Antimicrobial Stewardship in District Hospitals in Vietnam

Dr Jaslyn Doshi

Primary Supervisor: Professor Greg Fox

Faculty of Medicine and Health

The University of Sydney

2025

A thesis submitted to fulfil requirements for the degree of Doctor of Philosophy

Table of Contents

Tables

Figures

Authorship statement

Chapter 1: This chapter is my own work.

Chapter 2: I formulated the research question, search strategy and conducted the literature search on the specified databases. I performed the title, abstract and full text search in English language to assess articles for inclusion. I extracted data from each included article. I performed descriptive analysis on all studies(English and Vietnamese) included in the thesis and performed the meta-analysis to find pooled estimates of similar study findings. I created all the figures. All sections of the manuscript were prepared by me (introduction, methods, results, discussion, tables, figures, and supplementary material).

Chapter 3: I was involved in the study design and application of Ethics approval, along with the supervising author. I engaged with an external partner from The University of Melbourne for the use of an audit tool called National Antimicrobial Prescribing Survey (NAPS) as a co-primary outcome measure in this study. I conducted fieldwork in Vietnam alongside a team of Vietnamese researchers and physician partners to implement the project. My roles included developing antibiotic guidelines, training local staff on implementation of intervention, providing online training for the use of NAPS audit tool, participating in selected feedback sessions to hospitals and collecting data for outcome measures. Additionally, I was a blind assessor on all audits for antimicrobial prescribing appropriateness. I had access to data collected in the NAPS database, Excel and REDCap. I performed descriptive analysis on all outcomes as well as preliminary statistical analysis for antimicrobial consumption and antimicrobial appropriateness with guidance from supervising authors. I received help from a statistician (QL) for further statistical analysis. All sections of the

manuscript were prepared by me (introduction, methods, results, discussion, tables, figures, and supplementary material).

Chapter 4: I was involved in the study design and application of Ethics approval, along with two supervising authors. I conducted fieldwork in Vietnam by meeting with research partner from National Institute of Hygiene and Epidemiology (NIHE) microbiology laboratory to discuss laboratory processes. I had access to data collected by the lab in form of an Excel spreadsheet, stored in OneDrive. I performed descriptive analysis of isolates as well as preliminary statistical analysis, with guidance from supervising authors (GJF, AHJ). I received help from a statistician(QL) for further statistical analysis. All sections of the manuscript were prepared by me (introduction, methods, results, discussion, tables, figures, and supplementary material). QL provided Supplementary Figure S4.2.

Chapter 5: I was involved in the study design and application of Ethics approval, along with the supervising author. I conducted fieldwork in Vietnam alongside a team of Vietnamese researchers and physician partners to implement the project. My role was an extension to that described in Chapter 3. I had access to data collected in the NAPS database, Excel and REDCap. I performed descriptive analysis on all outcomes as well as preliminary statistical analysis for antimicrobial consumption and antimicrobial appropriateness, with guidance from supervising authors. I received help from a statistician (QL) for further statistical analysis. All sections of the manuscript were prepared by me (introduction, methods, results, discussion, tables, figures, and supplementary material). QL provided Supplementary figure S5.4.

Chapter 6: This chapter is my own work.

Literature on antimicrobial resistance and antimicrobial stewardship evolved over the period between 2021 and 2025. Each chapter presents work, with data that was available at the time of writing and publication.

Acknowledgements

Completing this PhD thesis has been a challenging, but deeply rewarding journey, and I could not have reached this milestone without the support, guidance, and encouragement of so many incredible people.

First and foremost, I would like to express my sincere gratitude to my primary supervisor Professor Greg Fox, whose unwavering support and exceptional mentorship over the past four years have been instrumental in shaping this research. Your guidance and encouragement have inspired me to push boundaries and strive for excellence, and I am constantly in awe of your ability to seamlessly balance academia, clinical work, and family life with such dedication.

My co-supervisors Associate Professors Justin Beardsley and Matthew Watts, thank you the support and encouragement throughout this journey. Justin, your incredible ability to offer solutions to my random questions and your insights during the analysis and write-up phases were invaluable. Matt, thank you for always playing the role of life coach and giving me the boost of confidence when I needed it in both my clinical and research roles.

I am deeply grateful to my Vietnamese colleagues who were instrumental in executing the project, gathering data, answering my questions day and night for over four years. Yen Pham Ngoc, Thuy Ma and Linh Duong, I had so much fun collecting data, conducting audits, and working alongside the healthcare workers in the district hospitals with you. I learned so much from your genuine care for the health of the Vietnamese people, and I am proud to call you my friends. The memories we made during fieldwork will stay with me for a lifetime.

To my wonderful family, words cannot express how much your love and support have meant to me. This PhD journey has seen me through COVID-19, a marriage and welcoming a baby! To my husband, Shiva, you encouraged me to pursue this PhD even when I felt like an imposter attempting the impossible. You have been my rock and my biggest cheerleader—thank you for your limitless patience and understanding. I could not have completed this PhD without your sacrifices, especially

in caring for me and Dev during the final stretch. To my beautiful son, Dev, you are my greatest joy and the light and have kept me motivated in the final stretches of writing. To my parents, my brothers and their families, my in-laws, and Aunty Vasie, thank you for stepping in to look after Dev (and me!) at various times, giving me the focus I needed to complete this thesis.

