availability of medicines in the hospital* " (Participant 16, junior, paediatric ward, urban).
Prescribing based on habit	" *We rely on the prescribing app, the patient's condition, and our habits. For instance, when the patient has respiratory distress, for example, patient has pulmonary oedema, which there's no need for antibiotic. Sometimes it's a habit to start antibiotic thought the patient doesn't have fever, white cell counts are not high, but antibiotics are still given. Even if we don't give the patient antibiotics, other doctors would give antibiotics out of habit* " (Participant 9, junior, medical ward, rural). " *For cases that we give many types of medicines [combined antibiotics], is for those who have gastric perforation, for example. Like this, we need to give many medicines…. because we follow what we have been practicing* " (Participant 10, junior, surgical ward, rural). " *I use 2-3 types of antibiotics in case of infections in newborns, like ampi [ampicillin] and genta [gentamicin]. If still not confident, I would add cloxa [cloxacillin] for infection of newborns of late onset at home. When we're not sure what the bacteria is so we give them 3 types of medicine* " (Participant 14, senior, paediatric ward, rural).
Prescribing due to precautionary approach	" *We will immediately give IV for patients admitted because we don't want them to stay in the hospital long. If patients respond to our medicine, approximately three days then they want to leave hospital and we can continue with oral medicine.....First, we avoid all the people [relatives] who come and look after the patients. Two, the bacteria within the hospital, so we want to speed up [treatment process] so they can go home fast* " (Participant 5, senior, medical ward, urban).
Following specialist recommendations	" *We would not give antibiotics for digestive system which are not infected, like GI [gastrointestinal] bleeding. After GI tract examination and discussion with other doctors [GI specialist], antibiotic is suggested, then we'll prescribe antibiotics* " (Participant 4, senior, intensive care unit, urban).

Challenges to appropriate antibiotic prescribing

Prescribers also revealed that sometimes they have faced difficulties prescribing antibiotics appropriately. Lack of antibiotics in their settings was commonly mentioned among participants from central hospitals, including several important antibiotics that were not available in the country. Some said that the lack of antibiotics in their hospitals was not a big problem as patients' relatives could always find the antibiotics required in private pharmacies.

" *Currently, what is happening is that the culture results show MRSA [methicillin-resistant* Staphylococcus aureus*], and we want vanco [vancomycin] but it's not available. We have to buy it elsewhere, like other hospitals which sometimes it is available but sometimes not* " (Participant 2, junior, paediatric ward, urban).

" *We sometimes have to use lower effect medicines [narrow spectrum]. For example, ampho [amphotericin B] which is not available in Laos, is expensive and need to buy from Thailand. If ampho must be used but we don't have it and the patient cannot afford it, then we have to change to an oral medicine* " (Participant 7, junior, medical ward, urban).

" *If antibiotic is not available in the hospital, just go buy it from outside. It is easy to find* " (Participant 5, senior, medical ward, urban).

Perceived long turnaround time of laboratory results was another problem raised by some participants, mostly from the provincial hospital. Some mentioned that they realized that the culture could take time, and therefore, they usually did not wait for the laboratory results to decide whether they should have started antibiotics or not, or to choose which antibiotics they should have prescribed. Sometimes the microbiological results came too late for the prescribers to switch the antibiotic to a more appropriate one as the patient might have gone home or died. Here are examples of how some participants expressed their experience of perceived delayed microbiological results affecting how they prescribed antibiotics.

" *We start with the highest antibiotic [broad spectrum] first until the report [culture result] comes then we reduce it. There was an ICU case that was given mero [meropenem] and vanco [vancomycin], until the report [culture result] came out*

*showing staph [*Staphylococcus*] for which cloxa [cloxacillin] can be used. To that point, it was already over 10 days and only two days remaining [to complete the course of meropenem and vancomycin], so we continued with the same medicines without changing to cloxa [cloxacillin]*" (Participant 3, junior, paediatric ward, urban).

" *Mostly the lab [laboratory] would provide us the rapid test results like CBC. We know that the hemoculture takes some time so we don't wait for that* " (Participant 14, senior, paediatric ward, rural).

" *Labs [laboratory] are not enough/adequate and not as timely as needed. Sometimes, we get the result after patients are released from the hospital or the patient has already passed away. Sometimes, the patients have already gone home, and we're unable to give them medicine [in time]* " (Participant 15, junior, intensive care unit, rural).

Another challenge which was revealed by some junior prescribers was a difference of opinion on prescribing decisions from and between their senior(s). This was raised in both central and provincial hospitals equally. However, most of them mentioned that informing and discussing the decisions with seniors was essential because they had to make sure that they would have their full support if something went wrong, and their seniors could give different views as they had more experience.

" *During working days/hours, many staff decide which medicine to give to the patient, but there's a challenge because of different views. For instance, one professor [senior] wants to give a particular medicine while another professor [senior] wants to give a different one. Eventually, we would choose the decision of the most senior doctor. If the most senior doctor is not present, then the next senior one would decide. Hence, doctors who newly graduated wouldn't have a say in the decision making* " (Participant 16, junior, paediatric ward, urban).

" *Most of the time if they [seniors] prescribe, then I'll follow the decision. But there are times when I question like: what if an infant aged 1- 2 years presents with pneumonia with common bacteria, then the senior prescribes azithro [azithromycin] but instead I want to give amox [amoxicillin]. In this situation I would question to see if they have any reason for that or it is based on their experience, this medicine [azithromycin] is more effective. So, I don't understand what they think. Sometimes I question, sometimes I don't. But if you ask how I manage my thoughts... well, I let it go if I don't want to have any problems* " (Participant 2, junior, paediatric ward, urban).

A few participants described their challenges in managing patients on inappropriate antibiotics where they had to follow the initial prescribing decision, or with specific patient characteristics such as allergic reaction to some antibiotics or having chronic disease, or who could not afford the cost of an antibiotic. When asked where they search for help if they had a question relating to antibiotic therapy, most participants said that they checked the information in textbooks/research articles/internet as well as asking opinions from seniors/colleagues. Some participants preferred to only ask seniors/colleagues as this was quicker.

" *If the ward [ward doctor] has been giving the medicine for 1-2 days, then we'll have to continue using it. This is another reason that we cannot avoid. If they've been given meropenem, then we can't go back to the old medicine as we are not sure if patients would get better or get worse* " (Participant 8, senior, intensive care unit, urban).

" *We have to discuss with the family first before change and adjust the medicine: we currently don't have this medicine in the hospital and need to purchase from other hospital or outside pharmacy. If the patient's family say they cannot afford to buy the medicine, we'll need to find a way out* " (Participant 4, senior, intensive care unit, urban).

" *I mainly discuss with my colleagues for what we're not sure. We cannot decide alone. we have to jointly decide for a particularly difficult case to be accountable. We have to ensure safety first* " (Participant 7, junior, medical ward, urban).

Uptake of the new Lao antimicrobial prescribing guidelines

The first comprehensive antimicrobial prescribing guidelines in Laos were distributed to all prescribers in these two hospitals in 2021. These in-depth interviews focused on prescribers' perceptions of these new guidelines. Only a few themes emerged when asking when the participants used antibiotic prescribing guidelines. Nearly all participants said that they used the guidelines when they were not sure about the dose and duration of the antibiotic therapy, especially when patients had kidney problems. Some participants checked the guidelines when they were facing uncommon situations. Choices of antibiotics were also mentioned; for example, the participants looked for alternative antibiotics because what they wanted to prescribe was not available. The main reason for not consulting the guidelines was already remembering them by heart, a trend observed in both provincial and central hospitals. A participant also said that she/he did not use guidelines often because s/he followed what s/he has been doing in the ward or the recommendation from senior colleagues, another participant said that s/he was not quite sure how to use the guidelines (mobile application) (Table 44).

Table 44: Understanding how Lao doctors used the first comprehensive antimicrobial prescribing guidelines

Themes	Quotations (participant ID)
When did you access Lao antimicrobial prescribing guidelines?	
Searching for dose and duration of antibiotic treatment	" *I occasionally open the app because I always see patients and use the medicines often. I'll open it for special cases, like patients with kidney failure where we would need to adjust medicine dose. Therefore, we have to check on the appropriate dose for the level of kidney issue so that it doesn't affect the kidney* " (Participant 6, senior, medical ward, urban). " *Most of the time, it's when the patient has kidney issues and I'd like to provide the correct dose for kidney. Doses in general, I don't really refer to it [guidelines], because I use [medicines] often and I can remember. But I need to check the dose for patients with kidney and liver disease* " (Participant 2, junior, paediatric ward, urban). " *I look at what antibiotics to give, alternative medicine but I mostly check doses and duration of treatment* " (Participant 15, junior, intensive care unit, rural).
Facing uncommon situation	" *I mostly use the guidelines when I encounter a problem in treating a patient. For instance, we find low white blood cell on day 3, 4 or 5 of dengue fever; but on day 6, the level of white blood cells turns so high. Sometimes we are not sure about this strange situation whether patient has sepsis or not* " (Participant13, senior, medical ward, rural). " *I already remember most local infections… Let's say, I use it [guidelines] when I encounter issues* " (Participant 11, senior, paediatric ward, rural).
Searching for choice of antibiotic therapy	" *Alternative medicine. For instance, if the hospital runs out of a medicine, then an alternative medicine can be given. The district hospital would call to consult us about the medicine based on the condition of the patient. If the medicine is not available, we'll recommend them to give an alternative medicine based on the app* " (Participant 9, junior, medical ward, rural).
Why did not you access Lao prescribing guidelines often?	
Facing the same diseases and already remember the recommendations	" *I mostly do not open the book [guidelines] for the disease which I remember, for example sepsis, I already remember. As we know for baby aged less than 2-3 weeks, we use ampi [ampicillin], genta [gentamicin]. The dose is 50-100, let say we decided to use 50 …*" (Participant 14, senior, paediatric ward, rural). *" As I said, I opened the pocketbook once or twice. It says to use ceftri-azithro [ceftriaxone – azithromycin] and I then remember it. When there's a case of pneumonia again, I will use the same medicines in the same dose, like this over and over again "* (Participant 9, junior, medical ward, rural).

Prescribing based on habit	" *Well, in our ward, we just follow what we have been doing in terms of giving medicines* " (Participant10, junior, surgical ward, rural).
Not sure how to use it	" *I have to admit that I have never opened the pocketbook version of the guidelines, I have occasionally used the mobile phone application version …. But I do not understand if I should type the name of the antibiotic agent and then information comes up, or I have to go to each organ system [options to be selected in the application] and then I could find the information of the medicine* " (Participant 3, junior, paediatric ward, urban).

When asking participants to share their opinions on how their colleagues used the guidelines, the majority of them mentioned that they have seen their colleagues access the guidelines but not often. Some participants mentioned that personality was important as some colleagues just did not like reading or just followed what they have been doing in the past. Another reason for using guidelines less frequently could be because they have already remembered the guidelines or how to prescribe. Workload was also mentioned. Few participants mentioned about other guidelines/textbooks which were more commonly used in their areas.

" *We have discussed often in our ward, especially our ICU ward. We've discussed when antibiotics should be used or when we have faced difficult/complex disease like rabies or tetanus. We check the guidelines together to find out which antibiotics we should use because the guidelines have everything* " (Participant 13, senior, medical ward, rural).

" *It is a habit. For example, if patient comes with pneumonia or meningitis, doctors will prescribe the same medicines that they've used often which make the patient get better. Unless the patient doesn't get better, then they will check the guidelines/textbook to see whether the medicines they prescribe are correct or not. It's a habit. I've also done this before* " (Participant 3, junior, paediatric ward, urban).

" *They don't open it [guidelines] because their work is overloaded. For instance, in other countries, like Thailand, their doctors are on duty for eight hours and they take a rest. For us, we work from 8 o'clock of today to 8 o'clock of the following day. Some people are on duty three days in a row without rest. When they have little time, they want to rest their eyesight* " (Participant 11, senior, paediatric ward, rural).

" *We use Harrison's [textbook] in our general internal medicine wards. When we discuss with our seniors/professors, we have to refer to that book. Each senior/professor prefers a different textbook. Me, as senior, I encourage people to*

use this guideline [antibiotic prescribing guidelines] " (Participant 1, senior, medical ward, rural).

The participants were also asked to share their opinions on the guidelines. Most participants mentioned that the guidelines were appropriate. The majority of participants said that they preferred the mobile phone application version to the pocketbook version as it was convenient and easy to search for the information. A few claimed that the pocketbook version suited them better as they did not feel comfortable with technology. When asking about their ideal guidelines or what they wanted to improve in these guidelines, eight out of 12 participants shared their views that they already agreed with these current guidelines. Some proposed different searching options (e.g., search by antibiotic agent or by pathogen) and updating guidelines every one to three years was suggested.

Factors influencing better antibiotic prescribing and guidelines uptake

Participants proposed that improving and updating knowledge on antibiotic therapy were important to support appropriate use. This should not only be for prescribers in hospitals but also medical students. Engaging and raising awareness on good use of antibiotics could also support prescribers to prescribe more appropriately. Some participants suggested that restricting and monitoring the use of antibiotics could be effective solutions.

" *Overseas, they have control measures on the use of antibiotics. If they were to order carbapenem for example, general practitioners could order use for 2-3 days, if more than that they would need to consult the infectious disease doctor. The pharmacy will not dispatch the medicine if they cannot define these requirements. In our country, if ceftazidime were to be used, it is allowed to be used for 24-48 hours, more than that the infectious disease doctor need to be consulted to see if it's reasonable enough to extend use. Any hospitals could deploy these instructions, depending on how we want to determine our [requirements/measures] …. if there are unjustified use of antibiotics, we could strong feedback. If they have received strong feedbacks many times, there may be some changes* " (Participant 6, senior, medical ward, urban).

" *I think that there must be a training at provincial hospital level relating to the appropriate use of antibiotics as well as the dangers of the use. It could be twice a year. We should create a chat group to discuss about these topics regularly to make sure that the technical staff/doctors see the importance of the antibiotics. The local hospital can surely do these trainings but it will not be as impactful as having professors from central level to talk about these issues* " (Participant 14, senior, paediatric ward, rural).

" *All doctors must encourage each other and being a role model. If anybody sees the inappropriate use or overuse of antibiotics, they must give feedback every time* " (Participant 15, junior, intensive care unit, rural).

Many participants also suggested that more advertisement and engagement about the Lao antimicrobial prescribing guidelines as well as enabling easy access with instructions on how to use it (mostly mobile phone application version) could help to improve the guidelines uptake. A few participants said that monitoring and giving feedback on the use could be an option to encourage people to use the guidelines. Improving working hours was brought up; they argued that long working hours (24 hours on the duty day) was the main obstacle to uptake because people were already tired. Senior prescribers or heads of the wards were frequently mentioned when asking about the key person to support the uptake of the guidelines. Participants suggested that seniors and heads of the ward should support, enforce and monitor their use as well as being role models of guideline usage because junior staff usually followed the decision of the heads. A few participants said that the directors of hospitals should be more proactive and higher levels of civil servants, like the staff of the Ministry of Health, should get involved as it would be more powerful and this could gain more trust from the prescribers. Here are some quotations from the study participants:

" First, for people to know more about the app, those doctors who use it should advertise it. Second, we need to advertise more, it could be a poster in the elevator if it is allowed. If not, the poster should be put in each ward dashboard therefore people can see it " (Participant 16, junior, paediatric ward, urban).

“ We have to use medicine as they [seniors] suggest. If the seniors said that this medicine is better than that medicine, we will have to follow them. If the younger/junior one change [how to prescribe antibiotics appropriately] while the older/senior ones don’t change. We still work for them, therefore we have to follow them ” (Participant 12, junior, intensive care unit, rural).

“ *I really use it [guidelines], my boss encourages me to use it* ” (Participant 11, senior, paediatric ward, rural).

“ *Higher level [ministry of health] should recommend the use as wider group of people will know it. It is similar to advertising a product, the more people know about it, the more they use it. Same as this guideline, if there is a recommendation from the high level or from experts in this field, people will trust it* ” (Participant 8, senior, intensive care unit, urban).

Discussion

Findings from the qualitative study provide details insights on how Lao doctors prescribe antibiotics, as well as the main challenges to appropriate antibiotic prescribing they face. Participants revealed that they prescribed antibiotics based on several factors. Clinical judgement was the most common factor, followed by availability of existing resources such as laboratory results and antibiotics in their settings. Prescribing based on habit, prescribing due to adopting a precautionary approach (e.g., concerns about hospital-acquired infection) and following specialist recommendations also contributed to antibiotic prescribing decisions. Data on antimicrobial use in hospitals in Laos were limited until recently (141, 152), and information on the prescribing behaviours of Laos doctors was even scarcer. A large antibiotic prescribing behaviour survey of 386 Lao doctors from 25 hospitals across Laos, showed that half (49%) of participants were confident with their antibiotic prescribing; 22% (86/386) of doctors claimed that their prescribing was driven by antibiotic availability rather than the cause of the infection. In addition, 50% of surveyed participants admitted that patient demands played an important role in their antibiotic prescribing decisions (104). A mixed-methods research project aiming to understand how healthcare providers (30 participants) from the Lao capital and a province prescribed antibiotics to pregnant women during their pregnancy and delivery, showed that the majority of participants prescribed antibiotics not only to treat infection or as surgical prophylaxis for caesarean section, but also to prevent post-partum infection in uncomplicated vaginal delivery with episiotomy as a result of a lack in confidence in hygiene in the delivery room (149). Appropriate antibiotic prescribing is a complex topic and involves various factors, especially in LMICs such as Laos. This study found that limited access to

appropriate antibiotics was the main obstacle to prescribing appropriately. We have described limited access to certain antibiotics in Laos when applying the international antibiotic use guidelines such as the WHO AWaRe (Access, Watch, Reserve) antibiotic book in the country (251). Only 29 of the 39 antibiotics in the AwaRe book were available in Laos with no access to WHO Reserve group antibiotics for Gram-negative bacteria resistant to Watch group antibiotics(251). Participants in this study mentioned that they have faced unavailability of several Access and Watch group antibiotics in their hospitals on multiple occasions. Long turnaround time of laboratory results was mentioned frequently by study participants. Most participants understood the culture process could take some days but often they could not switch to recommended antibiotics based on the culture results as a consequence. Microbiological diagnosis in Laos has improved recently thanks to support from the Lao government, and the UK Fleming Fund, with 11 hospitals across the country now able to perform basic conventional cultures with one central hospital and a national centre acting as reference laboratories. Increasing access to microbiological diagnosis is important as well as improving basic knowledge of microbiology among physicians. Other studies have also found that appropriate antibiotic prescribing was influenced by numerous factors such as medical knowledge, experience, awareness, misconceptions, loss of ownership of prescribing decisions, precautionary approaches, expectation of patients and families, workload/lack of staff and available resources (246, 252, 253). In our study, most participants claimed that antibiotic demands from patients/families did not affect their prescribing decision. However, some misconceptions of antibiotic effects were found, as some prescribers were reluctant to de-escalate unnecessary broad-

spectrum antibiotics already prescribed on another ward before transfer to their ward.