I am incredibly lucky to have such amazing friends, who have provided emotional support, distractions and a safe space to vent. Tasnim and Sayontonee, our group chat was my lifeline, keeping me sane through this journey. Thank you both for being my moral support, shoulders to cry on, and just my cheerleaders in general. Tas, I am so grateful to have "accidentally" landed this PhD project through you! To my “sisters”, Saiyuri and Krish, your own PhD journeys inspired me and helped motivate me when times were tough. Karunya, Eashwar, Joshi thank you for feeding me, distracting me and lifting my spirits. Kailaesh, thank you for tolerating my stats and Excel questions early on, it helped me all the way through. My countless friends who have been a part of this last 4 years, your friendship has been a source of strength and comfort.

I am also grateful for the input from all my co-authors who contributed towards the project itself, and providing edits to the manuscript. Annaleise, I learnt so much from collaborating with you not only in microbiology, but also from your diligence with the smallest of details. I am also thankful for the support from Greg’s research team and the wider University of Sydney team, who provided a nurturing research environment. I learned a lot from all of you. Zac, you were a lifesaver in carrying out the complex analyses required for this research, and your patience was incredible—I can never thank you enough! Special thanks to my Vietnamese and Australian partners and collaborators, whose expertise and collaboration were vital to this project.

Last, but not least, I would like to thank God and my Guru, Sathya Sai Baba, who has been the ultimate guide, not only through this thesis but in every step of my life.

Thank you all—from the bottom of my heart.

Abbreviations

AMR	antimicrobial resistance
AMS	antimicrobial stewardship
AST	antimicrobial susceptibility testing
COVID-19	Coronavirus disease-19
CPE	carbapenemase-producing Enterobacterales
CRE	carbapenem-resistant Enterobacterales
DDD	Defined Daily Dose
DOT	Days of Therapy
ESBL	extended spectrum beta-lactamase
GAP	Global Action Plan
GLASS	Global Antimicrobial Resistance and Use Surveillance
HCW	healthcare worker
ICU	intensive care unit
IPC	infection prevention and control
LMIC	low- and middle-income countries
LOT	Length of Therapy
MIC	Minimum inhibitory concentration
MoH	Ministry of Health
MRO	multidrug-resistant organism
MRSA	Methicillin-resistant *Staphylococcus aureus*
NAP	National Action Plan
NAPS	National Antimicrobial Prescribing Survey
NIHE	National Institute of Hygiene and Epidemiology
WHO	World Health Organisation
WASH	Water, Sanitation and Hygiene

Chapter 1: Introduction

The discovery of antibiotics was one of the most transformative achievements in medical history. In 1928, Alexander Fleming's serendipitous observation of *Penicillium notatum* marked the beginning of the golden age of antibiotic discovery that peaked in the mid-20th century.[1] Antibiotics drastically reduced mortality from bacterial infections. Since then, numerous classes of antimicrobials have been developed, targeting bacteria, fungi, viruses, and parasites.[1] However, their overuse and misuse in healthcare, agriculture, and livestock farming has fuelled the rapid emergence of antimicrobial resistance (AMR), rendering some infections untreatable.[2] This resistance emerges when microbes evolve in response to selective pressures from antimicrobial exposure. The accelerating spread of AMR, combined with the slow development of new antimicrobials contributes to prolonged illness, higher mortality rates, and escalating healthcare costs, placing humanity at a critical juncture.[2]

This introduction will explore the nature of AMR, its global epidemiology and implications for human health. It will then explore the specific challenges of AMR in Vietnam, a lower middle-income country in Southeast Asia. Subsequently, the role of antimicrobial stewardship in combating AMR will be discussed, including in Vietnam. Finally, this chapter will conclude with a description of the VRESIST series of projects that were aimed to understand and develop local solutions to AMR in Vietnam.

Antimicrobial resistance

Definition and mechanisms of AMR

AMR occurs when bacteria, viruses, fungi, and parasites develop resistance to antimicrobials through genetic mutations or acquisition of resistance genes, often in response to selective pressure from exposure to antimicrobials.[3] The World Health Organisation's (WHO) Global Antimicrobial Resistance Surveillance System (GLASS) has documented high rates of resistance for common pathogens that are responsible for severe infections which are increasingly difficult to treat. These include *Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus,* and *Mycobacterium tuberculosis*.[2,4]

While AMR affects a wide range of pathogens — including Plasmodium species, viruses, and fungi — bacterial resistance has received particular attention due to its high prevalence in healthcare-associated infections, the wide use of antibiotics across sectors, and the limited availability of rapid diagnostic tools.

Mechanisms of AMR [5]

AMR arises through several mechanisms that enable bacteria to survive exposure to antimicrobial agents. These are broadly categorised into four main types: (1) limiting drug uptake, (2) active drug efflux, (3) drug inactivation, and (4) modification of the drug target.[5] Each mechanism contributes to either intrinsic or acquired resistance and varies in prevalence between Gram-negative and Gram-positive bacteria due to structural and physiological differences.

1. Limiting Drug Uptake

   Gram-negative bacteria, such as *Pseudomonas aeruginosa* and members of the Enterobacterales, possess an outer membrane with lipopolysaccharide (LPS) that impedes the entry of many antibiotics. Hydrophilic antibiotics like β-lactams typically rely on porin channels to penetrate this barrier. Resistance can emerge when bacteria reduce the expression of these porins or alter their

structure, as seen in *Klebsiella pneumoniae* and *Escherichia coli* with resistance to carbapenems. In Gram-positive bacteria, uptake limitation is less common, but *Enterococcus faecalis* exhibits intrinsic resistance to aminoglycosides due to restricted penetration of polar molecules. Additionally, biofilm formation—such as by *Staphylococcus epidermidis* or *Pseudomonas aeruginosa*—further limits drug penetration, contributing to persistence and tolerance.