The last edition of the Lao national standard treatment guidelines was released in 2012 which included recommendations for antibiotic therapy for some of the most common infectious diseases. The first antibiotic prescription behaviour survey in Laos conducted in the same year showed that 65% (249/383) of participants preferred local antibiotic prescribing guidelines to the international guidelines but 22% (85/386) mentioned that local guidelines could make their prescribing more challenging rather than supporting it. However, the authors did not describe the reasons in detail (104).

Gray et al. published the first qualitative study on the uptake of the paediatric guidelines in Laos in 2017. The research team described a number of factors influencing the uptake of the guidelines, for example: comprehension, accessibility (physical availability, language, simplicity, training in use), trust and acceptance, social influences (e.g., support from seniors, being role models of using guidelines), patient expectations and reinforcement (198). This current study explored how Lao prescribers used the first comprehensive antimicrobial prescribing guidelines in the Lao language. The majority of participants said that they were satisfied with the guidelines in terms of the simplicity, accessibility and comprehensiveness. This is consistent with our guideline satisfaction survey which showed a high acceptance rate for both the paper-based and app-based prescribing guidelines.

Most participants admitted that they did not use the guidelines often because they are familiar with most diseases encountered during their practice and they already remembered the guideline recommendation. The participants mentioned that they have also seen their colleagues using the guidelines but not often. Many of them

still prescribed based on what they have been doing before. Information about how physicians/prescribers use antibiotic prescribing guidelines or treatment guidelines are not well documented.

Beizen et al. identified how Australian general practitioners (GPs) accessed and used guidelines to support their antibiotic prescribing decisions. The research team mentioned that GPs' attitudes played an important role in accessing guidelines. For example, more experienced GPs were less likely to use the guidelines because they claimed that they already knew how to prescribe. The use of the guidelines was also affected by trust and acceptance of the guidelines (e.g., there might be distrust of the evidence source or concern about economic motives behind the guidelines), patient demands, accessibility (e.g., cost of the guidelines, ease of access), workload (e.g., too busy in the practice and no time to update oneself) (254-256).

Previous studies have suggested that to be able to improve the uptake of clinical practice/antibiotic use guidelines, the guidelines must be transparent in the development process, comprehensive but simple, easy and free or low cost to access, with training and promotion of their use (198, 255, 256). Our first Lao antimicrobial prescribing guidelines, available in Lao language, were provided to all prescribers in participating hospitals at no cost, in both pocketbook and mobile phone application formats, along with training on their use. However, the findings from our study align with previous evidence from other research.

Interestingly, more than 97% of prescribers in the guideline satisfaction surveys reported that both PP-G and App-G improved their AMS knowledge. This was not consistent with the AMS knowledge survey scores results from this study for which only 5% of participants pass the AMS assessment at the end of the study. A mixed-methods study in seven hospitals in Vietnam conducted in 2018, revealed that

improving AMS programmes in hospitals required complex strategies with a diversity of stakeholders and leaders. Forming AMS committees should be included in the initial stage (257). Participants from our qualitative study also mentioned that directors of the wards and hospitals should promote and monitor guideline use, and high-level authority figures such as from the Ministry of Health should get involved to improve appropriate use of antimicrobials in Laos.

A limitation of this study was that the main investigator was a key member of the guideline development team. Some participants might therefore not have felt comfortable critiquing the guidelines as much as they wanted to. On the other hand, this could have been seen as a good opportunity for participants to send direct messages to the developer in a constructive way. More female prescribers were interviewed in this study because the majority of the participants from participating wards of these two hospitals were women (69% and 85%). Another limitation was the different medical training background of participants between central and rural hospitals and the fact that not all specialties were represented. Therefore, some information might not be representative of prescribers across the country. It is possible that practice and uptake of guidelines could vary between departments for other reasons such as difference in case-mix, however, we think this was unlikely on these general wards.

Appropriate antibiotic prescription relies on several factors. Findings from this study suggest that improving clinical knowledge of prescribers, assuring easy access to basic and life-saving antibiotics should be considered. Antibiotic prescribing guidelines could support the rational use of antibiotics and enhance antimicrobial stewardship programmes. To ensure that the guidelines are used regularly, prescribers should be aware of what information they could obtain from the

guidelines to support their decision, and recommendations must be updated regularly. Heads of the wards, directors of hospitals and higher authorities should support, monitor and provide feedback on their use to encourage all prescribers to access the guidelines.

Chapter 6: Implementing the WHO AWaRe antibiotic book guidance in lower resource settings: the case of Lao PDR

Abstract

In 2022, WHO released the WHO AWaRe (Access, Watch, Reserve) antibiotic book to promote the rational use of antibiotics. Here, we review the AWaRe antibiotic book from the perspective of implementation in low resource settings, using Laos as a case study. Not all recommendations in the AWaRe antibiotic align with the epidemiology of infectious diseases and antimicrobial susceptibility patterns in Laos and other LMICs e.g., common infectious diseases such as melioidosis, rickettsial disease and leptospirosis are do not included in the AWaRe book. Conversely, some infectious diseases such as *Clostridioides difficile*-associated diarrhoea are in the AWaRe antibiotic book but rarely considered in Laos with no diagnostic tests available. Only 29/39 (74%) antibiotics in the AWaRe book are available in Laos, with no Reserve group antimicrobials available. The AWaRe book stimulates countries such as Laos to consider alternative diagnoses and include additional antimicrobials in the national list of essential medicines. However, it should be updated to include missing regional important pathogens. Comprehensive antibiotic use guidelines alone might not assure appropriate use of antibiotics. Access to antibiotics is challenging in low resource settings in terms of unavailability in the country (low demand or small market size), patchy access, especially for those living in remote areas, and unaffordability. All these systemic factors can contribute to inappropriate use of antibiotics. Improved access to antibiotics, strengthening diagnostic capacity and promoting antibiotic stewardship should be combined.

Background

Antimicrobial resistance (AMR) is widely considered to be one of the top health threats worldwide. Although AMR occurs naturally, evidence shows that misuse and overuse of antimicrobials accelerate the development of acquired resistance (12, 163). In many LMICs, there are fewer antibiotics available than in high income countries, and it can be difficult to access them, particularly in remote areas. While, increasing access to antibiotics is crucial, multifaceted strategies are also required to improve quality of care and appropriate use of antibiotics (258-260). Comprehensive antimicrobial prescribing guidelines with proper training and appropriate implementation approaches have been proposed as an option to improve the rational use of antibiotics (186).

In 2022, WHO released the first WHO AWaRe (Access, Watch, Reserve) antibiotic book, an adjunct to the Essential Medicines List, with the aim of providing "…short, clinical guidance on the management of common infections" in hospital and primary health care settings (197). This global guideline includes 39 antibiotics and covers 34 common infection presentations in adults and children, focusing on empirical treatment. Among the 39 antibiotics, 20 (51.2%) are in the Access antibiotic group, 11 (28.2%) in the Watch group and eight (20.5%) in the Reserve group (197). The WHO AWaRe Antibiotic Book is not intended to replace existing local or national prescribing guidelines. While high-income countries (HICs) tend to have institutional level guidelines, currently, many LMICs still do not have national guidelines (196) and so it provides a useful template for adapting to the local context. For countries with guidelines, it can act as a reference standard against which to benchmark. There are expected to be challenges to implementing the guidelines in some LMICs,

e.g., due to lack of laboratory diagnostics, human resources, and access to recommended antimicrobials (261).

The first comprehensive Lao antimicrobial prescribing guidelines were made available in 2021. These guidelines were developed based on the current local antimicrobial susceptibility patterns and Antimicrobial Use (AMU) situation in Laos, existing local treatment guidelines and international recommendations (134, 135). Currently, the guidelines only recommend antibiotics which are registered in the country, with two exceptions: vancomycin (for treatment of MRSA bacteraemia only) and nitrofurantoin (for ESBL producing *E. coli* urinary tract infection, due to high rates of resistance to all other antibiotics). Here we review the WHO AWaRe antibiotic book from the perspective of implementation in low resource settings, using Laos as a case study. Our framework of evaluation considers the epidemiology of infectious diseases and AMR in Laos, the current situation with regard to antimicrobial use, availability and access, and practical considerations such as feasibility, including systemic barriers at hospital or policy level.

Infectious disease and AMR epidemiology in Laos

Laos is a land-linked country in the WHO Western Pacific region, sharing borders with Vietnam, Thailand, China, Myanmar and Cambodia. Antimicrobial treatable infectious diseases such as melioidosis, rickettsial disease and leptospirosis are well documented in Laos (33, 73, 141, 262, 263). In a study of the epidemiology of febrile illness in Laos between 2008 and 2010, dengue fever was the leading cause of febrile illness diagnosed in 8% (156/1,927; 95% CI: 7%-9%) patients, followed by scrub typhus in 7% (122/1,871; 95% CI: 5%-8%), Japanese encephalitis virus in 6% (112/1,924; 95% CI: 5%-7%), leptospirosis in 6% (109/1,934; 95% CI: 5%-7%),) and other bloodstream infections (BSIs) in 2% (43/1,938; 95% CI: 1.6%-3%) (33). HIV

prevalence in Laos is 0.3% (264) and malaria incidence has declined dramatically over the last two decades, now being restricted to a small number of southern provinces (265). Diagnostic microbiology is mainly available in a few hospitals in Vientiane, the capital city, although services have been expanded to provincial hospitals in the last two years, with financial support from a UK Fleming Fund country grant (266). Data generated by the Microbiology Laboratory of Mahosot Hospital, a large central hospital in Vientiane, in 2022, showed that among 7,913 blood cultures taken, the most common pathogen causing bacteremia in patients of all ages was *Burkholderia pseudomallei* at 134 (1.7%; 95% CI: 1.4%-2%), followed by *Escherichia coli* at 111 (1.4%; 95% CI: 1.2%-1.7%) and *Staphylococcus aureus* at 69 (0.9%; 95% CI: 0.7%-1%) (LOMWRU, unpublished data). The main AMR concern in Laos currently is an increase in numbers of BSIs caused by extended spectrum beta lactamase (ESBL)-producing *Escherichia coli.* Rates of ESBL-*E. coli* isolated from blood increased from 7% (95% CI: 0.9%-25%) of all *E. coli* isolates in 2004 to 35% (95% CI: 24%-46%) in 2016 (141) and reached 58.5% (95% CI: 49%-68%) in 2022. Rates of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia have also risen, currently around 26% (95% CI: 16%-38%) in 2022 (LOMWRU, unpublished data).

The WHO AWaRe book covers 34 common infection presentations. The majority of them are included in the Lao antimicrobial prescribing guidelines (134, 135). However, treatment recommendations for the most common infections in Laos, and across much of SEA, such as melioidosis, rickettsial diseases and leptospirosis are not included in the WHO AWaRe book. As a result, for some syndromes recommendations do not match the epidemiology of infectious diseases and antimicrobial susceptibility patterns in Laos and more generally across Asia. For

example, Lao antimicrobial prescribing guidelines suggest ceftazidime (to cover melioidosis) combined with amikacin (to cover ESBL producing *E. coli*) as a primary choice for empirical treatment of septic shock and meropenem as an alternative choice. Bacterial meningitis is another example; causes of central nervous system (CNS) infections in Laos from 2003 to 2011 (66) showed that zoonotic diseases (rickettsial diseases and leptospirosis) were common, causing 7.5% (80/1,065; 95%CI: 6%-9%) of suspected CNS infections in Laos, after Japanese encephalitis virus at 8.8% (94/1,065; 95%CI: 7%-11%) (66). Therefore, our local guidelines suggest ceftriaxone combined with doxycycline for suspected bacterial CNS infections (Table 45). A recent publication from Varghese et al. suggested that the combination of intravenous (IV) doxycycline and azithromycin was more effective than doxycycline or azithromycin alone for severe rickettsial diseases (267). This should be taken into a consideration to update Lao national prescribing guidelines for severe infections. However, parenteral doxycycline and azithromycin are not currently available in Laos.

Conversely, some topics in the WHO AWaRe book are not included in Lao prescribing guidelines such as *Clostridoides difficile* infection, acute diverticulitis, infectious uveitis which could be reconsidered. Although only five patients with *C. difficile* infection have been ever reported in Laos in a research study, it may be underreported since *C. difficile* diagnosis is not routinely available (89).

Table 45: Recommended antibiotic treatment for selected severe clinical presentations in adults in Lao antimicrobial prescribing guidelines versus the WHO AWaRe book

Lao antimicrobial prescribing guidelines – adults (134)	WHO AWaRe book – adults (197)	Comments
Empirical treatment for suspected bacterial meningitis	**Empirical treatment for suspected bacterial meningitis**	
Ceftriaxone 2g, IV every 12 hours ***PLUS*** Doxycycline 200mg, PO first dose, then 100mg every 12 hours ***OR*** (if severe penicillin allergy) Chloramphenicol 1-2g, IV every 6 hours **add** ampicillin or amoxicillin if risk factors for *Listeria monocytogenes* infection **add** aciclovir 10mg/kg, IV every 8 hours if suspected meningoencephalitis	**First choice** Cefotaxime 2g, IV every 6 hours ***OR*** Ceftriaxone 2g, IV every 12 hours **add** ampicillin or amoxicillin if risk factors for *Listeria monocytogenes* infection **Second choice** Amoxicillin 2g, IV every 4 hours ***OR*** ampicillin 2g, IV every 4 hours ***OR*** benzylpenicillin 4 million IU (2.4g), IV every 4 hours ***OR*** chloramphenicol 1g, IV every 6 hours	Doxycycline was added to Lao guidelines to cover zoonotic disease such as rickettsia and leptospirosis which were commonly found as a cause of CNS infections in Laos (66).
Empirical treatment for septic shock	**Empirical treatment for septic shock**	
Ceftazidime 2g, IV every 8 hours ***PLUS*** Amikacin 25-30mg/kg/day, IV every 24 hours **or** Gentamicin 7mg/kg/day, IV every 24 hours	Cefotaxime 2g, IV every 6 hours ***OR*** Ceftriaxone 2g, IV every 12 hours ***PLUS*** ***Unknown origin*** Amikacin 15mg/kg, IV every 24 hour ***or*** Gentamicin 5mg/kg, IV every 24 hours	Melioidosis is a leading cause of death from sepsis in Laos and treatment is with ceftazidime and not ceftriaxone (73).

add metronidazole if suspect abdominal sepsis	***Lower respiratory tract infection*** Clarithromycin 500mg, IV every 12 hours ***Intra-abdominal infection*** Metronidazole 500mg, IV every 8 hours ***Urinary tract infection*** Amikacin 15mg, IV every 24 hours ***Skin and soft tissue infection*** Metronidazole 500mg, IV every 8 hours (add Vancomycin 15-20mg/kg, IV every 12 hours if MRSA suspected) ***OR (alone; without cefotaxime or ceftriaxone combination)*** Piperacillin/tazobactam 4g+500mg, IV every 6 hours ***or*** Meropenem 2g, IV every 8 hours	More than 50% of invasive *E. coli* infections are ESBL positive and resistant to gentamicin (LOMWRU, unpublished data) so Lao guidelines recommend amikacin first line, however it is only available in Vientiane capital. Clarithromycin IV, Piperacillin/tazobactam and vancomycin are not in the national list of essential medicines in Laos (192).

Antibiotic use in Laos

According to the first hospital antimicrobial use point-prevalence survey in Laos (152), the use of antimicrobials among admitted patients in five provincial hospitals and one central referral hospital was ~70% from 2017 to 2020. Antibiotics from the WHO Access group accounted for 50% prescriptions which was below the WHO target (60%); while 49% were Watch group and 0.8% were Not Recommended (ceftriaxone/sulbactam at 91% (30/33; 95% CI: 91%-98%) and cefoperazone/sulbactam at 9% (3/33; 95% CI: 2%-24%)). The survey revealed that ceftriaxone was heavily used at all surveyed hospitals, accounting for 2,596/6,555 (39.6%; 95% CI: 38%-41%) of all prescriptions. Ceftriaxone made up 38.4% of prescriptions for treating infections and 720/1,424 (50.6%; 95% CI: 48%-53%) of all surgical prophylaxis prescriptions (152). The use of antibiotics in outpatient departments or for milder infections showed that the use of Access group accounted for 67% (2,365/3,520; 95% CI: 66%-69%) prescriptions and the use of Watch group was 33% (1,155/3,520; 95% CI: 31%-34%) during 2021 and 2022 (268). Data on the use of antibiotics in primary healthcare settings in Laos are limited. However, a recent study of more than 25,000 consultations in health centres in southern Laos found only around 10% result in an antibiotic prescription (*Koukeo Phommasone pers. comm. 2023*).

Availability and access to antibiotics in Laos

The WHO AWaRe book includes 39 antibiotics. The most recent list of national essential medicines (NEML) registered with the Lao Food and Drug Department (FDD), Lao Ministry of Health in 2019, included 29 antibiotics (either oral or parenteral or both administration routes; excluding anti-tuberculosis and anti-

leprosy medicines). Of these 29 agents, 15 (52%) were in the WHO Access group and 14 (48%) were in the WHO Watch group. No medicine from the Reserve group has been registered in Laos (Table 46) (192). While on the one hand this prevents inappropriate use it also means that a small number of patients with multidrug resistant infections are not able to access the medicines they need.

Table 46: List of recommended antibiotics from the WHO AWaRe book which are not in the Lao NEML in 2019 in Laos

Access group
Cefazolin, clarithromycin (injection), clindamycin, nitrofurantoin, spectinomycin, trimethoprim-sulfamethoxazole (injection), trimethoprim
Watch group
Cefuroxime, piperacillin/tazobactam, vancomycin
Reserve group (none are currently in the Lao NEML)
Aztreonam, carumonam, cefiderocol, ceftaroline-fosamil, ceftazidime/avibactam, ceftobiprole-medocaril, ceftolozane/tazobactam, colistin injection, colistin (oral), dalbavancin, dalfopristin/quinupristin, daptomycin, eravacycline, faropenem, fosfomycin injection, iclaprim, imipenem/cilastatin/relebactam, lefamulin, linezolid, meropenem/vaborbactam, minocycline (injection), omadacycline, oritavancin, plazomicin, Polymyxin-B (injection), Polymyxin-B (oral), tedizolid, telavancin, tigecycline

Comparing the national guidelines in Laos to the WHO AWaRe antibiotic book highlights antimicrobials which would be useful to introduce in Laos as well as some instances where there is a more practical alternative already in use, or where there are barriers to following the AWaRE recommendations. Mahosot Hospital Microbiology Laboratory reported 172 *E. coli* isolates from urine specimens in 2022, of which 61.6% (106/172; 95% CI: 54%-69%) were ESBL- producing *E. coli*. Of 105

tested, 99% (104/105; 95% CI: 95%-100%) were susceptible to nitrofurantoin (LOMWRU, unpublished data), which is recommended in the WHO AWaRE antibiotic book. However, nitrofurantoin is not available in Laos. Access to and use of nitrofurantoin might facilitate reduction in the use of Watch group antibiotics and may both decrease the number of hospital admissions with ESBL-producing *E. coli* BSI and slow down the spread of ESBL-producing bacteria by reducing the use of ceftriaxone in Laos.

Cefazolin, a first-generation cephalosporin, is the first-choice antibiotic for surgical prophylaxis of clean procedures, or cefazolin combined with metronidazole for contaminated procedures or bowel surgery (193). The AWaRe book mostly recommends cefazolin for surgical prophylaxis (197). Cefazolin is not in the registered essential medicine list for Laos (192). Based on antibiotic availability in Laos, Lao antimicrobial prescribing guidelines recommend amoxicillin/clavulanic acid or ceftriaxone with or without metronidazole for surgical prophylaxis (134, 135). Repeated point prevalence surveys from 2017 to 2020 have shown that the use of antibiotics in surgical departments accounted for one third of all antimicrobial prescriptions in Lao hospitals. Most antibiotic use for surgical prophylaxis lasted more than one day, which is not recommended (141). Cefixime, an oral third generation cephalosporin antibiotic in the Watch group, was among the top five antibiotics (185/3,520 (5%; 95% CI: 4.5%-6%)) prescribed in outpatient departments in Laos during 2021 and 2022 in six hospitals across the country. The main purpose of the prescription was for treatment of presumed sexually transmitted infections (61/185 (33%; 95% CI: 26%-40%)). However, it was also used for respiratory infection (45/185 (24%; 95% CI: 18%-31%)), urinary tract infections (28/185 (15%; 95% CI: 10%-21%)) and pharyngitis (27/185 (15%; 95% CI: 10%-

20%)) for which Access antibiotics can be prescribed (268). Even though guidelines are available, achieving the appropriate use of antibiotics can still be challenging. The AWaRe book cautiously recommends meropenem as a secondary choice for sepsis/septic shock, bacterial meningitis, febrile neutropenia and some gastrointestinal tract infections. Meropenem was included in the Lao NEML in 2019 and the Lao antimicrobial prescribing guidelines recommend meropenem as an alternative choice for septic shock, melioidosis and infection with laboratory confirmation of ESBL-producing pathogens. Meropenem was among the top ten antibiotics prescribed among admitted patients in six hospitals in Laos from 2021 to 2022 (268) and carbapenem resistance has been reported in Laos since 2015 (34). Vancomycin has been introduced in some hospitals in Vientiane, for patients diagnosed/suspected with methicillin-resistant *S. aureus* (MRSA) bacteremia. The use of vancomycin in Laos is challenging as a result of unpredictable supply, cost, and the fact that it is not included in the NEML. Lack of therapeutic drug monitoring (TDM) could lead to toxicity or risk being sub-therapeutic (269). Clindamycin is proposed in the AWaRe book for treatment of MRSA skin and soft tissue infections, which is inexpensive (USD 0.12/tablet in Laos), but the majority of isolates in Laos currently are not susceptible to this agent, which is also not widely available. Current practice in Laos is to use trimethoprim-sulfamethoxazole which is available, inexpensive and to which all isolates are susceptible currently.

Practical considerations

Recommendations (choice, dose and duration) on antimicrobial prescribing differ country by country (196). Access to up-to-date standard antibiotic prescribing guidelines is needed for all health workers to prescribe appropriately and to control the spread of AMR. However, in practice, in low resource settings such as Laos, comprehensive prescribing guidelines alone might not be sufficient. Unlike in high-income countries where the use of broad-spectrum antibiotics, like meropenem, is usually discussed with infectious disease specialists before prescribing there are currently no restrictive antimicrobial stewardship policies in Laos.

Poor antibiotic access is a global issue and lack of economic incentives have been shown to be the major reason for pharmaceutical companies not producing or marketing them (270). This is likely to be worse in small LMICs with low demand and small market size, like Laos, leading to a perception of no return on investment to register or market them in these countries (271). Unavailable antibiotics in the country or uneven availability with people living in remote areas unable to access certain antibiotics, or high cost of antibiotics could lead to poor prescribing and poor patient outcomes. On the other hand, some broad-spectrum antibiotics which are not included in Lao-NEML, are circulating in some larger hospitals (152, 192), risking faster spread of AMR. However, this might also reflect the need for certain antibiotics for the country and updating of the NEML (in Laos it is updated every three years and the last version was in 2019) based on local scientific evidence and international recommendations. Limited access to microbiology diagnosis and poor understanding of diagnostic stewardship are other challenges to following guidelines and prescribing appropriately. Monitoring the use of antibiotics and strengthening drug and therapeutics committee in each hospital may help to

overcome this. An up-to-date NEML that reflects prescribing guidelines, adherence to prescribing recommendations by clinicians and prioritization of antimicrobial stewardship by health governance bodies will likely increase the demand for the right kind of antibiotics, providing an incentive for pharmaceutical companies to market them.

The WHO AWaRe book is very welcome as global antibiotic use guidelines, which incorporate useful information to diagnose infectious diseases and laboratory considerations. LMICs developing national guidelines need to adapt them to the local epidemiology of infectious diseases and antimicrobial susceptibility patterns. For example, melioidosis is a common cause of sepsis in Laos and other Southeast Asian countries but has been largely overlooked in the WHO AWaRE book, as have rickettsial infections. In other settings with a high burden of HIV, tuberculosis has been described as a common sepsis presentation (272). Incorporating some of these regional variations in infectious disease epidemiology in future editions of the WHO AWaRE book would be very useful for countries and make them truly global guidelines. Countries submitting all antimicrobial susceptibility data to WHO GLASS rather than just selected bug-drug combinations could facilitate this. At the same time, the lack of diagnostic capacity in many LMICs makes creating locally appropriate guidelines challenging. There is evidence that guidelines frequently do not take local antimicrobial susceptibility into account (273). In addition, lack of access to several antibiotics is a barrier to implementing the guidelines. In a small country like Laos, there might not be much incentive for manufacturers to try and register antimicrobials. Harmonization of medicine registration across ASEAN countries could help this issue especially for new medicines for diseases especially common in Asia, such as melioidosis and scrub typhus (274).

Conclusion

Recommendations in the AWaRe book provide a useful reminder to health workers and policy makers in countries such as Laos to consider expanding access to key antimicrobials and promote their appropriate use, as well as expanding infectious disease diagnosis and antimicrobial stewardship efforts, and making sure that the antimicrobial prescribing guidelines are updated regularly. However, they should adapt them to local infectious disease epidemiology and antimicrobial susceptibility data. Having easy access to antibiotics and comprehensive antibiotic use guidelines does not guarantee appropriate use or prevent overuse if diagnostic capacity is lacking and antibiotic stewardship is not promoted.

Chapter 7: Discussion and conclusion

Overview of major research findings

This thesis has examined the current state of hospital antimicrobial use (AMU) in Laos, as this is likely to be a major contributor to AMR. The aims of this thesis were to enhance the understanding of AMU in the country by assessing existing data and identifying gaps that need to be addressed to inform AMU and AMR policy in Laos.

Additionally, this thesis investigated the impact of the first Lao antimicrobial prescribing guidelines on adherence. These guidelines were delivered through both a traditional pocketbook format and a mobile application format; the latter is currently used around the world. This represents the first interventional study on antimicrobial use in hospitals in Laos.

Furthermore, the thesis explores how Lao doctors have adopted the newly released guidelines, aiming to identify the most suitable delivery method for the Lao context and addressing challenges to improve uptake and ensure the appropriate use of antimicrobials. The key findings of this thesis were:

1. **Available data on AMR and AMU in Laos were limited and sparse:**

A review of AMU and AMR data in Laos from 1994 to 2020 revealed only 80 relevant peer-reviewed and grey literature articles, mostly related to human health (83%). The majority of AMR data were from one microbiology laboratory in a central hospital in Laos. ESBL-producing *Escherichia coli* bacteraemia increased fivefold from 2004 to 2016, rising from 7% to 35%, with carbapenem-resistant strains first emerging in 2015. AMR data on other GLASS pathogens were not common. AMR

in livestock was poorly documented. There was scant data on AMU in humans before 2017 and none in livestock and the environment.

2. **Laos had the highest percentage of inpatient antimicrobial use, compared to published data from other Asian countries and one of the highest in the world**

The first hospital antimicrobial use surveillance in Laos was conducted in 2017. The findings of surveillance in six hospitals across Laos from 2017 to 2020 showed that at any one time around 71% (95%CI: 70%-73%) of inpatients in Lao hospitals are prescribed antimicrobials. The appropriateness of use according to available local treatment guidelines (based on correct antimicrobial agent) was only 26%, with 99% of inappropriate prescriptions being for surgical prophylaxis. One-third of all prescriptions could not be assessed for guideline adherence due to the lack of local guidelines for certain infectious diseases. Another reason for this high AMU rate was the unnecessary use of antimicrobials for prophylaxis for uncomplicated normal vaginal delivery. Additionally, outdated local treatment guidelines contributed to poor guideline adherence. Rolling out new guidelines and initiating antimicrobial stewardship interventions were proposed urgently based on these findings.

3. Mode of antimicrobial prescribing guidelines delivery: mobile phone application or traditional paper-based format, did not lead to a demonstrable impact on guideline adherence in the Lao context

The first Lao antimicrobial prescribing guidelines were developed and implemented as a part of this DPhil project and the first antimicrobial stewardship interventional trial was conducted in the same six hospitals in Laos which had participated to PPS. The findings showed that the guideline adherence among inpatients in the App-G group was 27% higher than the PP-G group with no marked difference after adjusting for with sequence of intervention implementation, time, the patient's age, gender, department, prescribing indications, and types of prescription (empiric or targeted) and accounting for random effects of time and clusters (aOR=1.27, 95% CI: 0.84-1.90), p=0.249). When comparing the PP-G group to the pre-guideline group, adherence remained similar (aOR=0.99, 95% CI: 0.65-1.52, p=0.979). While, adherence in the App-G group was 24% higher than in the pre-guideline group (aOR=1.24, 95% CI: 0.81-1.90, p=0.315), though this difference was not significant. Guideline adherence in the outpatient setting was not different between PP-G and App-G groups; or even when compared to the pre-guideline period. This limited effect may be attributed to the study being underpowered to detect significant differences. Continuous efforts are needed to implement and strengthen adherence to guidelines, regardless of their format. However, this trial was conducted during the Covid-19 pandemic which may have influenced adherence and uptake of the guidelines, as could other factors.

4. **Prescribers reported that lack of antimicrobials was one of the key factors driving inappropriate use of antimicrobials in their settings**

In-depth interviews were conducted with 16 prescribers from two hospitals in Laos to understand how they prescribed antimicrobials and factors influencing the uptake of the first Lao antimicrobial prescribing guidelines. Most participants stated that they considered multiple factors before prescribing antibiotics, with clinical judgment being the most common. Challenges included the lack of certain antibiotics and turnaround times for laboratory results, making appropriate prescribing difficult. While participants found the new guidelines comprehensive and convenient, they admitted to infrequent access due to their familiarity with treatment protocols. Recommendations for improving appropriate antibiotic use included improving knowledge, increasing access, and raising awareness of the guidelines. Additionally, support, monitoring, and feedback from healthcare leaders were suggested to encourage guideline use.

5. **Antimicrobial prescribing guidelines are essential for improving appropriate use. However, systemic factors can lead to inappropriate use. It is crucial to consider the country's context before implementing these interventions.**

WHO released the AWaRe antibiotic book in 2022 to promote the appropriate use of antibiotics. Evaluating these international guidelines in the Lao context (Chapter 5) showed that some recommendations in the AWaRe book do not align with the epidemiology and antimicrobial susceptibility patterns in Laos, and across Asia, where diseases like melioidosis and leptospirosis are common but not found in the book. Nearly one-third of the recommended antibiotics in the AWaRe book are not

available in Laos, including no Reserve group antimicrobials. The AWaRe book encourages countries like Laos to consider alternative diagnoses and add essential antimicrobials to their national lists but should be updated to include regionally important pathogens. Access to antibiotics is challenging with unavailability, especially in remote areas, and unaffordability, contributing to inappropriate use. Improved antibiotic access, increased diagnostic capacity, and antibiotic stewardship are essential to address these challenges.

Influence on healthcare policy

These findings have significant implications for shaping AMU/AMR policies in Laos. Policies could allocate increased funding and resources for comprehensive AMR and AMU monitoring nationwide, helping to establish a robust and sustainable national database to track trends and guide future interventions. Given the lack of data on the burden of AMR in Laos, particularly in terms of deaths and severe outcomes linked to drug-resistant infections, such a comprehensive database would provide critical insights to inform policy decisions and develop strategies to reduce mortality and combat the growing threat of antimicrobial resistance.

Both mobile and paper-based formats have the potential to support guideline adherence in Laos. Policies should focus on making these guidelines available in multiple formats to accommodate diverse prescriber preferences and promote widespread adoption. However, prioritizing digital formats is more practical moving forward, as they allow for regular updates and can significantly reduce printing and distribution costs. Additionally, policies should establish standardized processes for guideline development, ensuring that guidelines are updated regularly based on both national and international scientific evidence.

The findings of this thesis re-emphasize that antimicrobial stewardship programs must be urgently implemented in all hospitals. Policies should instruct regular audits of antimicrobial use, establish protocols for prescription approvals (e.g., certain antibiotics require approval from an infectious disease specialist before they can be prescribed), empower pharmacists and introduce training programs for healthcare providers on appropriate antimicrobial use. Additionally, policies should focus on ensuring the consistent availability of essential antimicrobials, making certain that hospitals have access to the necessary medications when needed.

This thesis highlights that a multifaceted approach to address the factors contributing to inappropriate antimicrobial use, should be promoted. The strategies should include improving quality of medical training, infrastructure improvements, implementing systemic reforms, investing in diagnostic capacity, and considering policies that encourage more engagement (e.g., using health technology to enhance prescribing decisions to encourage more adherence to guidelines).

Potential research directions

Future research should focus on reduction of the high percentage of antimicrobial prescriptions with low guideline adherence in Laos. This means unnecessary antimicrobial prophylaxis should be improved. A mixed-method antimicrobial stewardship intervention should be implemented at Obstetrics and Gynaecology and surgical departments to understand their prescribing behaviours and identify the most appropriate intervention.

This DPhil was conducted during the Covid-19 pandemic. It would be valuable to apply the same research methodology (outlined in Chapter 3) to other healthcare

settings post-pandemic to better understand the impact of the interventions. The initial idea for the research methodology of Chapter 3 was to keep it as pragmatic as possible (not be actively involved in individual prescribing decisions of prescribers in participating hospitals); future research should explore more proactive interventions to determine if these could lead to better adherence to guidelines. For instance, an antimicrobial stewardship intervention with close monitoring and real-time feedback from healthcare leaders in hospitals could improve outcomes.

Focusing on specific prescribing indications uncovered by this research could be more effective, for example, future research could focus on guideline adherence improvement for the most common indications such as pneumonia, sepsis or upper respiratory infections. Additionally, behaviour-change research could improve guideline uptake in the future.

It is crucial to investigate the cost implications for hospitals when patients receive guideline-adherent treatment compared to non-adherent treatment as this is of interest to policy makers. Research should explore patient outcomes and guideline adherence when there is unrestricted access to antimicrobials. This could involve piloting specific antimicrobials in central referral hospitals, where infrastructure is adequate, but access to certain antimicrobials remains limited.

Antimicrobial prescribing practices in OPD settings in Laos need further investigation and improvement. Implementation of an innovative intervention (digital evidence-based support tool) to assist prescribers in making accurate diagnoses and appropriate antimicrobial prescriptions should be evaluated. In addition, investing in educational interventions such as provision of comprehensive training

sessions on antimicrobial stewardship, continuous medical education, and support through workshops, could be implemented.

This DPhil research does not address the issue of antibiotic use in the community, particularly the widespread availability of over-the-counter antibiotics. Some of the major drivers of antibiotic misuse may lie outside of hospital settings. In many LMICs, easy access to antibiotics without a prescription contributes significantly to inappropriate use and rising antimicrobial resistance. To fully combat these issues, future efforts must also focus on regulating community-level antibiotic sales and raising public awareness about the dangers of over-the-counter antibiotic use, acknowledging the need for access to antimicrobials in remote areas. Additionally, environmental contamination and antibiotic use in livestock play crucial roles in driving AMR. In Laos, it is vital to explore these factors to understand the main drivers of AMR in the local context.

In conclusion, this thesis generates valuable AMU baseline data for Laos, and introduced the country's first antimicrobial prescribing guidelines. The findings from this thesis have the potential to inform AMU/AMR policies aimed at improving and sustaining appropriate antimicrobial use. While evidence on the impact of antimicrobial prescribing guidelines is currently limited, this thesis encompasses the entire process from guideline development to the assessment of their impact. The thesis raises several critical questions that allow further investigations to identify the most effective solutions for addressing AMU/AMR challenges in Laos.