2. Modifications of drug targets

Bacteria can alter the structure of antibiotic targets to reduce binding affinity. For β-lactams, *Staphylococcus aureus* acquires the mecA gene, encoding PBP2a, which has low affinity for β-lactam antibiotics and results in methicillin resistance (MRSA). In vancomycin-resistant enterococci (VRE), van genes modify the D-Ala-D-Ala termini of peptidoglycan precursors, reducing drug binding. Macrolide resistance arises via ribosomal methylation by erm genes, commonly seen in *Streptococcus pneumoniae* and *Staphylococcus aureus*. Fluoroquinolone resistance is mediated by mutations in DNA gyrase (e.g., gyrA) and topoisomerase IV (e.g., parC), reducing drug binding in *Escherichia coli* and *Staphylococcus aureus.*

3. Active Drug Efflux

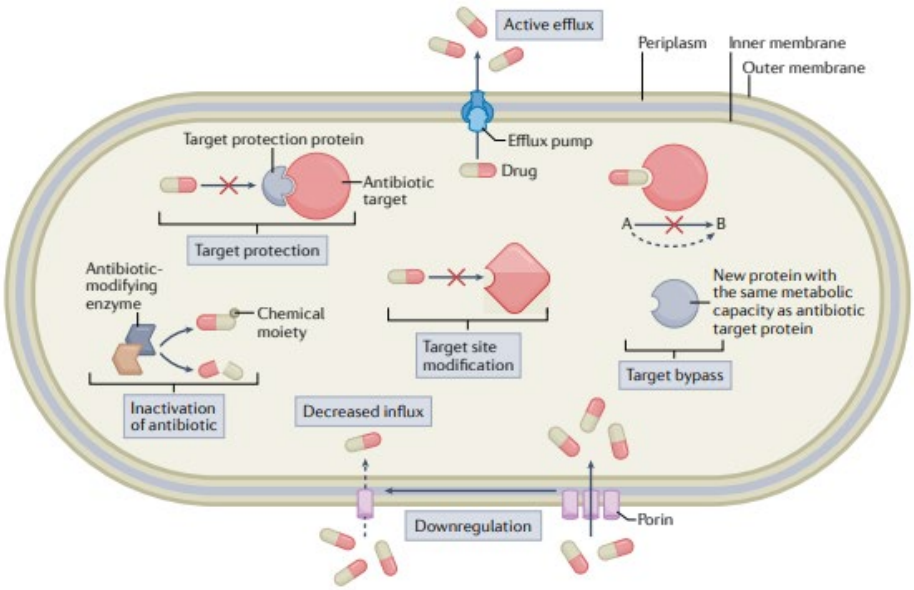
Efflux of antimicrobial agents is a common mechanism by which bacteria reduce intracellular drug concentrations and diminish drug efficacy. This process involves membrane-bound transport systems that actively expel a range of structurally diverse antibiotics from the bacterial cell. Efflux pumps are present in both Gram-negative and Gram-positive bacteria and may be encoded chromosomally or acquired via plasmids. These systems may be constitutively expressed or induced in response to environmental triggers, and in some cases are associated with broad substrate specificity, enabling resistance to multiple drug classes simultaneously.

4. Drug Inactivation

   Bacteria can enzymatically inactivate antibiotics either by hydrolysis or chemical modification. The most clinically significant example is β-lactamase production, which hydrolyses the β-lactam ring of penicillins and cephalosporins. Extended-spectrum β-lactamases (ESBLs), such as $bla_{CTX\text{-}M}$ enzymes, are prevalent in *Escherichia coli* and confer resistance to third-generation cephalosporins. Carbapenemases, including bla_{KPC} and $bla_{NDM\text{-}1}$, further inactivate carbapenems and are found in *Klebsiella pneumoniae* and *Acinetobacter baumannii*. Enzymatic modification, such as aminoglycoside acetyltransferases, can inactivate drugs like gentamicin by adding acetyl, phosphoryl, or adenyl groups—common in *Enterococcus* spp. and *Pseudomonas* spp.

These diverse mechanisms, often occurring in combination, enable microbes to survive various antibiotic treatment regimens, leading to poor outcomes in patients with bacterial infections. This has been summarised in Figure 1.1.

Figure 1.1: Overview of common molecular mechanisms of antibiotic resistance



(From Darby et.al 2023)[6]

Highly prevalent and clinically significant organisms with these resistance mechanisms include extended-spectrum beta-lactamase (ESBL)-producing bacteria and carbapenem-resistant Enterobacterales (CRE), both of which were listed among the WHO bacterial priority pathogens in 2024.[7] ESBL-producing organisms produce enzymes that degrade a broad range of β -lactam antibiotics, such as penicillins and cephalosporins, which are commonly used to treat bacterial diseases. CRE, on the other hand, are Enterobacterales that have developed resistance to carbapenems, a last-line antibiotic class reserved for severe infections. These resistant bacteria are associated with poor treatment outcomes and high mortality rates.[8]

Compounding this challenge, the world is facing a crisis in both the development of new antibiotics and equitable access to existing treatments. The antibiotic research and development pipeline remains insufficient to keep pace with rising prevalence of resistant infections, while the high cost of second-line therapies further limits access to effective treatment, particularly in resource-poor settings.[2]

Key Drivers of Antimicrobial Resistance

Antibiotic use is a key factor driving selection pressure and the development of resistance.[9] A lack of public awareness and easy access to self-medication without a prescription in some low-income settings lead to antibiotics being among the most purchased drugs worldwide. A significant portion is used unnecessarily, where physicians may prescribe them without a confirmed diagnosis or for self-limiting bacterial and viral infections, exacerbated by limited access to quality and timely diagnostics. In high-income countries, patients with resistant infections often have access to expensive, newer-generation antibiotics. In contrast, in low-resource settings, where infectious diseases are more prevalent, patients may struggle to access or afford second-line treatments, exacerbating the burden of AMR.[9]