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Appendices

Appendices to Chapter 1

Appendix 1: Data sources of WHO GLASS pathogens in Laos: published and unpublished records from 1994 to 2020

Study	Study period	Search	Study site	Pathogens
Higa et al. 1994 (48)	1992 and 1993	Peer-reviewed	Vientiane City	*Staphylococcus aureus*
Higa et al. 1995 (81)	1992-1995	Peer-reviewed	Laos, no specific location	*Vibrio cholerae*, *Shigella* spp.
Mahosot Hospital 1995 (275)	1995	Report	Vientiane City	*Staphylococcus aureus, Enterococcus* spp., *Acinetobacter* spp., *Salmonella* Typhi, *Enterobacter cloacae, Gonococcus, Shigella flexneri, Shigella dysenteriae, Shigella sonnei,* EPEC, *Escherichia coli, Proteus mirabilis, Proteus vulgaris, Klebsiella oxytoca, Klebsiella pneumoniae,* Group D *Streptococcus, Pseudomonas aeruginosa, Pseudomonas* spp., *Candida* spp.*, Staphylococcus saprophyticus*
Iwanaga et al. 1997 (49)	1995-1996	Peer-reviewed	Vientiane City	*Staphylococcus aureus*
Yamashiro et al. 1998 (58)	1996-1997	Peer-reviewed	Vientiane City	*Shigella flexneri, Shigella sonnei, Shigella boydii, Shigella dysenteriae, Shigella* spp.*, Salmonella* spp., EPEC, ETEC, EIEC, EHEC, *Vibrio parahaemolyticus, Vibrio hollisae, Vibrio cholerae, Campylobacter jejuni* and *Campylobacter coli.*
Sithivong et al. 2002 (50)	1993-2001	Peer-reviewed	Vientiane City	*Staphylococcus aureus*

Kakinohana et al. 2002 (276)	1998 and 2001	Peer-reviewed	Vientiane City	*Staphylococcus aureus*
Phantouamath et al. 2003 (61)	2000-2002	Peer-reviewed	Vientiane City	*Neisseria gonorrhoeae*
Hongsakhone 2004 (31)	2002-2004	Thesis	Oudomxay Province	*Salmonella* Typhi, *Escherichia coli* and Unidentified Gram-negative bacilli
Higa et al. 2004 (277)	2001-2002	Peer-reviewed	Vientiane City	*Staphylococcus aureus*
Phongmany et al. 2005 (52)	2001-2003	Peer-reviewed	Vientiane City	*Salmonella* Typhi
Phetsouvanh et al. 2006 (46)	2000-2004	Peer-reviewed	Vientiane City	Organisms isolated from blood culture: *Salmonella* Typhi, *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Burkholderia pseudomallei, Salmonella* spp*., Streptococcus pneumoniae,* and so on
Thammalangsy et al. 2006 (62)	2001-2002	Peer-reviewed	Vientiane City	*Neisseria gonorrhoeae, Chlamydia trachomatis, Candida* spp., *Trichomonas vaginalis*
Sihavong et al. 2007 (63)	2000-2001	Peer-reviewed	Vientiane City	*Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis, Candida* spp.
Bounsavath 2008 (32)	2003-2006	Thesis	Huaphan Province	*Salmonella* Typhi, *Escherichia coli, Klebsiella pneumoniae* and *Staphylococcus aureus*
Moore et al. 2010 (65)	2003-2009	Peer-reviewed	Vientiane City	*Streptococcus pneumoniae*
Elliot et al. 2012 (47)	2000-2011	Peer-reviewed	Vientiane City	*Staphylococcus aureus*
Stoesser et al. 2012 (28)	2004-2009	Peer-reviewed	Vientiane City	ESBL producing *Escherichia coli*
Phakhounthong et al. 2012 (25)	2010-2011	Thesis	Vientiane City	*Escherichia coli, Enterococcus faecalis, Klebsiella pneumoniae, Acinetobacter baumannii, Enterobacter cloacae, Staphylococcus aureus, Burkholderia pseudomallei, Pseudomonas aeruginosa, Proteus mirabilis, Gardnerella vaginalis, Streptococcus bovis,*

				Serratia marcescens, Streptococcus faecalis B*, Staphylococcus* coagulase negative*, Salmonella* group D
Mayxay et al. 2013 (33)	2008-2010	Peer-reviewed	Luang Namtha and Salavan Provinces	*Salmonella* Typhi, *Escherichia coli, Burkholderia pseudomallei, Klebsiella pneumoniae, Staphylococcus aureus, Streptococcus suis, Streptococcus* Group A*, Streptococcus* Group C, *Salmonella enterica* Group C
Anderson et al. 2014 (45)	2000-2011	Peer-reviewed	Vientiane City	*Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Enterococcus faecalis, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus pneumoniae, Burkholderia pseudomallei, Acinetobacter baumannii, Listeria monocytogenes, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella* spp.
Olaitan et al. 2014 (42)	2012-2013	Peer-reviewed	Laos, no specific location	*Klebsiella pneumoniae, Klebsiella oxytoca*
Parry et al. 2015 (56)	1995-2012	Peer-reviewed	Laos, no specific location	*Salmonella* Typhi, *Salmonella* Paratyphi
Stoesser et al. 2015 (29)	2011	Peer-reviewed	Vientiane City and Vientiane Province	Enterobacteriaceae
Nakayama et al. 2015 (37)	2012 and 2013	Peer-reviewed	Savannakhet Province	*Escherichia coli*
Mirabel et al. 2015 (278)	2006-2012	Peer-reviewed	Vientiane City	*Streptococcus pyogenes, Streptococcus oralis, Streptococcus mutans, Streptococcus anginosus, Streptococcus sanguinis, Streptococcus agalactiae, Escherichia coli, Enterococcus faecalis, Staphylococcus aureus,* coagulase negative *S*taphylococci

Chansamouth et al. 2016 (53)	2006-2010	Peer-reviewed	Vientiane City	*Escherichia coli, Salmonella* Typhi, *Staphylococcus aureus, Klebsiella oxytoca*
Yeap et al. 2017 (51)	2012-2014	Peer-reviewed	Vientiane City	*Staphylococcus aureus*
Phuong et al. 2017 (59)	2000-2012	Peer-reviewed	Vientiane City	Non-typhoidal *Salmonella*
Darton et al. 2018 (60)	1994-2012	Peer-reviewed	Vientiane City	*Shigella flexneri* and *Shigella sonnei*
Pouangsouvanh et al. 2018 (64)	2011-2015	Peer-reviewed	Vientiane City	*Neisseria gonorrhoeae*
LOMWRU 2018 (68)	2018	Report	Laos, no specific location	NA
Rudge et al. 2019 (44)	2015-2016	Peer-reviewed	Vientiane City	*Streptococcus* spp., *Haemophilus influenzae, Klebsiella pneumoniae, Staphylococcus aureus, Escherichia coli*
Dubot-Peres et al. 2019 (66)	2003-2011	Peer-reviewed	Vientiane City	*Streptococcus pneumoniae, Mycobacterium tuberculosis, Escherichia coli, Streptococcus agalactiae, Neisseria meningitidis,* Group C *Salmonella,* Group B *Salmonella,* Group D *Salmonella, Salmonella* Typhi, *Streptococcus suis, Klebsiella pneumoniae, Haemophilus influenzae* type B, *Burkholderia pseudomallei, Staphylococcus aureus, Morganella morganii*
Hadjadj et al. 2019 (279)	2012	Peer-reviewed	Laos, no specific location	*Klebsiella pneumoniae*
Roberts et al. 2020 (54)	2000-2018	Peer-reviewed	Laos, except Borkeo Province, Savannakhet Province, Champasak Province, Sekong Province and Attapeu Province	*Salmonella* Typhi

Chang et al. 2020 (26)	2010-2014	Peer-reviewed	Laos, no specific location	*Escherichia coli*
Wyres et al. 2020 (36)	2015-2016	Peer-reviewed	Laos, no specific location	*Klebsiella pneumoniae*
Microbiology/LOMWRU (23)	2000-2016	Dataset	Vientiane City	Blood culture dataset – Multiple pathogens
Microbiology/LOMWRU (24)	2017-2020	Dataset	Vientiane City	Laboratory Information Management System (LIMS) – Multiple pathogens

Note: EPEC= Enteropathogenic *E. coli*, ETEC=Enterotoxigenic *E. coli*, EIEC= Enteroinvasive *E. coli,* EHEC= Enterohemorrhagic *E. coli*.

Appendix 2: Data sources of other bacteria of local and regional importance in Laos: published and unpublished records from 1994 to 2020

Study	Study period	Search	Study site	Pathogens
Dance et al. 2014 (74)	2003-2012	Peer-reviewed	Laos, no specific location	*Burkholderia pseudomallei*
Microbiology/LOMWRU (23)	2000-2016	Dataset	Laos, no specific location	*Burkholderia pseudomallei*
Tantibhedhyangkul et al. 2010 (77)	NA	Peer-reviewed	Vientiane City	*Orientia tsutsugamushi*
Phuklia et al. 2019 (79)	NA	Peer-reviewed	Vientiane City	*Orientia tsutsugamushi*
Boss et al. 2019 (80)	2006-2016	Peer-reviewed	Laos, no specific location	*Leptospira* spp.
Higa et al. 1995 (81)	1992-1995	Peer-reviewed	Laos, no specific location	*Vibrio cholerae*
Iwanaga et al. 2000 (82)	1998	Peer-reviewed	Vientiane City, Khammuan Province, Savanakhet Province and Champasak province	*Vibrio cholerae*
Phantouamath et al. 2001 (83)	1993-1999	Peer-reviewed	Laos, no specific location	*Vibrio cholerae*
Iwanaga et al. 2004 (84)	1993-2000	Peer-reviewed	Laos, no specific location	*Vibrio cholerae*
Rattanavong et al. 2016 (85)	2004-2013	Peer-reviewed	Vientiane City	*Streptococcus* pyogenes (Group A *Streptococcus*)
Vannarath et al. 2016 (88)	2010-2012	Peer-reviewed	Vientiane City	*Helicobacter pylori*
Cheong et al. 2017 (89)	2013	Peer-reviewed	Vientiane City	*Clostridioides difficile*
Batty et al. 2019 (86)	2007-2018	Peer-reviewed	Laos, no specific location	*Neisseria meningitidis*
Iem et al. 2013 (69)	2010	Peer-reviewed	Vientiane City, Khammuan Province and Luang Prabang Provnice	*Mycobacterium tuberculosis*
Iem et al. 2019 (71)	2016-2017	Peer-reviewed	Borkeo Province, Bolikhamxay Province, Vientiane City, Champasack Province, Khammuane Province, Luang Namtha Province, Luang Prabang Province, Oudomxay Province, Phongsaly Province, Salavan Province, Savannakhet Province, Sekong Province,	*Mycobacterium tuberculosis*

			Ventiane Province, Xayabury Province	
Somphavong et al. 2019 (70)	2010-2011	Peer-reviewed	Borkeo Province, Bolikhamxay Province, Vientiane City, Champasack Province, Khammuane Province, Luang Namtha Province, Luang Prabang Province, Oudomxay Province, Phongsaly Province, Salavan Province, Savannakhet Province, Sekong Province, Vientiane Province, Xayabury Province, Huaphan Province, Xienkhuang Province	*Mycobacterium tuberculosis*

Appendix 3: Evidence of antimicrobial resistance in animals in Laos

Study	Study period	Search	Study sites	Pathogens
Boonmar et al. 2008 (90)	2007	Peer-reviewed	Vientiane City	*Salmonella* spp.
Boonmar et al. 2013 (91)	2011	Peer-reviewed	Champasak, Province	*Salmonella* spp.
Sinwat et al. 2016* (92)	2013-2014	Peer-reviewed	Savannakhet Province and Vientiane City	*Salmonella* spp.
Sunn (MSc thesis) (93)	2016-2017	Thesis	Vientiane City	*Salmonella* spp. and *Escherichia coli*
Chang 2016* (41)	2016	Thesis	Xiengkhuang Province	*Escherichia coli*
Olaitan et al. 2015* (95)	2012	Peer-reviewed	Laos, no specific location	*Escherichia coli*
Thu et al. 2019* (97)	2013-2014	Peer-reviewed	Savannakhet Province and Vientiane City	*Enterococcus faecalis* and *Enterococcus faecium*

Note: * described antimicrobial resistance data in both human and animal

Appendix 4: Data sources of antimicrobial use in human and animal in Laos

Study	Study period	Sector	Search	Study site	Antimicrobials and details investigated
Syhakhang et al. 2004 (106)	1997 and 1999	Human health	Peer-reviewed	Savannakhet Province	Ampicillin, tetracycline, chloroquine
Keohavong et al. 2006 (108)	2003-2004	Human health	Peer-reviewed	Laos, no specific location	Rational use of antimicrobials
Sihavong et al. 2006 (111)	2002	Human health	Peer-reviewed	Vientiane City and Champasak Province	Understanding and use of health information among adult population self-medicating with reproductive tract infection
Khennavong et al. 2011 (113)	2003-2004 & 2005	Human health	Peer-reviewed	Vientiane City and Savannakhet Province	Urine investigation for previous antimicrobial usage
Sihavong et al. 2011 (280)	2002-2006	Human health	Peer-reviewed	Vientiane City and Champasak Province	Treatment seeking behaviour for sexually transmitted infections - qualitative study
Quet et al. 2015 (104)	2012	Human health	Peer-reviewed	Khammuane, Luang Prabang, Sekong Provinces, Vientiane City	Knowledge, attitude and practice of antibiotic prescriptions of Laos doctors
Phonlavong and Kitikannakorn 2018 (112)	2017	Human health	Peer-reviewed	Vientiane City	Knowledge, beliefs and care seeking behaviour about antibiotics
keohavong et al. 2019 (109)	2016	Human health	Peer-reviewed	Savannakhet Province	Assess patterns of antibiotic prescriptions among children under 5
Tabernero et al. 2019 (107)	2012	Human health	Peer-reviewed	Savannakhet, Salavan, Sekong, Champasak and Attapeu Provinces	Assess the availability and quality of antimalarials and antibiotics in private sectors in five southern provinces of Laos

Haenssgen et al. 2019 (115)	2017-2018	Human health	Peer-reviewed	Salavan Province	Antibiotic-related knowledge, attitude and practice in Salavan Province, Laos
Haenssgen et al. 2020 (114)	2017-2018	Human health	Peer-reviewed	Salavan Province	Assess the relationship between precarity, other forms of deprivation and healthcare-seeking behaviour in Salavan Province, Laos
LOMWRU database (110)	2017-2018	Human health	Dataset	Vientiane City, Salavan, Vientiane, Xiengkhuang, Luang Namtha Provinces	Proportion of hospital antimicrobial prescription and most common prescribed antimicrobials
Labatut and Suter 2010 (122)	2007-2009	Animal health	Peer-reviewed	Sayabury Province	Use of antibiotics in elephants in Laos (oxytetracycline, penicillin-streptomycin, Negasunt (including sulfonamide), mebendazole, Dufamec (ivermectin + praziquantel), and Archifen (chloramphenicol))
Theungphachan 2012 (41)	2012	Animal health	Report	Laos, no specific location	Report (including list of available antimicrobials in animal sector)
Phanthavong 2016 (118)	2016	Animal health	Thesis	Vientiane City	Use of antibiotics in pets (cephalexin, amoxicillin and clavulanate)
Innoula 2017 (119)	2017	Animal health	Thesis	Vientiane City	Use of antibiotics in pets (enrofloxacin and gentamicin)
Boudakham 2017 (120)	2017	Animal health	Thesis	Vientiane City	Use of antibiotics in pets (amoxicillin and Oxy-Mycin (oxytetracycline))
Keovilay 2017 (121)	2017	Animal health	Thesis	Savannakhet Province	Use of antibiotics in pets (enrofloxacin and sulfonamides)

Appendices to Chapter 3

Appendix 5: List of guidelines topics of paediatric and adult antimicrobial prescribing guidelines

1. Paediatric antimicrobial prescribing guideline

Paediatric guidelines	
Infectious disease topics for treatment of infections	
Central nervous system	**Urinary tract/Genitourinary system**
Bacterial meningitis	Urinary tract infection (UTI) - uncomplicated
Viral meningitis/Encephalitis	Upper UTI/Pyelonephritis
Tuberculosis meningitis	UTI – Catheter associated
Head and neck	Vaginal discharge
Conjunctivitis	**Bone and joint**
Dental infections	Open fracture
Endophthalmitis	Osteomyelitis
Epiglottitis	Skin and soft tissue
Facial cellulitis/Peri-orbital cellulitis	**Abscesses, carbuncles and furuncles**
Mastoiditis	Bites: Animal
Otitis externa	Bites: Human
Acute otitis media (AOM)	Cellulitis
Retropharyngeal abscess	Impetigo
Sinusitis	Post-operative wound infection
Suppurative parotitis	Puncture wounds
Tonsillopharyngitis	Pyomyositis
Acute rheumatic fever	Burns
Cardiovascular system	**Specific conditions**
Central venous catheter infection	Neonatal sepsis
Infective endocarditis	Sepsis in infant above one month
Respiratory system	Abdominal sepsis
Common cold	Febrile neutropenia
Seasonal influenza	Septic shock
Bronchitis and bronchiolitis	Dengue
Pertussis (Whooping cough)	Rickettsiosis
Pneumonia: Neonatal	Leptospirosis
Pneumonia: Community acquired	Enteric fever (Typhoid and Paratyphoid)
Pneumonia: Hospital acquired	Fever of Unknown Origin (FUO)
Pneumonia: Aspiration	Malaria
Pleural effusion and empyema	Melioidosis
Pulmonary tuberculosis (PTB)	Rabies (after symptom onset)
Gastrointestinal system	Severe malnutrition
Gastroenteritis	Tetanus
Cholera	Diphtheria
Dysentery	Tuberculosis
Intestinal parasites	
Necrotizing enterocolitis	
Peritonitis	

Surgical prophylaxis	**Medical prophylaxis**
Head and neck procedures	Prevention of neonatal infection
Cardiovascular procedures	Bacterial meningitis – *Neisseria meningitidis*
Gastroduodenal procedures	Bacterial meningitis – *Haemophilus influenzae*
Biliary tract procedures	Rabies exposure
Appendicectomy/Obstructed small intestine procedures	Asplenia
Colorectal procedures	
Cystoscopy with manipulation (ureteroscopy, biopsy)	
Orthopedic procedures	
Antibiotic stewardship	
Good antibiotic use	
Oral bioavailability	
Penicillin allergy	
Renal impairment adjusted doses	
List of antimicrobials in this guideline	
Notifiable diseases	
Sources of information (references)	

2. Adult antimicrobial prescribing guideline

Adult guideline	
Infectious disease topics for treatment of infections	
Central nervous system	**Genito-Urinary system**
Bacterial CNS infections	Prostatitis
Viral CNS infections	Epididymo-orchitis
Cryptococcal infection	Cystitis/Urethritis
Bacterial cerebral abscess	Pyelonephritis
Rickettsia	Vaginal discharge/Cervicitis
Tuberculosis meningitis	Lymphogranuloma Venereum
Parasites	Vaginitis
Cardiovascular system	Chancroid
Tunneled catheter related bloodstream infections	Genital warts
Bacterial pericarditis	Genital Herpes Simplex Virus infection
Infective endocarditis	Syphilis
Acute rheumatic fever	**Obstetric & Gynaecology system**
Head and neck	Ante-natal infections
Conjunctivitis	Postpartum endometritis/Postpartum infection
Dental abscess	Septic abortion
Ulcerative gingivitis	Perineal infection
Epiglottitis	Mastitis/Breast abscess
Mastoiditis	Antibiotic prophylaxis in OBGY procedures
Orbital cellulitis	**Bone and joint**
Sinusitis	Open fracture
Otitis	Osteomyelitis
Suppurative parotitis	Septic arthritis (native joint)
Tonsillopharyngitis	Prosthetic joint infection (PJI)
Respiratory system	Skin and soft tissue
Common cold	Skin abscess
Seasonal influenza	Cellulitis/Erysipelas
Pertussis or Whooping cough	Necrotizing fasciitis
Community acquired pneumonia (CAP)	Folliculitis/Furuncles/Impetigo
Hospital acquired pneumonia (HAP)	Diabetic foot infection
Bronchiolitis	Infected wound
Bronchitis/Acute bacterial exacerbation of chronic bronchitis	Burns (infected wound)
Bronchiectasis	Bites
Chronic Obstructive Pulmonary Disease (COPD)	**Sepsis**
Pleural empyema	Sepsis of unknown origin
Lung abscess	Septic shock
Pneumocystis jiroveci Pneumonia (PCP)	Neutropenic sepsis
Pulmonary Tuberculosis (PTB)	**Specific conditions**
Gastrointestinal system	Melioidosis
Acute infectious diarrhea	Enteric fever (Typhoid and Paratyphoid)
Cholera	Rickettsiosis
Amoebic/Shigellosis	Leptospirosis
Enteric fever (Typhoid and Paratyphoid)	Dengue fever
Biliary tract infection	Malaria