In the agricultural sector, economic incentives drive antibiotic use for growth promotion and disease prevention in livestock, introducing constant selective pressure on bacteria in farm environments.[10] These resistant bacteria can enter the human population through contaminated food, water, and direct contact, further spreading resistance. The persistence of antibiotics in agricultural runoff also contaminates water sources, fostering environmental reservoirs of resistance that further threaten public health.[10]

Other major drivers are inadequate water, sanitation, and hygiene (WASH) as well as infection prevention and control (IPC), which facilitate the transmission of resistant bacteria already present in the environment and healthcare settings. Without these practices, resistant pathogens can persist in water sources, on surfaces, and between individuals, resulting in a vicious cycle of widespread infection, and causing an over-reliance on antibiotics.[11]

Consequences of antimicrobial resistance

AMR threatens modern medicine by making infections harder to treat and increasing risks across multiple medical conditions.[2] Multidrug-resistant bacteria compromise recovery from surgical site infections, while resistant bloodstream infections in neutropenic cancer patients undergoing chemotherapy lead to higher mortality. Similarly, presence of antibiotic-resistant pathogens during a caesarean section heightens the risk of maternal and neonatal sepsis. Transplant recipients, reliant on immunosuppressive therapy, face life-threatening infections from resistant organisms that can potentially jeopardise graft survival. In intensive care, ventilator-associated pneumonia caused by multidrug-resistant bacteria prolongs hospital stays, often requiring last-resort and often toxic antibiotics.[12] These resistant infections result in increased morbidity and mortality, prolonged illness and extended hospitalisations.

Beyond individual patient outcomes, AMR poses significant public health risks, particularly when an outbreak occurs. Resistant pathogens can spread rapidly within healthcare settings and the community. Furthermore, the global movement of people and goods facilitate the cross-border spread of resistant organisms, making AMR an international health security concern.[13]

In 2019, bacterial AMR was directly responsible for 1.27 million deaths and contributed to 4.95 million deaths globally.[14] A study of AMR trends from 1990-2021 found deaths from AMR decreased by more than 50% among children younger than five, largely due to improvements in WASH. However deaths increased by over 80% for adults 70 years and older, raising concerns in a rapidly aging global population.[15] Additionally, the number of deaths attributable to AMR is projected to increase by 69.6% by 2050.[15] These estimates however are derived from large-scale modelling studies, which are valuable for advocacy and planning, but rely on assumptions and incomplete data and should therefore be interpreted with appropriate caution.

Beyond its health impacts, AMR also increases healthcare costs, imposing significant economic burdens. The World Bank has estimated that AMR could lead to an additional US$ 1 trillion additional healthcare costs annually by 2050, and global gross domestic product (GDP) losses ranging from US$ 1 trillion to US$ 3.4 trillion per year by 2030.[2] Moreover, with AMR, low-income countries would experience larger drops in economic growth than wealthy countries, resulting in increased economic inequality between countries. The differential impacts on GDP result from higher infectious disease prevalence in these settings and a greater dependence on labour incomes in countries with lower per capita incomes.[16]

Detection and surveillance of antimicrobial resistance

Traditionally, AMR detection has relied on culture-based antimicrobial susceptibility testing (AST), which remains essential in clinical microbiology. While phenotypic testing provides direct evidence of bacterial response to antibiotics, it offers limited insight into underlying resistance mechanisms, as genetically distinct clones can exhibit identical resistance patterns.[17] To improve resolution, genetic typing methods such as multi-locus sequence typing (MLST) analyse specific genetic markers, but they cover only a small fraction of the genome.

In contrast, whole-genome sequencing (WGS) provides single-nucleotide level insights, allowing for the identification of AMR genes, pathogen identity, virulence factors, and evolutionary lineage. The advent of next-generation sequencing and metagenomic approaches has further revolutionised AMR surveillance, offering an even deeper understanding of pathogen evolution and resistance mechanisms. Comparative phylogenetic analysis allows researchers to assess genetic relatedness between isolates, and when integrated with epidemiological and clinical data, it enhances understanding of AMR transmission patterns.[17]

Effective surveillance of AMR is essential for tracking resistance patterns, guiding treatment decisions, and informing public health interventions.[2] However, inadequate surveillance programs in low- and middle-income countries (LMICs) make it difficult to quantify the burden of AMR. The launch of WHO GLASS project in 2015 has improved global reporting efforts,[18] but research remains limited in genetic-based AMR studies in these settings.

Antimicrobial resistance in low- and middle-income countries

AMR affects people across all regions and income levels, with particularly severe consequences in LMICs. Poverty, unequal access to healthcare, and weak IPC measures facilitate the spread of multi-resistant organisms.[2] Limited diagnostic capacity and overburdened health systems further drive inappropriate antibiotic use, as clinicians often rely on empirical treatment in the absence of microbiological confirmation.

Vietnam, a rapidly developing lower middle-income country in Southeast Asia is no exception to these challenges, facing a particularly severe burden of AMR in recent years.[19] Understanding the epidemiology of AMR in Vietnam is crucial for developing targeted interventions to combat its spread.

The epidemiology of antimicrobial resistance in Vietnam

In 2019, AMR was directly responsible for approximately 14,300 deaths in Vietnam and associated with an additional 52,500 deaths, surpassing mortality rates from diseases such as diabetes, kidney disorders, and tuberculosis.[20] The main pathogens associated with mortality were *Staphylococcus aureus, Escherichia coli, Acinetobacter baumannii, Streptococcus pneumoniae*, and *Klebsiella pneumoniae*, commonly associated with lower respiratory infections, bloodstream infections and intra-abdominal infections.[20] The main contributors to AMR in Vietnam are the overuse of antimicrobial drugs in agriculture, as well as animal and human health – including both hospitals and the community.[21]

In 1986, deregulation of the retail medication trade and privatisation of pharmaceutical industry saw an increase in private pharmacies from zero to 6000 in seven years, to 62500 in 2019, translating to a massive increase in consumption, especially in antibiotics.[22,23] Despite a national law enacted in 2005

requiring suppliers to dispense antibiotics only with a prescription, they remain readily available over the counter due to a lack of enforcement. Additionally, inappropriate prescribing of antimicrobials that are too broad-spectrum, or when not required, further drives resistance through continuous antibiotic selection pressure.[9,21]

Surveillance data highlight the growing burden of AMR in Vietnam, with resistance increasing across multiple pathogens. A nationwide AMR surveillance study conducted in 13 tertiary hospitals compared bacterial isolates from 2012-2013 with those from 2016-2017. The study reported increased prevalence of resistant *Pseudomonas aeruginosa ,* Enterobacterales, and carbapenem-resistant *Acinetobacter baumanii.*[24] Additionally, common respiratory pathogens responsible for community-acquired pneumonia, *Streptococcus pneumoniae* and *Haemophilus influenzae*, exhibited higher resistance to commonly used antibiotics.[24] Longitudinal studies in rural Vietnam further illustrate this trend. Resistance in *Streptococcus pneumoniae* to commonly used antibiotics in children more than doubled, increasing from 31% to 80% between 1999 and 2014.[25] A multi-country study across four Asian countries confirmed that these respiratory pathogens had the lowest susceptibility to common antibiotics in Vietnam, indicating the highest resistance rates.[26]

Carbapenem resistance is also an increasing concern. A large study of 2,000 inpatients across 12 Vietnamese hospitals found that over half were colonised with carbapenem-resistant *Enterobacterales* (CRE). [27] Hospitalisation duration, hospital-acquired infections, and prior carbapenem treatment were identified as independent risk factors for colonisation, highlighting the hospital environment as a key area of focus for targeted interventions. Beyond healthcare settings, the spread of AMR has also been demonstrated in the broader ecosystem, as a systematic review demonstrated high levels of resistance in *Escherichia coli* and non-typhoidal Salmonella across samples from humans, animals and the environment in Vietnam.[28] Although these studies

demonstrate the landscape of AMR in Vietnam, data remains limited in certain settings.[21] Surveys of AMR in Vietnam have predominantly been undertaken at a small number of tertiary healthcare facilities, which are not representative of the national healthcare system. In particular, the prevalence of AMR has not been studied in detail within lower levels of the Vietnamese healthcare. Genomic studies aimed at understanding the prevalence and diversity of resistance mechanisms in multidrug-resistant organisms in Vietnam also remain limited.

One study identified a high prevalence of ESBL-producing organisms and carbapenem-resistant *Klebsiella pneumoniae* among intensive care unit inpatients at two hospitals in Hanoi. Notably, isolates from both hospitals carried an identical array of AMR genes, despite being geographically and clinically separate, suggesting the endemic circulation of this strain within Hanoi.[29] Further genomic studies would be useful to characterise the genetic diversity, evolution, and transmission pathways of resistant bacteria in Vietnam, which could provide valuable insights into their persistence and spread.

National and global responses to antimicrobial resistance

Given the widespread impact of AMR in Vietnam and globally, along with its ease of transmission across borders, effective mitigation will require coordinated efforts at global, national, and local levels. Global organisations, such as the WHO, Food and Agricultural Organisation (FAO), World Organisation for Animal Health (WOAH), and United Nations Environmental Programme (UNEP) provide technical guidance and lead initiatives to combat AMR. Together, they established the Quadripartite Secretariat for One Health to address risks at the human-animal-ecosystems interface.[30]

From a human health perspective, the Global Action Plan (GAP) on AMR was introduced at the May 2015 World Health Assembly, establishing a comprehensive strategy to combat AMR.[31] The GAP outlined five key objectives; improving awareness and education on AMR, strengthening surveillance and research, optimising antimicrobial use in human and animal health, reducing the incidence of infections through effective prevention and control measures, and ensuring sustainable investment in AMR response efforts.[31]

A core component of the GAP was the development of National Action Plans (NAPs), providing countries with a framework to tailor AMR strategies to their specific healthcare systems and challenges. Following its introduction, nations worldwide began formulating NAPs, with a primary focus on enhancing AMR surveillance, promoting antimicrobial stewardship, strengthening infection prevention and control (IPC), and encouraging research into new treatment strategies.[32] A central component in AMR strategies outlined in the GAP and NAPs was antimicrobial stewardship.

Antimicrobial stewardship

Rationale for antimicrobial stewardship programs

Antimicrobial stewardship (AMS) is a coordinated effort to optimize antimicrobial use at individual, national, and global levels, reducing inappropriate antibiotic use in healthcare, agriculture, and in animal health.[33] In healthcare settings, AMS programs implement strategies to minimise unnecessary antimicrobial use and prioritise agents that are less likely to select for resistant microorganisms. This is done in line with treatment guidelines and local susceptibility patterns. Effective AMS programs not only reduce inappropriate antimicrobial use, but also improve patient outcomes and reduce adverse consequences of antimicrobial use (including antimicrobial resistance,

toxicity and unnecessary costs).[34] Along with IPC and surveillance, AMS programs are a key strategy in preventing AMR and decreasing preventable infections.[34]