(Acute cholecystitis/Acute cholangitis/Biliary sepsis)	
Helicobacter pylori infection	Intestinal parasites
Liver abscess	Paragonimus (Lung fluke)
Appendicitis	Histoplasmosis
Peritonitis	Tuberculosis
	HIV/AIDs
	Talaromycosis (Penicilliosis)
	Fever of Unknown Origin (FUO)
	Tetanus
Surgical prophylaxis	**Medical prophylaxis**
Head and neck procedures	Asplenia
Cardiovascular procedures	Infective endocarditis
Gastroduodenal procedures	
Biliary tract procedures	
Appendectomy/Obstructed small intestine procedures	
Colorectal procedures	
Cystoscopy with manipulation (ureteroscopy/ biopsy)	
Transrectal prostate biopsy	
Urologic procedures	
Orthopedic procedures	
Antibiotic stewardship	**Renal impairment adjusted doses**
Good antibiotic use	**List of antimicrobials in this guideline**
Oral bioavailability	**Notifiable diseases**
Oral switch	**Sources of information (references)**
Penicillin allergy	

Appendix 6: Point Prevalence Survey Data Collection Form (inpatient and outpatient)

Appendix 6.1: Inpatient data collection form (Ward Form)

Evaluating the impact of a Lao-language antimicrobial prescribing guidelines on antimicrobial prescribing in Laos						
Hospital Antimicrobial Prescribing Survey Form						
Ward Form						
Date of Survey		Surveyor name	☐ Vilada	☐ Danoy	☐ _____	
(dd-mmm-yyyy)						
Hospital name	☐ MS	☐ VTP	☐ SVK	☐ SV	☐ XK	☐ LNT
OPD/IPD	☐ OPD	☐ IPD		Ward name	☐ Dropdown list	
Department type						
	☐	Medicine				
	☐	Surgery				
	☐	Paediatrics				
	☐	OBGY				
	☐	ICU				
Total number of admitted patients by 8:00am on the day of survey				Numeric		
Total number of bed (including extra bed)				Numeric		

Note: OPD=Outpatients, **IPD**=Inpatients, **MS**=Mahosot, **VTP**=Vientiane Province, **SVK**=Savannakhet, **SV**=Salavan, **XK**=Xiengkhuang, **LNT**=Luang Namtha, **OBGY**=Obstetrics and Gynaecology, **ICU**=Intensive Care Unit

Appendix 6.2: Inpatient data collection form (Patient Form)

Evaluating the impact of a Lao-language antimicrobial prescribing guidelines on antimicrobial prescribing in Laos					
Hospital Antimicrobial Prescribing Survey Form					
In-Patient Form					
Survey number	Activity	Age (≥2years)	Age (1-23m)	Age (<30days)	Weight (kg)
	M S IC				
	Gender:	Male/Female			
	Antimicrobial 1	Antimicrobial 2	Antimicrobial 3	Antimicrobial 4	Antimicrobial 5
Antimicrobial name					
Antimicrobial start date					
Single Unit Dose					
Unit (g, mg, IU)					
Doses/day					
Route (P, O, R)*					
Diagnosis					
Diagnosis site					
Type of Indication					
Reason in Note (yes/no)					
Is a stop/review date documented? (yes/no)					
Treatment (empiric/targeted)					
The next section is to be filled in only if the treatment choice is based on microbiology data (Treatment=targeted) AND the organism is one of the following					
MRSA (yes/no)					
VRE (yes/no)					
ESBL-producing Enterobacteriaceae (yes/no)					
3rd generation cephalosporin resistant Enterobacteriaceae non-ESBL producing or ESBL status unknown (yes/no)					

Carbapenem-resistant Enterobacteriaceae (yes/no)					
ESBL-producing non-fermenter Gram-negative bacilli (yes/no)					
Carbapenem-resistant non-fermenter Gram-negative bacilli (yes/no)					
Targeted treatment against other MDR organisms (yes/no)					
Targeted treatment against other confirmed laboratory results (yes/no)					
Treatment based on biomarker data (yes/no)					
If yes, which biomarker (CRP, PCT or other)		Value		Unit (in µg/L, mg/L)	

Note: **M**=Medicine, **S**=Surgery, **IC**=Intensive Care, **m**=Month, **g**=Gram, **mg**=Miligram, **IU**=International Unit, **P**=Parenteral, **O**=Oral, **R**=Rectal, **MRSA**=Methicillin-resistant *Staphylococcus aureus*, **ESBL**=Extended-spectrum beta-lactamase, **MDR**=Multidrug resistance, **CRP**=C-reactive protein, **PCT**= Procalcitonin.

Appendix 6.3: Outpatient data collection form

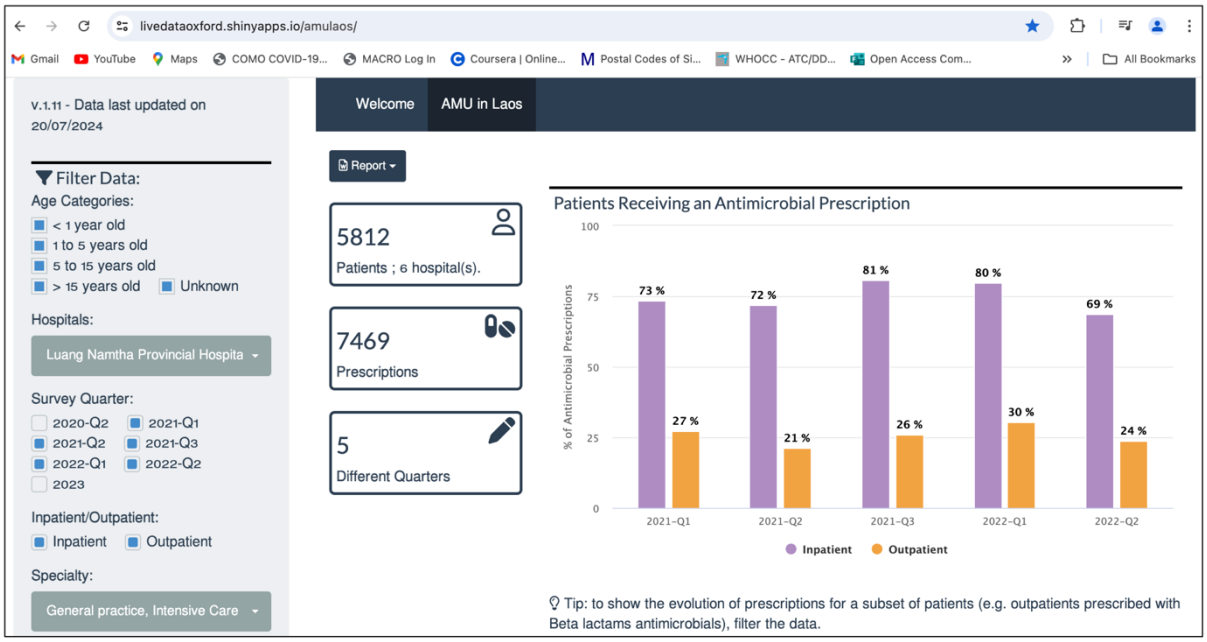
Evaluating the impact of a Lao-language antimicrobial prescribing guidelines on antimicrobial prescribing in Laos					
Hospital Antimicrobial Prescribing Survey Form					
Outpatient Form					
Date of Survey (dd-mmm-yyyy)	Add calendar	Surveyor name	☐ Vilada	☐ Danoy	☐ _____
Hospital name	☐ MS	☐ VTP	☐ SVK	☐ SV	☐ XK
OPD type	☐ Drop down list		☐ LNT		
Total number of consulted patients between 8:00 am and 4:00pm on the day of survey				Numeric	
Survey number	Activity	Age (≥2years)	Age (1-23m)	Age (<30days)	Weight (kg)
	Gender:	Male/Female			
	Antimicrobial 1	Antimicrobial 2	Antimicrobial 3	Antimicrobial 4	Antimicrobial 5
Antimicrobial name					
Single Unit Dose					
Unit (g, mg, IU)					
Doses/day					
Route (P, O, R)					
Diagnosis					
Diagnosis site					
Type of Indication					
Reason in Note (yes/no)					
Is a stop/review date documented? (yes/no)					
Treatment (empiric/targeted)					
If targeted, specify:					
Antimicrobial stop date					

Note: OPD=Outpatients, **IPD**=Inpatients, **MS**=Mahosot, **VTP**=Vientiane Province, **SVK**=Savannakhet, **SV**=Salavan, **XK**=Xiengkhuang, **LNT**=Luang Namtha, **m**=Month, **g**=Gram, **mg**=Miligram, **IU**=International Unit, **P**=Parenteral, **O**=Oral, **R**=Rectal.

Appendix 7: Point prevalence Survey (PPS) of hospital antimicrobial use report

PPS reports of inpatients and outpatien surveys were available within one month after each survey. The reports could also directly downloaded from the AMU dashboard: https://laoamr.net, which is publicly available. Everybody can access the results of the survey but not the raw data. AMU-Laos App displays prevalence of antimicrobial prescriptions at each time point in different participating hospitals, and an overview of antimicrobial prescriptions (e.g., classes, agents, route and indications) and pattern of the prescription by age, by specialty in both inpatients and outpatients. However, paper reports were also provided by the research team to the participating wards/doctors because some might have had limited access to computers and internet.

Figure 1: Antimicrobial use dashboard



Appendix 8: Antimicrobial Stewardship (AMS) knowledge survey questionnaires

Antibiotic stewardship (AMS) knowledge survey

(Multiple answers are possible. Please circle your answers)

Date: __/__/___, Graduation year from medical school: _____ Speciality: _____

Department: _____, Hospital: _____.

1. **Facts of antimicrobial resistance (AMR):**
    a. Overuse or misuse of antimicrobials is accelerating the process of AMR
    b. AMR can occur naturally
    c. AMR can spread between people, animals and environment
    d. Poor infection control encourages the spread of AMR
2. **Misuse or overuse of antibiotics include:**
    a. Prescribing an oral narrow spectrum antibiotic (e.g., amoxicillin) to treat the common cold
    b. Always using broad spectrum antibiotics as first choice
    c. Completing an antibiotic treatment course even though the patient is feeling better
3. **Which of the following is/are NOT correct?**
    a. Antibiotics kill both good and bad bacteria
    b. Antibiotics kill both viruses and bacteria
    c. Humans can become resistant to antibiotics
    d. Bacteria can become resistant to antibiotics

4. **What is considered as good practice in antibiotic prescribing in general practice?**
    a. Prescribe antibiotics with a clear clinical justification where a bacterial infection is suspected or proven
    b. Prescribe according to local antimicrobial susceptibility patterns
    c. Only prescribe when culture results are available
    d. Collect specimens for culture before starting antimicrobial therapy (but not delay therapy)
5. **What should consider before prescribing antibiotics?**
    a. Previous antibiotic history
    b. Previous infection with drug resistant organism
    c. Allergy to antibiotic
    d. Availability of antibiotic
6. **What should be consider when reviewing empiric antibiotic therapy?**
    a. Change antibiotics based on culture result
    b. Always keep IV therapy until patients discharge from hospital, then switch to oral
    c. Stop antibiotic if no evidence of infection
    d. Change to broader spectrum antibiotics if patients do not feel better
7. **Which of the following phrases is correct for choice of IV or oral antibiotic therapy?**
    a. Always start IV antibiotic first, then switch to oral antibiotic for all in-patients
    b. IV antibiotic needs to be kept for at least 3 days before switching to oral antibiotic

c. Keep IV therapy for the whole course of bacterial meningitis treatment

8. What should be considered before switching from IV to oral therapy?

a. Equivalent treatment efficacy

b. No malabsorption problem

c. availability of suitable oral antimicrobial drug

d. Signs and symptoms of infection improving

9. Which of the following antimicrobials are well absorbed from the gut and have excellent penetration into cells and tissues?

a. Co-amoxiclav (e.g augmentin)

b. Metronidazole (e.g., flagyl)

c. Ciprofloxacin

d. Chloramphenicol

10. What are clinical signs of severe penicillin allergy (type I)?

a. Anaphylaxis

b. Maculopapular rash

c. Laryngeal oedema

d. Usually occurs with 1 to 4 hours after exposure

11. What medications are contradicted in patients with severe penicillin allergy?

a. Co-amoxiclav (e.g augmentin)

b. Metronidazole (e.g flagyl)

c. Ciprofloxacin

d. Cloxacillin

12. Antibiotic prophylaxis for elective surgery should usually be given for:

a. A maximum of 24 hours
b. A maximum of 3 days
c. A maximum of 7 days
d. Until discharge from hospital

13. Good practice for clean wound/surgery procedures regarding antibiotic prophylaxis is:

a. No antibiotic prophylaxis is needed
b. A single dose of IV combined antibiotic prophylaxis (e.g., ceftriaxone + metronidazole) is needed
c. IV mono-antibiotic prophylaxis for a maximum of 3 days is enough
d. A maximum of 5 days of oral antibiotic prophylaxis is needed

14. Which phrases are correct relating to viral respiratory infection:

a. Antibiotics should be given to prevent bacterial complications in seasonal flu patients
b. Antibiotics have no effect on colds
c. Empirical treatment of bacterial co-infection of seasonal flu, should be for highly suspected cases only

15. A 3-year-old girl comes to you complaining of 4 days of fever, running nose, sneezing, sore throat, cough with normal vital signs, which antibiotic you recommend?

a. Amoxicillin
b. Penicillin
c. Single dose of ceftriaxone
d. No antibiotic is needed

16. Which statements are correct relating to the use of gentamicin?

a. Gentamicin can cause serious nephrotoxicity and ototoxicity
b. Gentamicin is often used for serious Gram-negative bacterial infections
c. Gentamicin is cleared by the kidney; it is important to assess renal function before starting and during treatment courses
d. Creatinine clearance should be monitored if drug level monitoring is not available

17. Which of the following is NOT effective in preventing the emergence or spread of antimicrobial resistant organisms?

a. Good hand hygiene
b. Treating infections for a longer period to prevent resistance
c. Avoiding the use of antibiotics for treatment of colds and flu
d. Vaccination

18. A 35-year-old man comes to you complaining of 2 days watery stool (~4-5 times a day), no history of fever, which antibiotic will you recommend?

a. Ciprofloxacin
b. Co-trimoxazole
c. Azithromycin
d. No antibiotic is needed, oral rehydration only

Appendix 9: Pre-guideline prescribing behaviour survey form

Date: __/__/___, Graduation year from medical school: _____ Speciality: _____

Department: _____, Hospital: _____.

1. **How frequently do you prescribe antimicrobial (s)?**

   □ Daily □ Nearly every day □ Weekly □ Monthly □ Never

2. **How often do you access any antimicrobial prescribing guidelines?**

   □ Daily □ Nearly every day □ Weekly □ Monthly □ Never

3. **Do you have a smart phone?** □ Yes □ No □ Sometimes; If answer is "No", you do not have to answer question 4, 5 and 6

4. **Do you carry your smart phone with you at work?** □ Yes □ No

5. **Do you have any antimicrobial prescribing guideline App installed on your smart phone?**

   □ Yes □ No; If answer is "No", you do not have to answer question 6

6. **How often do you access any antimicrobial prescribing mobile phone App?**

   □ Daily □ Nearly every day □ Weekly □ Monthly □ Never

Appendix 10: Introductory session of therapeutic and prophylactic antimicrobial prescribing guidelines

Appendix 10.1: Introductory session of therapeutic and prophylactic antimicrobial prescribing guidelines (Paper-based guidelines)

The purpose of the session was to introduce paper versions of therapeutic and prophylactic antimicrobial prescribing guidelines in both adult and paediatric version to all doctors in study hospitals. This session did not cover how to diagnose infectious diseases or prescribe antimicrobials.

Trainees: this session gprovided to all hospital doctors in all study participant hospitals at the start of the study (month 0).

Date, time and venue: the session took a maximum of 30 minutes with 10 minutes of discussion/questions. Session date, time and venue were informed to all doctors one week in advance and again 3 days before starting the session. The session was run in each hospital separately after conducting point prevalence survey (PPS) of hospital antimicrobial use and after all doctors have completed survey form on AMS knowledge for baseline data. Verbal consent was asked from participants to record participant's names, age, sex, working positions, departments, years of work and phone number onto the session registration sheet.

Instructor: The principal investigator of the study was the session instructor. Training was provided in the format of a PowerPoint presentation, following by question and discussion.

Session material: paper versions of both adult and paediatric prescribing guidelines were distributed to doctors who participate to this session. A handout of the introductory session (the same standard session for all hospitals) were also provided.