Evidence for the effectiveness of AMS programs

AMS frameworks have been implemented in over 177 countries, encompassing over 90% of the global population.[35] A Cochrane review including 221 studies from around the world found high-certainty evidence that AMS interventions improved the alignment between antibiotic prescribing and local guidelines, and reduced duration of antibiotic treatment.[36] AMS interventions also reduced length of inpatient stay and did not show a difference in mortality. A meta-analysis of 145 studies found that certain AMS activities improved patients outcomes, including promotion of guideline-adherent empirical therapy, timely de-escalation of antibiotics, switching from intravenous to oral antibiotic therapy, therapeutic drug monitoring, restricted use of broad spectrum and second-line antibiotics, as well as providing Infectious Diseases specialist bedside consultation for severe infections.[37] Guideline-adherent empirical prescribing also led to a 35% relative risk reduction in mortality. A more recent systematic review of 52 studies showed that AMS interventions reduced antimicrobial consumption by 28% and antibiotic prescriptions by 10% in hospitals, general practice and nursing home settings.[38]

An important limitation of most published reviews of AMS interventions is that most included studies were undertaken in high-income countries, where policy regulation, resources for surveillance, education and training infrastructure were more robust. In contrast, evidence for the effectiveness of AMS programs in low- and middle-income countries was less certain. A systematic review of 27 studies from 2 low-income and 11 middle-income countries showed that while the majority of interventions reported a positive effect, most studies were of low quality.[39] Community-based

studies on AMS interventions are limited, but a narrative review found that education-based interventions for community healthcare workers and the public were most effective in this setting.[40]

Key elements of antimicrobial stewardship

Effective AMS requires several key elements to ensure its successful implementation. The WHO policy guidance document on establishing integrated AMS activities outlines a framework consisting of five key pillars, which encompass essential interventions and strategies rooted in public health principles (Figure 1.2)[41]

Figure 1.2: WHO list of integrated AMS interventions and activities in healthcare and community settings

PILLAR 1: **Establish and develop national coordination mechanisms for antimicrobial stewardship and develop guidelines**
1. Establish and maintain a national coordinating mechanism for AMS that is functional at national, subnational and district levels.
2. Develop national treatment and stewardship guidelines, standards and implementation tools.
PILLAR 2: **Ensure access to and regulation of antimicrobials**
3. Improve access to essential, quality-assured, safe, effective and affordable antimicrobials.
4. Regulate social triggers and remuneration policies that promote responsible antimicrobial prescription and dispensing behaviours.
5. Legislate and regulate responsible and appropriate use and disposal of antimicrobials.
PILLAR 3: **Improve awareness, education and training**
6. Improve awareness and engagement to support behavioural change of antimicrobials use.
7. Strengthen health worker capacity through the provision of tailored education and training packages according to health worker roles and functions.
PILLAR 4: **Strengthen water, sanitation and hygiene and infection prevention and control**
8. Enhance WASH in health facilities and communities.
9. Implement IPC core components in health facilities.
PILLAR 5: **Surveillance, monitoring and evaluation**
10. Surveillance of antimicrobial use and consumption.
11. Surveillance of AMR.
12. Monitoring and evaluation of AMS activities.

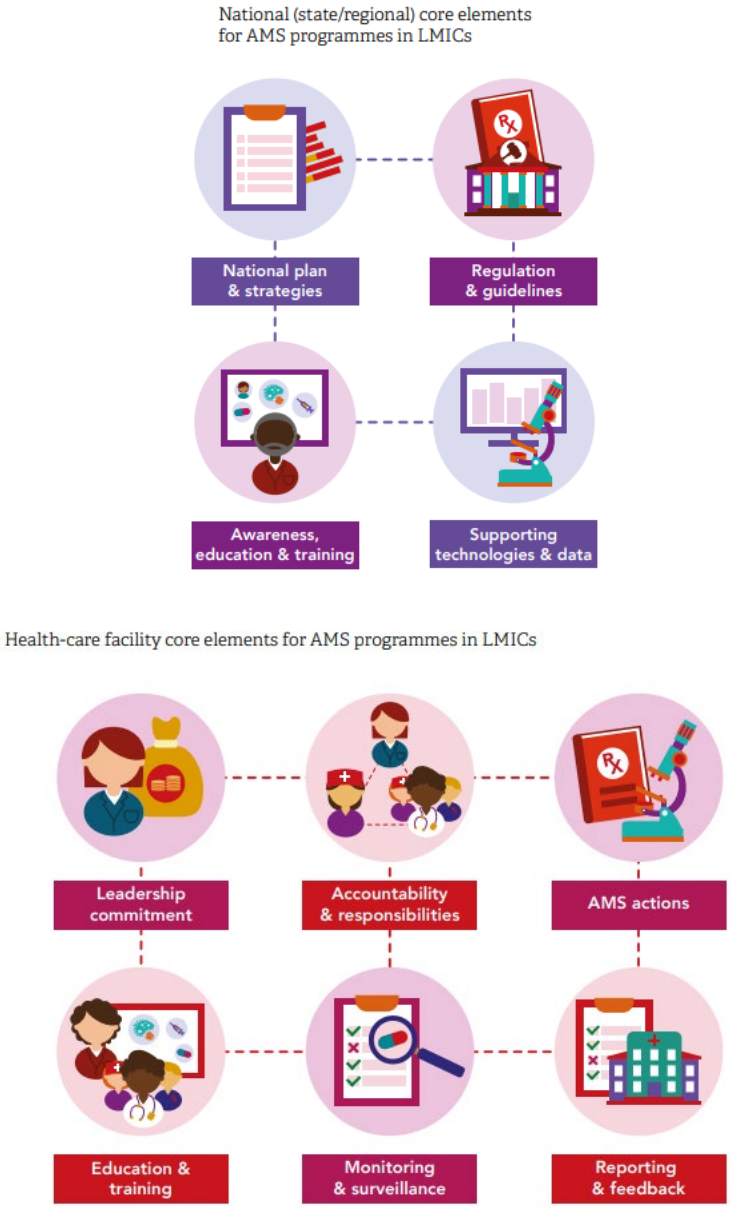
(From World Health Organisation, Integrated AMS activities[41])