Session details include introduction of the guidelines, objectives of guidelines, guidelines skeleton and how to use these guidelines, see details as below:

1. **Introduction to the guidelines** - This guideline was based on:
    - existing Lao treatment guidelines
    - current data on infectious disease pathogens and antimicrobial susceptibility patterns in Laos
    - international antimicrobial prescribing/treatment guidelines (e.g., WHO, CDC, NICE, IDSA, Sanford)
    - both Lao and international clinicians, international infectious diseases experts and microbiologists contributed to this guideline
2. **Giving the purpose of the having these guidelines:**
    - To support therapeutic clinical decision-making of Lao clinicians
    - To guide the reasonable use of antimicrobials to optimize cure and control antimicrobial resistance in Laos
    - To promote the use of essential medicines registered with the Lao Food and Drug Department
    - To diminish the cost of care for infectious diseases whilst ensuring optimal treatment
    - To promote patient safety by diminishing risks of allergy or toxicity
    - To promote the use of microbiology laboratory techniques for infectious disease diagnoses and for guiding treatment
3. **Explanation of overall guideline skeleton**
    - Therapeutic section
    - Prophylactic section

- AMS section
- References
- Contact details

4. **How to use these guidelines**

- Guidelines provide the principal uses of antimicrobials. The antimicrobial prescribing guidelines are separated into paediatric and adult guidelines for ease of use.
- These guidelines include recommendations for therapy, prevention and AMS
- This guideline mostly suggests empiric treatment as facilities to microbiological diagnosis in Laos is limited

Structure:

- Common and important infectious diseases are arranged by involved organ systems
- Each infectious disease section includes causative pathogen(s) of the diseases, choices of antimicrobial regimen (primary and alternative), doses, duration and important notes on allergy or toxicity or to help guide treatment
- Sources of information and contact details of developers and coordinators are displayed at the end of the guidelines for users who need further information
- This guideline also refers to some specific Lao treatment guidelines (e.g., Dengue guideline for diagnosis and treatment, Lao PDR or National Guidelines for the Use of Antiretroviral Therapy in Adults and Children) to avoid duplication

Appendix 10.2: Introductory session of therapeutic and prophylactic antimicrobial prescribing guidelines (App-based guidelines)

Introductory session of the antimicrobial prescribing guideline mobile phone App were provided to all doctors at study hospitals in different time periods.

Training objective was to introduce MicroGuide mobile phone App of therapeutic and prophylactic antimicrobial prescribing guidelines in both adult and paediatric version to all doctors in study hospitals. This session covered how to install, register, use and update the App. The session did not cover how to diagnose infectious diseases or prescribe antimicrobials.

Trainees: this session was provided to all hospital doctors in all study hospitals at the start of the intervention period of each pair of hospitals (month-4, month-8 and month-12).

Training date, time and venue: the session took maximum 4±1 hours in total (including installation and registration step by step, also include discussion/questions). Training date, time and venue were informed to all doctors one week in advance and again 3 days before starting the session. The session was run in each hospital separately (2 hospitals on month-4, another 2 on month-8 and the last 2 hospitals on month-12) after conducting point prevalence survey (PPS) of hospital antimicrobial use. Verbal consent was asked from participants to record each participant's name, age, sex, working position, department, years of work and phone number onto the session registration sheet.

Instructor: the principal investigator of the study was the training instructor. Training was provided in the format of PowerPoint presentation and showing the real process of each step, followed by questions and discussion.

Training material: A handout of the training was provided to all participants (the same standard session for all hospitals).

Training details: training session included introduction to the MicroGuide, how to register, how to install, how to use step by step and how to update the App.

Appendix 11: Antimicrobial Stewardship (AMS) Training

Training objective: to raise awareness of antibiotic good prescribing practices

Trainees: this session was provided to all hospital doctors in all study hospitals at the start of the intervention period of each paired hospital (month-4, month-8 and month-12).

Training date, time and venue: the session took a maximum of 30 minutes with 10 minutes of discussion/questions. Training date, time and venue were informed to all doctors one week in advance and again 3 days before starting the session. The session was run in each hospital separately (2 hospitals on month-4, another 2 on month-8 and the last 2 hospitals on month-12) after conducting point prevalence survey (PPS) of hospital antimicrobial use, completing prescriber feedback survey and after finished introductory session of the prescribing guideline mobile phone App. Verbal consent was asked from participants to record participant's names, age, sex, working positions, departments, years of work and phone number onto the session registration sheet.

Instructor: the principal investigator of the study was the training instructor. Training was provided in the format of PowerPoint presentation, followed by question and discussion.

Training material: Handout of the training was provided to all participants (the same standard session for all hospitals).

Training details: All training details already existed in the prescribing guidelines. The majority of training was on the section of AMS and some part of the training was from the therapeutic and prophylaxis sections. This training session included good practice of antibiotic prescriptions, the idea and benefits of intravenous

therapy to oral therapy switch, choice of prescription when patients report penicillin allergy.

Training evaluation: All participating hospitals joined AMS knowledge survey three times during the study period (1st time= at the start of the project, 2nd time= before entering to the intervention period and 3rd time= at the end of the project)

Appendix 12: Prescriber feedback survey on paper-based prescribing guidelines

Prescriber feedback survey on paper-based prescribing guidelines

Date: __/__/___, Year of graduation from medical school: ___, Speciality: _____,

Department: _____ Hospital: _____

1. Have you ever seen these paper-based antimicrobial prescribing guidelines?

□ Yes □ No ; If answer is “No”, you do not have to continue this survey

2. If yes, have you ever used it?

□ Yes □ No ; If answer is “No”, you do not have to continue this survey

If the answer is “Yes”, please continue the survey

3. Complete this table below**: Instruction**-please indicate your level of agreement with the statement listed below (by ticking the box:

Prescriber’s opinions	Strongly agree (5)	Agree (4)	Neutral (3)	Disagree (2)	Strongly disagree (1)	No opinion
Appropriate name of guidelines						
Structure and design are intuitive and user-friendly						
Appropriate language used						
Prescribing instructions (antibiotic of choice, dose and duration) are easy to follow						
Bulky guidelines and inconvenient to carry						

Covered relevant topics to routine practice						
Recommended antimicrobials are available in my hospital						
Guidelines restrict my choice of antibiotics						
Useful prophylaxis section						
Useful extra information						
Able to search for information easily						
Able to access information using references						
Guidelines encourage me to document the indication for antimicrobial on hospital charts						
Guidelines encourage me to document the duration for antimicrobial on hospital charts						
Useful AMS section						
Guidelines increased my knowledge of AMS						

4. How frequently do you prescribe antimicrobial (s)?

□ Daily □ Nearly every day □ Weekly □ Monthly □ Never

5. How often do you access this provided paper-based prescribing guidelines?

□ Daily □ Nearly every day □ Weekly □ Monthly □ Never

6. How often do you access other prescribing guidelines?

□ Daily □ Nearly every day □ Weekly □ Monthly □ Never

7. How would you rate these paper-based prescribing guidelines overall?

□ Very good and fitting with Lao context □ Good but need a bit more editing

□ Moderate and need more editing □ Not good and need to review many sections

Please give comments in the box below:

Appendix 13: Prescriber feedback survey on App-based prescribing guidelines

Prescriber feedback survey on mobile phone app prescribing guidelines

Date: __/__/__, Year of graduation from medical school: ___, Speciality: _____, Department: _____, Hospital: _____

1. Have you ever seen this antimicrobial prescribing guideline mobile phone application?

□ Yes □ No ; If answer is “No”, you do not have to continue this survey

2. If yes, have you ever used it?

□ Yes □ No ; If answer is “No”, you do not have to continue this survey, If the answer is “Yes”, please continue the survey

3. Complete this table below**:** Instruction: please indicate your level of agreement with the statement listed below (by ticking the box):

Prescriber’s opinions	Strongly agree (5)	Agree (4)	Neutral (3)	Disagree (2)	Strongly disagree (1)	No opinion
Structure and design are intuitive and user-friendly						
Offline mode makes it easy for me to access the guidelines anywhere						
Language font size and colour are easy to read						
I can find information which I look for more easily than from paper-based guidelines						
Prescribing instructions (antibiotic of choice, dose and duration) are easy to follow						
Links to extra information (data on antibiotic susceptibility						

pattern, causes of infections in Laos, international recommendation) are useful						
App guideline encourages me to document the indication for antimicrobial on hospital charts						
App guideline encourages me to document the duration of antimicrobial on hospital charts						
App guideline has increased my knowledge of AMS						
Antimicrobial stewardship training increased my knowledge of AMS						

4. How often do you prescribe antimicrobial (s)?

□ Daily □ Nearly every day □ Weekly □ Monthly □ Never

5. How often do you access paper-based prescribing guidelines?

□ Daily □ Nearly every day □ Weekly □ Monthly □ Never

6. Do you carry your smart phone (with this prescribing guideline App) with you at work?

□ Yes □ No □ Sometimes

7. How often do you access the provided mobile phone app prescribing guideline?

□ Daily □ Nearly every day □ Weekly □ Monthly □ Never

8. How often do you access other prescribing guidelines?

□ Daily □ Nearly every day □ Weekly □ Monthly □ Never

9. How would you rate this app overall?

□ Very good and I will continue to use it

□ Good but needs a bit more editing and I will continue to use it

□ Good but I prefer paper-based version □ moderate but I prefer paper-based version

□ Not good and I prefer paper-based version

□ Others _____

Please give comments to improve this app:

Appendix 14: Lao Antimicrobial Prescribing App (LAMPA) – Statistical Analysis Plan

Study title: Evaluating the impact of a Lao language mobile phone antimicrobial use guideline application on antimicrobial prescribing in Laos

Short title: LAMPA (Lao Anti-Microbial Prescribing App)

Version 0.13; Date 4th September 2023

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Funder: Wellcome Trust

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Introduction

Antimicrobial resistance (AMR) is a major global public health concern with rising frequencies of AMR in key pathogens to key antimicrobials. The evidence suggests that this increase is accelerated by use, misuse or overuse of antimicrobials (12). Awareness of AMR is relatively recent in Laos but it is a growing concern. Few data on hospital antimicrobial use exist in Laos (141). High proportions of inpatient antimicrobial use in Laos have been reported (152). The Lao National standard treatment guidelines (STG) were first established in 1998 and the latest version was published in 2012. There are sporadic specific local treatment guidelines with updated versions every few years. The first Lao antimicrobial prescribing guidelines were made available for use in 2021 (134, 135). Antimicrobial prescribing guidelines delivered by mobile phone app are now widespread in many countries. Some evidence suggests that antibiotic guidelines on a mobile phone app increased guideline adherence by prescribers, reduced unnecessary antibiotic use in hospital, reduced poor outcomes, improved quality of care and reduced antimicrobial consumption cost (222, 228, 229). There is evidence that multi-activity antimicrobial stewardship (AMS) programs could significantly reduce the proportion of therapeutic and prophylactic antibiotic prescriptions in both in- and outpatients from a study of a large patient population from China (281).

This document sets out the statistical analysis plan for the LAMPA study, an open cohort stepped-wedge cluster randomized controlled trial (SW-CRT) to compare the proportion of antimicrobial prescriptions adherent with prescribing guidelines delivered by mobile phone application (app) versus paper-based prescribing guidelines in both in- and outpatients in six general hospitals in Laos.

Study objectives

Primary objective

To compare the proportion of antimicrobial prescriptions adherent with prescribing guidelines delivered by mobile phone application (app) versus paper-based prescribing guidelines in both in- and outpatients in six general hospitals in Laos

Secondary objectives

1. To compare the proportion of patients admitted to hospital receiving an antimicrobial prescription before and after introduction of the paper-based prescribing guidelines; and the mobile phone app prescribing guidelines + AMS training
2. To compare the change in antimicrobial defined daily doses (DDDs) in both in- and out patients after introduction of paper-based versus mobile phone app prescribing guidelines plus antimicrobial stewardship (AMS) training to prescribers
3. To compare the change in proportion of inpatients and outpatients receiving antimicrobials via the intravenous (IV) route between paper-based and mobile phone app prescribing guidelines + AMS training
4. To compare the AMS knowledge level of the prescribers before and after prescribing guidelines delivered by mobile phone app and AMS training
5. To compare the prescriber satisfaction with/acceptability of paper-based prescribing guidelines versus mobile phone app prescribing guidelines

Analysis principles

Study design

The study design is an open cohort cross-sectional stepped wedge cluster randomized controlled trial (SW-CRT) in one central hospital (Mahosot Hospital (MS – 450 beds) and five provincial hospitals across Laos (Vientiane (VTP – 100 beds), Xiengkhuang (XK – 150 beds), Luang Namtha (LNT – 50 beds), Savannakhet (SVK – 200 beds) and Salavan (SV – 70 beds) Provincial Hospitals) for 16 months.

Sample size calculation

A point prevalence survey of hospital antimicrobial use in four general hospitals in Laos in 2017 showed 13% compliance to Lao treatment guidelines (LOMWRU unpublished data) but previous guidelines did not contain much information on antibiotic prescribing, therefore reliable baseline data are lacking. The sample size of 6 hospitals was estimated assuming 30% of antimicrobial prescription adherence with the paper-based prescribing guideline (reference), and assuming a 0.05 intra-cluster correlation coefficient, with an average of 40 doctors at each hospital, and a design effect of 0.446. Using the Stata package “steppedwedge” (282), we estimated that this will give us >80% power to detect a 15% minimum difference after introduction of the mobile phone app prescribing guidelines at a 0.05 significance level.

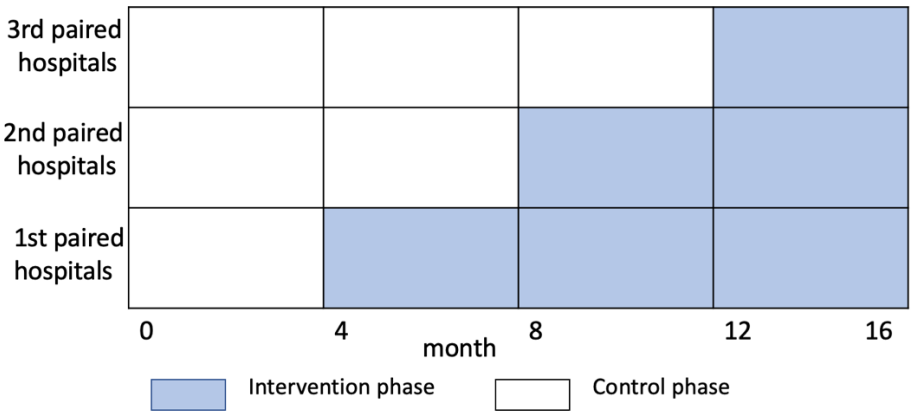
Randomization procedure

This is a 3-step trial with one baseline measurement. Six participating hospitals have been divided into 3 pairs based on the geographical location and convenience for conducting the surveys. The first paired hospitals include two provincial hospitals from the north of Laos (LNT and XK), the second pair includes hospitals in the center (MS-central referral hospital and VTP which is 80 km north of the capital). The third

pair includes two provincial hospitals from the south of Laos (SVK and SV). As there are only 3 orders to be assigned, clusters will be randomly assigned to one of three start dates to have access to the study intervention using simple random sampling. Randomization processes will be performed before the start of the project and the order of each paired hospital to intervention introduction will be recorded. Neither hospitals nor investigators will be blinded to the introduction of the intervention.

Study intervention

The intervention is antimicrobial prescribing guidelines delivered via a mobile phone application (MicroGuide) + antimicrobial stewardship training. The control is the paper-based version of the antimicrobial prescribing guidelines.



Study endpoints

Primary endpoint

The proportion of antimicrobial prescriptions fully adherent with prescribing guidelines delivered by mobile phone app versus paper-based prescribing guidelines at month 16.

Secondary endpoints

1. Proportion of patients admitted to hospital receiving an antimicrobial prescription before and after introduction of the paper-based prescribing guidelines; and the mobile phone app prescribing guidelines + AMS training at month 16.
2. Total antimicrobial defined daily doses (DDDs) prescribed in mobile phone app versus paper-based groups at month 16
3. Proportion of patients prescribed antimicrobials by the intravenous route in mobile phone app versus paper-based groups at month 16
4. AMS knowledge level of prescribers prescribed in mobile phone app versus paper-based groups at month 16
5. Prescriber satisfaction/acceptability of the prescribing guidelines in mobile phone app versus paper-based groups of 4 months' exposure in each group

Outcome measurement

Outcomes of this study will be measured by:

1. point prevalence survey (PPS) of hospital antimicrobial use
2. prescriber questionnaires (feedback survey on paper-based and app-based version of the guidelines)
3. AMS knowledge surveys of prescribers

The outcomes will be measured every four months. This will give five-outcome measurements in total (excluding baseline measurement at start), until the trial completes at month 16.

Data cleaning

All data will be entered by the PI and trained research staff. Only the PI of the project and project data management team will have access to the raw data. Data checking and cleaning will be done by the PI after each survey. Data inconsistency will be discussed with the research team immediately. Stata version 14 or higher will be used for data cleaning. The original version of the trial dataset will be kept separately. A do file (.do) of data cleaning will also be created.

Statistical software analysis

Analyses will be done using Stata 14.0 or higher.

Definitions of adherence to the guidelines:

1. Full adherence with the guidelines = using correct antimicrobial agent(s) and correct dose based on the provided antimicrobial prescribing guidelines. Except elective surgical prophylaxis which includes antimicrobial use duration (using correct antimicrobial agent(s), correct dose and correct duration based on the provided antimicrobial prescribing guidelines)
2. Partial adherence with the guidelines = using correct antimicrobial agent(s) with incorrect dose based on provided antimicrobial prescribing guidelines
3. Non-adherence with the guidelines = using a different antimicrobial agent(s) compared to that suggested in provided antimicrobial prescribing guidelines

Categorical variable:

a. Age category

The actual age will be collected and described in both continuous variable format and categorical variable format. Age will be categorized into different groups as below:

- 0 to <28 days (neonatal)
- 1 month to ≤ 1 year (infant)
- >1 year to ≤ 5 years
- >5 years to ≤ 14 years
- ≥ 15 years

b. Departments

There are 5 main types of departments in the participating hospitals, including medicine, surgery, paediatrics, obstetrics & gynaecology and intensive care unit (either children or adult or combine). Other wards falling outside these categories such as specialty or psychiatry will be categorized as “other”.

c. Number of antimicrobials

Number of antimicrobials per patient will be grouped into 3 categories including

- 1 antimicrobial
- 2 antimicrobials
- 3 or more and antimicrobials

d. Prescribing indication

- Treatment of infection = treatment of any suspected or confirmed infection
- Medical prophylaxis =

- Medical prophylaxis-general: e.g. gastrointestinal bleeding, liver cancer, prophylaxis for opportunistic infections in HIV patients, malnutrition, neonatal infection prophylaxis (including preterm delivery, low birthweight or birth asphyxia without sign or symptoms of infections)
- Medical prophylaxis-trauma: e.g., head, eye, chest, abdomen, knee, leg, arm trauma (mostly from road traffic crashes)
- Medical prophylaxis-vaginal delivery: normal delivery via vaginal route with or without episiotomy

- Surgical prophylaxis = Antimicrobial(s) given for prophylaxis purposes, e.g., elective surgery
- Unclear = Not enough information to indicate why antimicrobials were prescribed (e.g. pleural effusion or diarrhoea (only) without further information of possible cause)
- Unknown = Not known why antimicrobial(s) was given

1. Reporting baseline characteristics

Six hospitals participate in this study. They are grouped into 3 clusters (2 hospitals per cluster). There are 5 survey rounds in total for each hospital. Characteristics of variables (from OPD and IPD PPS; and prescriber surveys) from each cluster and phases (control vs intervention) are collected in each survey. They will be presented and compared on tables/charts as appropriate.

Normally distributed continuous baseline characteristics will be summarized with means and standard deviation or 95% confidence intervals. Skewed continuous data will be summarized using median and inter-quartile range (± range).

Categorical data will be presented as frequency and percentages. Test of trends, Chi-square or Fisher's exact tests will be used as appropriate. Variables such as number of years on medical career, specialty, and departments where prescribers are based will be summarized by hospital.

2. Analysis of primary outcome

The primary outcome is the proportion of antimicrobial prescriptions adherent with prescribing guidelines delivered by mobile phone app versus paper-based prescribing guidelines at month 16.

A logistic mixed effects regression model (to adjust for clustering) will be used to compare the proportion of antimicrobial prescriptions adherence measured cross-sectionally at month 0, 4, 8, 12 until month 16 after introduction of prescribing guidelines by mobile phone application versus paper-based. The model will compare all steps in the intervention from month 4 to month 16 with all steps in the reference arm from month 0 to month 12. Odds ratios and the corresponding confidence intervals will be obtained and reported. Tests of significance will be performed at 5% level.

Because calendar time is also a potential confounder in stepped-wedge trials, the model will be adjusted for the effect of time. The duration of exposure of each hospital to the reference or intervention arm will be included in the model as interaction term with the study arm in order to assess whether the duration of exposure is the effect modifier. Initially a model with fixed effect for time, implying a common secular trend across steps and clusters, will be analysed with adherence to guidelines as the outcome. The model will consider the correlation among the outcome's measurements from the same hospital (cluster) by adjusting for clustering in the model.

Sensitivity analysis will explore seasonal variations and variations in secular trends across clusters and allow treatment effect (i.e., effect of paper-based or mobile phone application on adherence) to vary across clusters and time. For example, a fixed effect interaction between time and each pair of hospitals (strata) for examining varying secular trend across clusters could be added to the model or the model may incorporate a random effects component between time and cluster. Heterogeneity in adherence across clusters may be considered as a fixed effect interaction between the intervention and strata or, by incorporating a random effect term for the intervention and for each pair of hospitals (strata). Sensitivity analysis will also consider whether adherence varied over time using a fixed effect term for the interaction between intervention and time. This model will only be estimable at time periods that have both intervention and control phases (weeks 4 to 16).

An *a priori* set of variables will be considered for inclusion in a multivariable model (see section Subgroup analysis). Interactions will be considered, as appropriate. The results will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) extension for the stepped wedge cluster randomized trial (SWCRT).

3. Analysis of secondary outcomes

Secondary outcome 1: Proportion of patients admitted to hospital receiving an antimicrobial prescription before and after introduction of the paper-based prescribing guidelines; and the mobile phone app prescribing guidelines + AMS training at month 16. Number of patients admitted to hospitals at the time of survey will be a denominator. The overall proportion of antimicrobial prescribing from 2017 to 2020 (before prescribing guidelines) will be compared with the overall proportion of antimicrobial prescribing after introduction to the prescribing guidelines (control

phase) and then the overall proportion and antimicrobial prescribing after introduction to the mobile phone-app version of the guidelines and AMS training (intervention phase). The analysis process of this secondary outcome will also follow the same strategy as secondary outcome analysis number 2.

Secondary outcome 2: Total antimicrobial defined daily doses (DDDs) prescribed in mobile phone app versus paper-based groups at month 16: DDD will be calculated using data (antibiotic agent, start date, dose and DDD of each antibiotic from www.whocc.no) from PPS in both IPD and OPD.

Secondary outcome 3: Proportion of patients prescribed antimicrobials by the intravenous (IV) route in mobile phone app versus paper-based groups at month 16: A logistic mixed effects regression model will be used to compare the overall proportion of the intravenous route: the proportion of the IV route antimicrobial prescriptions will be measured cross-sectionally at month 0, 4, 8, 12 until month 16 after introduction of prescribing guidelines by mobile phone application versus paper-based. The model will compare all steps in the intervention from month 4 to month 16 with all wedges in the reference arm from month 0 to month 12. The duration of exposure of each hospital to the reference or intervention arm will be included in the model as interaction term with the study arm in order to assess whether the duration of exposure is the effect modifier. The model will consider the correlation among the outcome's measurements from the same hospital (cluster) by adjusting for clustering in the model. Odds ratios and the corresponding confidence intervals will be obtained and reported. Tests of significance will be performed at 5% level.

As a single-time point survey, we will not be able to capture the duration of antimicrobial use in our participated hospitals, except antimicrobial use for elective

surgical prophylaxis (sigle dose or one day prophylaxis). Therefore, we cannot estimate the proportion of switching from intravenous antimicrobial to oral antimicrobial prescribing in a mobile phone group versus paper-based group in this study.

Secondary outcome 4: AMS knowledge level of prescribers in mobile phone app versus paper-based group at month 16: AMS knowledge level of prescribers will be assessed using questionnaires based on information in the prescribing guidelines. There are 18 questions in total. As each prescriber will participate in the antimicrobial stewardship knowledge survey 3 times (first time at baseline, second time at the beginning of the intervention phase and last time at the end of the study (month 16)), before the survey, eight randomly selected questions will be selected to assess the knowledge of each participating prescribers in each survey round. The questionnaires include both single and multiple answer questions. The overall proportion of correct answers in each time point will be compared using a paired test (baseline, after paper-based guidelines (before AMS training and introduction of mobile phone app guidelines) and after AMS training and introduction of mobile phone app guidelines). The scores are coded as 0/1, where 1 =correct and 0= incorrect. Then the knowledge level will be assessed using sum of a total score. Other factors such as extra AMR training program from hospital/MoH/other organizations, level of education and specialties of prescribers will also be taken into account using index test scores, adjusted for baseline (or previous) score in a Poisson or linear regression model, depending on distribution

Secondary outcome 5: Prescriber satisfaction/acceptability of the prescribing guidelines in mobile phone app versus paper-based groups of 4 months' exposure in each group: frequency of the use of paper-based and app-based version of the

guidelines and frequency of the use of other antimicrobial prescribing guidelines will be descriptively shown at month 0, 4, 8, 12 until month 16. The frequency of the use of the app-based guidelines can also be collected from MicroGuide app directly, as well as which topics the prescribers commonly visit.

Likert scale analysis will be used to evaluate prescriber satisfaction with/acceptability of paper-based compared to mobile phone app delivered antimicrobial prescribing guidelines. The satisfaction/acceptability scale will be assigned in six categories, including: strongly agree=5, agree=4, neutral=3, disagree=2, strongly disagree=1, no opinion/not use=0.

Mann-Whitney U test will be used to assess the differences between paper-based population and mobile phone app population. The satisfaction/acceptability scale will also be stratified by prescriber specialty, departments where they are based on and years of medical career.

Plans for sub-group analysis

Sub-group analysis will be considered to investigate the relationship between the outcomes of interest or exposure of interests and other collected variables for some specific questions such as the relationship between departments (IPD/OPD) and how doctors prescribed; or the relationship between number of antimicrobial prescribed and prescribing indications; or spectrum of antibiotics and prescribing indications; or topic most interest in the guidelines and guidelines compliance of that topics. Each variables listed below is a suspected confounder; our exploratory analysis may determine that some of these are in fact effect modifiers. If this is the case, interactions will be explored in models and these variables will be considered for sub-group analysis.

- Survey rounds

- Departments (IPD (paediatrics, obstetrics and gynaecology, medicine, surgery, ICU and other) and OPD)
- Number of antimicrobial prescribed (one or two or more than 2 antimicrobials)
- Route of administration (oral or IV)
- Prescribing indication (treatment of infection, prophylaxis or unknown/unclear)
- Spectrum of antibiotics (narrow and broad)
- AwaRe antibiotic classification
- Indication documented in patient records (e.g. pneumonia, sepsis, skin and soft tissue infection)
- Years of medical work of prescribers
- Specialty of prescribers
- Frequency of accessing paper-based version of the guidelines and mobile phone-app version of the guidelines (data will be collected from MicroGuide app)
- Topics of most interest of the guidelines (data will be collected from MicroGuide app)

Discussion and conclusion

The LAMPA trial could have a significant impact in Laos and in other LMICs, and inform policy globally, by improving prescribing and hence reducing AMR. This open cohort stepped-wedge cluster randomized controlled trial is appropriate in the Lao context because it requires fewer sites than a parallel cluster trial, but has similar observational periods for reference and intervention phases. As the interventions are delivered by one team travelling to each cluster in turn, implementation in stages

is more practical. In addition, all participating hospitals will have access to the novel interventions at the end of the study.

This is the first open cohort stepped wedge cluster randomized controlled trial on antimicrobial prescribing in Laos. This statistical analysis plan outlines the process to measure primary and secondary outcomes of interests and we also consider sub-group analyses. Like many other studies, we faced challenges during the covid-19 outbreak in Laos which delayed some of our survey rounds but otherwise, the trial was managed as planned. As many doctors were focused on covid-19, this may have affected the number of prescribers participating the AMS training and the number of patients. There were also some AMR activities (e.g.: strengthening microbiology laboratories and diagnostic stewardship under Fleming fund supports, AMS activities within a hospital) in some study sites separate from our trial. All of these factors will be considered during the interpretation of our study results.

In this statistical analysis plan, we outline details of the planned analysis in advance of LAMPA trial completion. Prior specification of the statistical methods and outcomes facilitate unbiased analyses of these important data.

Appendices to Chapter 4

Appendix 15: Guideline adherence: a subgroup analysis

Appendix 15.1: Partial adherence to prescribing guidelines

1. **Hospitalised patients**

Table 1: Univariate analysis of partial guideline adherence and potential confounders in inpatients post-guideline implementation

Variables	Total			Reference			Intervention		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Time:									
Month 6 after PP-G	1			1			-		
Month 11-12	0.96	0.75-1.24	0.762	0.95	0.73-1.24	0.712	1		
Month 16-17	0.86	0.68-1.1	0.233	0.76	0.54-1.07	0.117	0.87	0.42-1.8	0.7
Month 21-22	1.25	1-1.55	0.041	-	-	-	1.17	0.57-2.37	0.670
Age:									
≤ 1 year	1			1			1		
> 1to ≤5 years	0.7	0.44-1.11	0.131	1	0.47-2.12	0.996	0.53	0.3-0.96	0.036
> 5 to ≤14 years	0.69	0.43-1.1	0.121	1.68	0.88-3.23	0.116	0.28	0.13-0.59	0.001
≥15 years	0.66	0.51-0.86	0.002	1.07	0.71-1.61	0.763	0.48	0.34-0.69	<0.0001
Sex :									
Male	1			1			1		
Female	0.5	0.42-0.59	<0.0001	0.59	0.47-0.74	<0.0001	0.41	0.32-0.53	<0.0001
Department:									
Surgery	1			1			1		

Obstetrics and Gynecology	0.07	0.04-0.11	<0.0001	0.06	0.03-0.11	<0.0001	0.98	0.04-0.22	<0.0001
Medicine	1.53	1.23-1.92	<0.0001	1.08	0.8-1.45	0.626	2.43	1.7-3.47	<0.0001
Paediatrics	0.97	0.73-1.29	0.850	0.62	0.41-0.95	0.028	1.53	1.01-2.32	0.043
Intensive Care Unit	1.02	0.75-1.4	0.898	0.98	0.64-1.49	0.911	1.17	0.73-1.89	0.513
Other	0.42	0.3-0.59	<0.0001	0.39	0.24-0.63	<0.0001	0.5	0.31-0.83	0.007
Prescribing indication									
Prophylaxis	1			1			1		
Treatment	12.53	9.5-16.54	<0.0001	12.38	8.56-17.9	<0.0001	12.64	8.3-19.26	<0.0001
Type of prescriptions									
Empiric	1			1			1		
Targeted	11.55	65.81-19.6	<0.0001	3.92	1.9-8.1	<0.0001	29.33	11.7-73.53	<0.0001
Sequence of intervention									
Sequence 3	1								
Sequence 2	1.41	1.17-1.70	<0.0001	-			-		
Sequence 1	1.41	1.10-1.82	0.007	-			-		

Note: OR= odds ratio, **Other**= including VIP departments, ENT-EYE (Ear, Nose, Throat and Eyes), **Sequence 1** (Xiengkhuang+Luang Namtha)=started at month-6 after PP-G implementation, **Sequence 2** (Salavan+Savannakhet)=started at month-11 after PP-G, **Sequence 3** (Mahosot+Vientiane Province)=started at month-17 after PP-G. **P-values** were derived from the Wald Chi-Square test.

Table 2: Partial adherence to antimicrobial prescribing guidelines in PP-G vs App-G groups among inpatients

Characteristics	aOR (95% CI)	P-value
Guideline delivery method:		
PP-G	1	
App-G	0.99 (0.68-1.42)	0.942
Sequence of intervention		
Sequence 3 (MS+VTP)	1	
Sequence 2 (SVK+SV)	1.38 (0.91-2.09)	0.125
Sequence 1 (XK+LNT)	1.12 (0.69-1.80)	0.642
Age:		
≤1 year	1	
>1 to ≤5 years	0.57 (0.34-0.95)	0.031
>5 to ≤14 years	0.61 (0.35-1.06)	0.079
≥15 years	0.78 (0.49-1.26)	0.317
Sex:		
Male	1	
Female	0.80 (0.65-0.98)	0.034
Department:		
Surgery	1	
Obstetrics and Gynecology	0.26 (0.14-0.46)	<0.0001
Medicine	0.71 (0.53-0.94)	0.019
Paediatrics	0.54 (0.32-0.91)	0.022
Intensive Care Unit	0.50 (0.32-0.77)	0.002
Other	0.42 (0.28-0.63)	<0.0001
Prescribing indication:		
Prophylaxis	1	
Treatment	8.46 (6.09-11.77)	<0.0001
Type of prescription:		
Empiric	1	
Targeted	5.23 (3.00-9.14)	<0.0001

Note: PP-G=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **Other**=including VIP departments, ENT-EYE (Ear, Nose, Throat and Eyes), **aOR**= adjusted odds ratio, **XK**=Xiengkhuang, **LNT**=Luang Namtha, **SV**=Salavan, **SVK**=Savannakhet, **VTP**=Vientiane Provincial, **MS**=Mahosot**, Sequence 1** (Xiengkhuang+Luang Namtha)=started at month-6 after PP-G implementation, **Sequence 2** (Salavan+Savannakhet)=started at month-11 after PP-G, **Sequence 3** (Mahosot+Vientiane Province)=started at month-17 after PP-G. **P-values** were derived from the Wald Chi-Square test.

Table 3: Partial adherence to antimicrobial prescribing guidelines in pre-guideline vs guideline groups (PP-G and App-G) among inpatients

Characteristics	aOR (95% CI)	P-value
Guideline delivery method:		
Pre-guideline	1	
PP-G	1.10 (0.75-1.55)	0.601
App-G	1.08 (0.75-1.54)	0.687
Sequence of intervention		
Sequence 3 (MS+VTP)	1	
Sequence 2 (SVK+SV)	1.27 (0.93-1.73)	0.137
Sequence 1 (XK+LNT)	1.06 (0.74-1.52)	0.746
Age:		
≤1 year	1	
>1 to ≤5 years	0.83 (0.55-1.26)	0.395
>5 to ≤14 years	0.47 (0.29-0.77)	0.003
≥15 years	0.74 (0.49-1.11)	0.149
Gender:		
Male	1	
Female	0.84 (0.70-1.00)	0.053
Department:		
Surgery	1	
Obstetrics and Gynecology	0.22 (0.13-0.37)	<0.0001
Medicine	0.61 (0.47-0.78)	<0.0001
Paediatrics	0.58 (0.37-0.91)	0.017
Intensive Care Unit	0.47 (0.32-0.68)	<0.0001
Other	0.39 (0.27-0.57)	<0.0001
Prescribing indication:		
Prophylaxis	1	
Treatment	8.54 (6.41-11.39)	<0.0001
Treatment type:		
Empiric	1	
Targeted	5.76 (3.37-9.84)	<0.0001

Note: PP-G=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **Other**=including VIP departments, ENT-EYE (Ear, Nose, Throat and Eyes), **aOR**= adjusted odds ratio, **XK**=Xiengkhuang, **LNT**=Luang Namtha, **SV**=Salavan, **SVK**=Savannakhet, **VTP**=Vientiane Provincial, **MS**=Mahosot**, Sequence 1** (Xiengkhuang+Luang Namtha)=started at month-6 after PP-G implementation, **Sequence 2** (Salavan+Savannakhet)=started at month-11 after PP-G, **Sequence 3** (Mahosot+Vientiane Province)=started at month-17 after PP-G. **P-values** were derived from the Wald Chi-Square test.

2. Outpatients

Table 4: Univariate analysis of partial guideline adherence and potential confounders in outpatients post-guideline implementation

Characteristics	All		PP-G		App-G	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
Time:						
Month 6 after PP-G	1		1		-	
Month 11-12	0.73 (0.58-0.93)	0.011	0.66 (0.51-0.87)	0.003	1	
Month 16-17	0.75 (0.61-0.93)	0.007	0.51 (0.37-0.71)	<0.0001	0.94 (0.64-1.37)	0.733
Month 21-22	0.83 (0.68-1.01-2)	0.07	-	-	0.9 (0.62-1.29)	0.561
Age: ≤ 1 year	1		1		1	
> 1 to ≤5 years	0.83 (0.59-1.16)	0.269	0.73 (0.39-1.34)	0.309	0.87 (0.59-1.29)	0.486
> 5 to ≤14 years	1.06 (0.74-1.5)	0.754	0.95 (0.5-1.79)	0.872	1.08 (0.71-1.66)	0.708
≥15 years	0.36 (0.27-0.49)	<0.0001	0.31 (0.18-0.54)	<0.0001	0.38 (0.26-0.54)	<0.0001
Sex: Male	1		1		1	
Female	1 (0.86-1.17)	0.975	1.16 (0.92-1.45)	0.208	0.89 (0.73-1.09)	0.271
Prescribing indication:						
Prophylaxis	1		1		1	
Treatment	2.78 (0.54-14.38)	0.222	3.54 (0.37-34.17)	0.274	2.13 (0.19-23.59)	0.537
Sequence of intervention						
Sequence 3	1		-		-	
Sequence 2	0.96 (0.80-1.15)	0.672				
Sequence 1	2.13 (1.76-2.60)	<0.0001				

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **OR**=Odds Ratio, **Sequence 1** (Xiengkhuang+Luang Namtha)=started at month-6 after PP-G implementation, **Sequence 2** (Salavan+Savannakhet)=started at month-11 after PP-G, **Sequence 3** (Mahosot+Vientiane Province)=started at month-17 after PP-G. **P-values** were derived from the Wald Chi-Square test.