To support AMS implementation, WHO has developed several tools and resources. The "*WHO Practical Toolkit for AMS Programmes in Healthcare Facilities in Low- and Middle-Income Countries*" provides step-by-step guidance to help LMICs establish AMS programs in healthcare settings,[33] making it particularly relevant to Vietnam. Additionally, the WHO AWaRe (*Access, Watch, Reserve*) classification of antibiotics categorises antibiotics based on their impact on AMR,[42] serving as a valuable tool for antibiotic use surveillance.

At the national level, implementation of AMS in resource-limited settings begins with the development of a national action plan and localising AMS strategies.[33] Priority areas include the regulation and enforcement of prescription-only dispensing of antibiotics, promoting awareness, training and education at healthcare facilities, and supportive technologies such as access to diagnostics and surveillance data. Figure 1.3 shows the essential components that need to be in place for the effective implementation of AMS at the national level and healthcare facility level in LMICs.

However, structural policies alone are not sufficient. Successful AMS programs require sustained behaviour change among prescribers and healthcare workers.[43] The unifying goal of all AMS interventions is to foster long-term improvements in antimicrobial prescribing practices. Organisational culture and hierarchy play a critical role in shaping prescribing behaviour, influencing how AMS principles are adopted in clinical practice.[43] To drive meaningful change, interventions must ensure that staff not only possess the necessary knowledge and capability to implement AMS, but also have the motivation to change and access to tools and educational resources that support new prescribing behaviours.[44] Building on these key elements and tools, AMS programs employ a range of targeted interventions to improve antimicrobial use and AMR.

Figure 1.3: Core elements identified in the WHO Practical Toolkit for setting up AMS in healthcare facilities in LMICs



(From *WHO Practical Toolkit for AMS Programmes in Healthcare Facilities in Low- and Middle-Income Countries* 2019)[33]

AMS interventions

A wide variety of AMS interventions have been developed to address specific challenges in antimicrobial use and resistance. These can be categorised into three main groups: “enablement,” “persuasive,” and “restrictive” approaches, each influencing prescriber behaviour through distinct mechanisms.[34]

Enablement strategies

Enablement or structural strategies focus upon providing prescribers with the tools, resources, and support needed to prescribe appropriately. These approaches enable healthcare providers to access the information necessary to make evidence-based antibiotic choices. Approaches include increasing access to quality-assured laboratory testing for microscopy, culture, and antimicrobial susceptibility testing on clinical samples. These diagnostic tools enable accurate pathogen identification and support tailored antibiotic treatment. Increased access to other diagnostic tests, such as basic blood tests (e.g., complete blood count, inflammatory markers) and radiological investigations (e.g., chest X-rays, ultrasounds) can help to confirm bacterial infections and rule out non-bacterial causes, reducing unnecessary empirical antibiotic use.[33]

The establishment of AMS committees, teams, or local champions with in-depth knowledge of the local healthcare environment enable the implementation of AMS activities that are well-suited to the facility's specific needs. A qualitative study examining the cultural and contextual determinants of AMS programs found that the appointment of local champions and leaders in AMS had the ability to overcome entrenched hierarchical cultures that impact prescribing in hospitals in LMICs.[45] These local leaders serve as key influencers, fostering a culture of engagement and collaboration among healthcare workers to ensure AMS practices remain contextually relevant and effectively implemented.

Persuasive strategies

Persuasive strategies influence prescribers by improving their knowledge, attitudes, and decision-making regarding antimicrobial prescribing.[46] These strategies rely on education, feedback mechanisms, and clinical decision support to promote more rational prescribing behaviour.[34] Most research evaluating AMS in LMICs focus upon persuasive AMS strategies.[36,47] Programs that included a feedback process revealed greater effectiveness compared to any other type of combination of intervention strategies.[36]

Among persuasive interventions, antimicrobial treatment guidelines are the most widely used and impactful, particularly in LMICs,[36,47] where resource constraints often limit access to advanced diagnostic tools. Well-designed guidelines provide structured, evidence-based recommendations to guide appropriate antibiotic selection, dosage, duration, and route of administration for common infections. To maximize their effectiveness, it is crucial that guidelines remain regularly updated and aligned with local or national antimicrobial susceptibility patterns whenever possible.[33] Additionally, integrating AMS principles into guidelines—such as recommendations for de-escalation, narrowing therapy, and avoiding unnecessary broad-spectrum use—can help reduce selection pressure while ensuring optimal patient outcomes.[33] Ensuring accessibility and implementation is equally important. Incorporating guidelines into electronic prescribing systems or clinical decision support systems enhance their use in clinical practice.[48]

Another important intervention in this category is audit and feedback. Regular audit and feedback sessions involve AMS teams assessing prescribers' antibiotic use patterns and providing constructive input to improve prescribing practices. Prospective audit and feedback allow real-time review of antimicrobial prescriptions against antimicrobial guidelines, enabling immediate interventions to adjust therapy, discontinue unnecessary antibiotics, or switch to narrower-spectrum agents.