Table 5: Partial adherence to antimicrobial prescribing guidelines in PP-G vs App-G groups among outpatients

Variables	aOR (95% CI)	P-value
Guideline delivery method:		
PP-G	1	
App-G	0.82 (0.67-1.00)	0.047
Sequence of intervention		
Sequence 3 (MS+VTP)	1	
Sequence 2 (SVK+SV)	0.74 (0.58-0.93)	0.011
Sequence 1 (XK+LNT)	2.00 (1.58-2.56)	<0.0001
Age:		
≤1 year	1	
>1 to ≤5 years	0.76 (0.54-1.07)	0.114
>5 to ≤14 years	0.97 (0.68-1.39)	0.871
≥15 years	0.30 (0.22-0.41)	<0.0001

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **aOR**= adjusted Odds Ratio, **XK**=Xiengkhuang, **LNT**=Luang Namtha, **SV**=Salavan, **SVK**=Savannakhet, **VTP**=Vientiane Provincial, **MS**=Mahosot**, Sequence 1** (Xiengkhuang+Luang Namtha)=started at month-6 after PP-G implementation, **Sequence 2** (Salavan+Savannakhet)=started at month-11 after PP-G, **Sequence 3** (Mahosot+Vientiane Province)=started at month-17 after PP-G. **P-values** were derived from the Wald Chi-Square test.

Table 6: Partial adherence to antimicrobial prescribing guidelines in the Pre-guideline group vs guideline group (PP-G and App-G) among outpatients

Characteristics	aOR (95% CI)	P-value
Guideline delivery method:		
Pre-guidelines	1	
PP-G	1.17 (0.94-1.46)	0.168
App-G	0.95 (0.76-1.19)	0.674
Sequence of intervention		
Sequence 3 (MS+VTP)	1	
Sequence 2 (SVK+SV)	0.73 (0.60-0.90)	0.003
Sequence 1 (XK+LNT)	2.18 (1.77-2.70)	<0.0001
Age:		
≤1 year	1	
>1 to ≤5 years	0.74 (0.55-0.98)	0.036
>5 to ≤14 years	1.06 (0.79-1.44)	0.720
≥15 years	0.32 (0.25-0.42)	<0.0001

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **aOR**= adjusted Odds Ratio, **XK**=Xiengkhuang, **LNT**=Luang Namtha, **SV**=Salavan, **SVK**=Savannakhet, **VTP**=Vientiane Provincial, **MS**=Mahosot**, Sequence 1** (Xiengkhuang+Luang Namtha)=started at month-6 after PP-G implementation, **Sequence 2** (Salavan+Savannakhet)=started at month-11 after PP-G, **Sequence 3** (Mahosot+Vientiane Province)=started at month-17 after PP-G. **P-values** were derived from the Wald Chi-Square test.

Appendix 15.2: Adherence to guideline across age groups, departments and indications

1. Hospitalised patients

Table 1: Overall guideline adherence by age group among hospitalised patients

Age group	Total, n/N (%, 95% CI)	Pre-guideline, n/N (%, 95% CI)	PP-G, n/N (%, 95% CI)	App-G, n/N (%, 95% CI)
≤1 year	140/382 (37, 32-42)	47/109 (43, 34-53)	30/121 (25, 17-33)	63/152 (41, 33-50)
>1 to ≤5 years	50/168 (30, 23-37)	24/54 (44, 31-59)	9/45 (20, 9-35)	17/69 (25, 15-36)
>5 to <15 years	17/142 (12, 7-18)	2/33 (6, 0.7-20)	9/59 (15, 7-27)	6/50 (12, 4-24)
≥15 years	444/2550 (17, 18-21)	62/574 (11, 8-14)	183/1135 (16, 14-18)	199/841 (24, 21-27)

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training

Table 2: Overall guideline adherence by inpatient departments among hospitalised patients

Department	Total, n/N (%, 95% CI)	Pre-guideline, n/N (%, 95% CI)	PP-G, n/N (%, 95% CI)	App-G, n/N (%, 95% CI)
Surgery	123/846 (15, 12-17)	25/205 (12, 8-17)	53/413 (13, 10-16)	45/228 (20, 15-25)
Obstetrics and Gynaecology	15/558 (3, 1-4)	3/151 (2, 0.4-6)	7/251 (3, 1-6)	5/156 (3, 1-7)
Medicine	248/797 (31, 28-34)	28/166 (17, 11-23)	85/323 (29, 22-31)	125/308 (41, 35-46)
Paediatrics	131/421 (31, 27-36)	51/125 (41, 35-53)	27/131 (21, 14-28)	53/165 (32, 25-40)
Intensive Care Unit	95/298 (32, 27-37)	22/72 (31, 20-42)	32/115 (28, 20-37)	41/111 (37, 28-47)
Other	39/322 (12, 9-16)	6/51 (12, 4-24)	17/127 (13, 8-20)	16/144 (11, 6-17)

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training

Table 3: Overall guideline adherence by selected prescribing indications among hospitalised patients

Indications	Total, n/N (%, 95% CI)	Pre-guideline, n/N (%, 95% CI)	PP-G, n/N (%, 95% CI)	App-G, n/N (%, 95% CI)	OR (95% CI), P-value*
Treat infection	572/1862 (31, 29-33)	119/437 (27, 23-32)	195/745 (26, 23-29)	258/680 (38, 34-42)	1.72 (1.68-2.16) p<0.0001
Pneumonia	103/378 (27, 23-32)	38/117 (32, 24-42)	19/112 (17, 10-25)	46/149 (31, 23-39)	2.18 (1.19-3.00) p=0.010
Sepsis	89/238 (37, 31-44)	32/64 (50, 37-63)	28/90 (31, 22-42)	29/84 (35, 24-46)	1.17 (0.62-2.20) p=0.632
SST	4/143 (3, 0.8-7)	2/28 (7, 0.9-23)	1/70 (1, 0.04-8)	1/45 (2, 0.06-12)	-
Melioidosis	55/98 (56, 46-66)	4/8 (50, 16-84)	24/39 (62, 45-77)	27/51 (53, 38-67)	0.70 (0.30-1.64) p=0.415
UTI	30/72 (42, 30-54)	6/13 (46, 19-75)	14/34 (41, 25-59)	10/25 (40, 21-61)	0.95 (0.33-2.73) p=0.928
Surgical prophylaxis	31/754 (4, 3-6)	12/174 (7, 4-12)	10/326 (3, 1-6)	9/243 (4, 2-7)	1.21 (0.49-3.04) p=0.676
Medical prophylaxis	48/306 (16, 12-20)	4/77 (5, 1-13)	26/138 (19, 13-26)	18/91 (20, 12-29)	1.06 (0.54-2.07) p=0.860

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **SST**=Skin and Soft Tissue Infection, **UTI**=Urinary Tract Infection, P-value= from Wald test, comparing between PP-G and App-G, P-values were from Wald Chi-Square test.

Table 4: Overall guideline adherence by top three prescribing indications across age group among hospitalised patients

Age (year)	Prescribing indications	Total, n/N (%, 95% CI)	Pre-guideline, n/N (%, 95% CI)	PP-G, n/N (%, 95% CI)	App-G, n/N (%, 95% CI)	OR (95% CI), P-value*
≤1	Sepsis	73/139 (52, 44-61)	24/38 (63, 46-78)	22/50 (44, 30-59)	27/51 (53, 38-67)	1.4 (0.65-3.13) p=0.369
	Pneumonia	64/109 (59, 49-65)	23/35 (66, 48-81)	8/20 (40, 19-64)	33/54 (61, 47-74)	2.36 (0.82-6.73) p=0.109
	Tonsilopharyngitis	0/9 (0)	0/1 (0)	0/4 (0)	0/4 (0)	-
>1 to <15	Pneumonia	29/64 (45, 33-58)	13/30 (43, 25-62)	6/11 (54, 23-83)	10/23 (43, 23-65)	0.64 (0.15-2.72) p=0.546
	Tonsilopharyngitis	3/39 (8, 2-21)	2/10 (20, 2-56)	0/12 (0)	1/17 (6, 0.1-29)	-
	Appendicitis	0/26 (0)	0/7 (0)	0/11 (0)	0/8 (0)	-
≥15	Pneumonia	10/205 (5, 2-9)	2/52 (4, 0.5-13)	5/81 (6, 2-14)	3/72 (4, 0.9-12)	-
	Appendicitis	42/176 (24, 18-31)	6/25 (24, 9-45)	20/95 (21, 13-31)	16/56 (29, 17-42)	1.5 (0.70-3.21) P=0.296
	Peritonitis	49/136 (36,28-45)	6/38 (16, 6-31)	16/63 (25, 15-38)	27/35 (77, 60-89)	9.91(3.75-26.20) p<0.0001

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **SST**=Skin and Soft Tissue Infection, **UTI**=Urinary Tract Infection, * P-value= from Fisher's exact test or Pearson Chi-square test, compare between PP-G and App-G, P-values were from Wald Chi-Square test.

Table 5: Adherence to antimicrobial prescribing guidelines for pneumonia: a comparison between PP-G and App-G groups among inpatients

Characteristics	aOR (95% CI)	P-value
Guideline delivery method:		
PP-G	1	
App-G	1.34 (0.36-4.98)	0.666
Age:		
≤1 year	1	
>1 to ≤5 years	0.90 (0.30-2.67)	0.852
>5 to ≤14 years	0.88 (0.12-6.15)	0.895
≥15 years	0.03 (0.01-0.10)	<0.0001

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **aOR**=adjusted Odds Ratio, P-values were from Wald Chi-Square test.

2. Outpatients

Table 1: Overall percentage of guideline adherence by age group among outpatients

Age group	Total, n/N (%, 95% CI)	Pre-guideline, n/N (%, 95% CI)	PP-G, n/N (%, 95% CI)	App-G, n/N (%, 95% CI)
≤1 year	69/304 (23, 18-28)	22/97 (23, 15-32)	12/60 (20, 11-32)	35/147 (24, 17-31)
>1 to ≤5 years	158/625 (25, 22-29)	28/154 (18, 12-25)	46/158 (29, 22-37)	84/313 (27, 22-32)
>5 to <15 years	139/451 (31, 26-35)	31/111 (28, 20-37)	40/132 (30, 23-39)	68/208 (33, 26-39)
≥15 years	429/2188 (20, 18-21)	105/487 (22, 18-25)	165/862 (19, 16-22)	159/839 (19, 16-22)

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training

Table 2: Overall percentage of guideline adherence by selected prescribing indications among outpatients

Indications	Total, n/N (%, 95% CI)	Pre-guideline, n/N (%, 95% CI)	PP-G, n/N (%, 95% CI)	App-G, n/N (%, 95% CI)	OR (95% CI), P-value*
Treat infection	791/2918 (27, 25-29)	184/707 (26, 23-29)	262/942 (28, 25-31)	345/1269 (27, 25-30)	0.97 (0.80-1.17), p=0.744
Tonsillopharyngitis	220/1154 (19, 17-21)	43/297 (14, 11-19)	45/272 (17, 12-21)	132/585 (23, 19-26)	1.46 (1.00-2.12), p=0.047
Pneumonia	61/312 (20, 15-24)	16/95 (17, 10-26)	13/88 (15, 8-24)	32/129 (25, 18-33)	1.90 (0.93-3.88), p=0.076
UTI	95/232 (41, 34-47)	30/45 (67, 51-80)	36/101 (36, 26-46)	29/86 (34, 24-45)	0.61 (0.30-1.24), p=0.172
SST	20/204 (10, 6-15)	7/36 (19, 8-36)	7/99 (7, 3-14)	6/69 (9, 3-18)	1.24 (0.40-3.88), p=0.705
STI	34/136 (25, 18-33)	0/18 (0)	24/65 (37, 25-50)	10/53 (19, 9-32)	0.39 (0.17-0.93), p=0.034
Surgical prophylaxis	0	0	0	0	-
Medical prophylaxis	4/7 (57, 18-90)	2/3 (67, 9-99)	1/2 (50, 1-99)	1/2 (50, 1-99)	-

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **SST**=Skin and Soft Tissue Infection, **UTI**=Urinary Tract Infection, * P-value= from Fisher's exact test or Pearson Chi-square test, compare between PP-G and App-G, P-values were from Wald Chi-Square test.

Table 3: Overall guideline adherence by top three prescribing indications across age group among outpatients

Age (year)	Prescribing indications	Total, n/N (%, 95% CI)	Pre-guideline, n/N (%, 95% CI)	PP-G, n/N (%, 95% CI)	App-G, n/N (%, 95% CI)	OR (95% CI), P-value*
≤1 year	Tonsilopharyngitis	37/182 (20, 15-27)	12/56 (21, 11-34)	6/36 (17, 6-33)	19/90 (21, 13-31)	1.34 (0.49-3.68) p=0.573
	Pneumonia	24/66 (36, 25-49)	7/30 (23, 10-42)	3/8 (37, 8-75)	14/28 (50, 31-69)	1.67 (0.33-8.35) p=0.534
	Bronchitis	0/2 (0)	0/2 (0)	0/6 (0)	0/10 (0)	-
>1 to <15	Tonsilopharyngitis	140/611 (23, 20-26)	22/155 (14,9-21)	27/128 (21, 14-29)	91/328 (28, 23-33)	1.44 (0.88-2.34) p=0.146
	Intestinal parasite infection	87/123 (71, 62-78)	23/30 (77, 58-90)	36/52 (69, 55-81)	28/41 (68, 52-82)	0.96 (0.39-2.31) p=0.923
	Pneumonia	35/81 (43, 32-55)	9/23 (39, 20-61)	9/15 (60, 32-84)	17/43 (39, 25-55)	0.43 (0.13-1.45) p=0.175
≥15 years	Tonsilopharyngitis	43/361 (12, 9-16)	9/86 (10, 5-19)	12/108 (11, 6-19)	22/167 (13, 8-19)	1.21 (0.57-2.57) p=0.612
	STI	34/133 (25, 18-34)	0/17 (0)	24/64 (37, 26-50)	10/52 (19, 10-32)	0.40 (0.17-0.93) p=0.034
	Pneumonia	2/165 (1, 0.1-4)	0/42 (0)	1/65 (1, 0.4-8)	1/58 (2, 0.4-9)	-

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **STI**=Sexually transmitted Infection, * P-value= from Fisher's exact test or Pearson Chi-square test, compare between PP-G and App-G, P-values were from Wald Chi-Square test.

Table 5: Adherence to antimicrobial prescribing guidelines for tonsilopharyngitis: a comparison between PP-G and App-G groups among outpatients

Characteristics	aOR (95% CI)	P-value
Guideline delivery method:		
PP-G	1	
App-G	1.44 (0.67-3.08)	0.348
Age:		
≤1 year	1	
>1 to ≤5 years	1.20 (0.68-2.09)	0.529
>5 to ≤14 years	1.18 (0.65-2.15)	0.584
≥15 years	0.38 (0.20-0.71)	0.003

Note: **PP-G**=group with paper-based version of the antimicrobial prescribing guidelines, **App-G**= group with application-based version of the antimicrobial prescribing guidelines and antimicrobial stewardship training, **aOR**= adjusted Odds Ratio, P-values were from Wald Chi-Square test.

Appendices to Chapter 5

Appendix 16: Antimicrobial prescribing behaviours and guidelines uptake discussion guide

Facilitator's welcome, introduction and instructions to participants

Welcome and thank you for volunteering to take part in this interview. You have been asked to participate as your point of view is important. I realize you are busy and I appreciated your time.

Introduction:

This interview is designed to assess your current thoughts and feelings about your antimicrobial prescribing and the use of local antimicrobial prescribing guidelines in Laos which were discussed when you have joined the workshop in 2021. The interview will take approximately 60-90 minutes. May I record the discussion to facilitate its recollection? (If yes, switch on the recorder)

Anonymity:

Despite being recorded, I would like to assure you that the discussion remains anonymous. The recordings will be kept safely in a password protected file until they are transcribed word for word. The transcribed notes of the interview will contain no information that allowed individual subjects to be linked to specific statements. Please answer and comment as accurately and truthfully as possible. If there are any questions or discussions that you do not wish to answer, you do not have to do so; however please try to answer as much as possible. You can withdraw from the interview at any time if you wish without any negative consequences.

Ground rules

- There are no right or wrong answers
- You do not have to answer some questions if you do not wish to
- When you do have something to say, please feel free to say and take your time.

  It is important that I obtain your views as much as possible
- Do you have any questions? (answers).

Let's start by introducing yourself (Members of the research team should also introduce themselves and describe each of their roles)

Topic	Question
Factors influencing antibiotic prescribing	1. Could you talk me through how do you normally prescribe antibiotics? - How do you decide which antibiotic to prescribe/the dose/duration? - What factors influenced your autonomy of decision-making for antibiotic prescription? Prompt: your senior colleges? Your patients? Your peer colleges? Policy? - When/who do you review your prescription? - How do you decide when to escalate, de-escalate or stop giving antibiotics? - In what situations do you give combinations? Extend therapy time? Decide to use intravenous or oral antibiotics? - What challenges have you faced in prescribing antibiotics to your patients? - When do you usually search for help to prescribe antibiotics? Where/who do you usually search for help to support your prescribing? Prompt: what makes you choose that source over an alternative?
	2. Is it possible that different doctors prescribe different antibiotics for the same patients? - If so, why? - If not, why not?
	3. Can you think of anything that would help you to prescribe antibiotics to your patients?
Use of the antimicrobial prescribing guidelines	4. Have you used Lao antimicrobial prescribing guidelines so far? - If yes, can you describe how/when you use them? - If not, can you explain why?
	5. Where do you keep the guidelines (pocketbook or mobile phone app) during your practice?
	6. How do you find using the guidelines?

	- If easy, how? - If difficult, how and do you have any recommendation to make it easier?
	7. Did you notice that anything change in your/your colleagues' practices after the introduction of these guidelines? - If yes, what? - If not, why?
	8. Can you explain what your ideal guidelines would look like? And why you like it?
Factors influencing guidelines uptakes	9. What do you think could help support doctors prescribing decisions? Prompt would be good (e.g, laboratory, telephone advice, online)
	10. Why do you think some doctors use less/do not use Lao prescribing guidelines? (loss of the guidelines, no time, there are better guidelines, I do not like reading)
	11. Who do you think should play an important role in encouraging doctors to prescribe antimicrobials based on prescribing guidelines more frequent? (e.g., everybody including myself, colleagues, pharmacists, head of the ward, director of hospital, or Ministry of Health)
Wrap up	**Is there anything else you would like to say about our discussion?**

Thank you for participating. This has been a very successful discussion and your opinions will be a valuable asset to the study. We hope you have found the discussion interesting. If there is anything you are unhappy with or wish to complain about, please contact the PI or speak to me later.

I would like to remind you that any featuring in this interview will be anonymous.