Retrospective feedback, based on periodic prescribing data analysis, helps identify long-term trends and areas for improvement. Feedback can be delivered in various formats, including individualised discussions on a case-by-case basis, group or departmental sessions, and benchmarking reports comparing prescriber behaviour against hospital or national guidelines. Studies show that ongoing audit and feedback interventions significantly improve adherence to antimicrobial guidelines, leading to a measurable reduction in inappropriate antibiotic use.[36,49]

Clinical pharmacists, especially those with specialised training in AMS, play an important role in undertaking periodic post-prescription reviews. Pharmacist-led interventions have been shown to improved adherence to guidelines and reduced inappropriate prescribing, antimicrobial consumption, length of stay, and antimicrobial-associated *Clostridioides difficile* infection.[50,51]

Other persuasive strategies include educational initiatives, such as workshops, seminars and online training modules. These are designed to increase awareness of AMR, educate prescribers on usage of antimicrobial guidelines as well as apply principles of AMS. Additionally, integrating AMS principles into medical and pharmacy training programs ensure that future prescribers develop a strong foundation in rational antibiotic use, further strengthening AMS efforts in the long term. By focusing on changing the prescribing culture of medical practitioners, persuasive strategies promote sustainable improvements in antimicrobial use, while fostering a sense of accountability.

Restrictive strategies

Restrictive strategies enforce controls upon antimicrobial use by limiting access to certain antibiotics or mandating adherence to specific prescribing rules.[46] Key restrictive approaches include formulary restrictions, where access to certain antimicrobials is limited to specific indications or only with

approval by infectious disease specialists or AMS-trained pharmacists, and mandatory order forms, requiring prescribers to provide justification for antibiotic use. Additionally, the use of automatic stop orders help prevent unnecessary prolonged antibiotic use by setting predefined durations, particularly for settings such as surgical prophylaxis.[33]

While these strategies are effective in reducing unnecessary antibiotic use,[36] they require careful oversight to prevent unintended consequences, such as delays in patient access to appropriate treatment. Although restrictive interventions often lead to rapid reductions in antibiotic consumption, evidence suggest that their effectiveness plateaus after six months, with persuasive and restrictive interventions showing comparable long-term impact.[33] Furthermore, a systematic review comparing bundled AMS interventions with and without restrictive components found no significant difference in antimicrobial usage or the prevalence of multidrug-resistant organism carriage.[52]

Figure 1.4: Categories of antimicrobial stewardship interventions, including exemplar

INTERVENTION	WHAT IT IS
Persuasive (education)	• Educational meetings (e.g. basics on antibiotic use, case-based discussions, morbidity and mortality, significant event analysis, lectures on specified topics) • Distribution of and training on educational material (e.g. clinical practice guidelines) • Using local key opinion leaders (champions) to advocate for key messages • Reminders provided verbally, on paper or electronically • AMS e-learning resources made available to all health-care personnel • AMS education as part of continuing medical education
Persuasive (feedback)	• Audit with feedback to prescribers on their prescribing practice • AMS as a component of ward rounds (real-time feedback with educational component) • Patient handover meetings between two shifts with real-time feedback by consultants • Local consensus processes for changes in antibiotic treatment or surgical prophylaxis
Restrictive	• Formulary restrictions • Restricted prescribing of identified antibiotics (expert approval prior to prescription) (see Annex V) • Compulsory order forms for targeted antibiotics • Automatic stop orders (e.g. after a single dose of surgical prophylaxis) • Selective susceptibility reporting from the lab
Structural	• Rapid laboratory testing made available • Therapeutic drug monitoring

(From *WHO Practical Toolkit for AMS Programmes in Healthcare Facilities in Low- and Middle-Income Countries* 2019)[33]

Bundled interventions

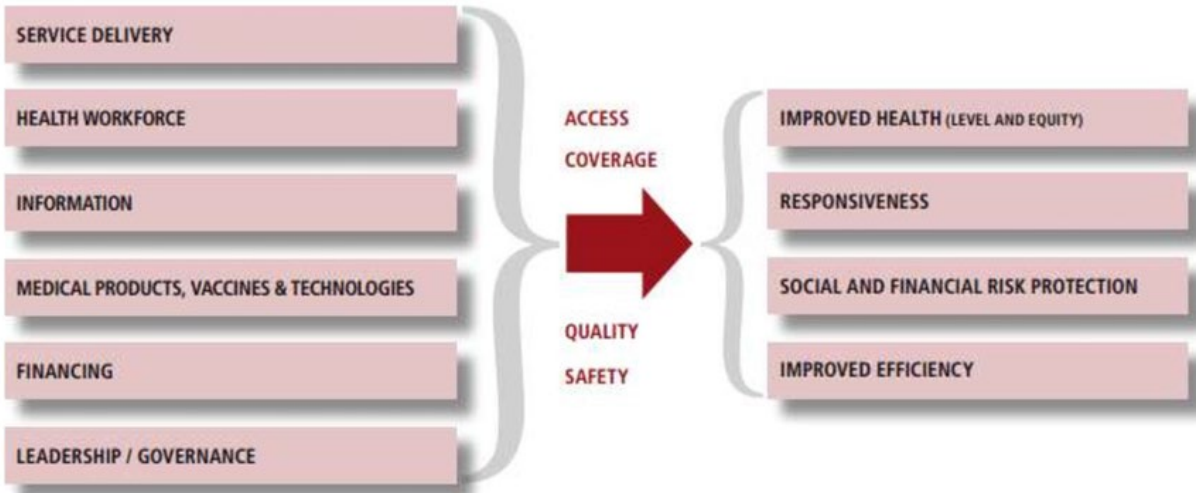
Effective AMS programs often combine these three approaches together to achieve the best outcomes. For example, in some healthcare settings, access to microbiological testing complements restrictive measures such as antibiotic formulary controls. Persuasive strategies can ensure that prescribers are educated and engaged with the AMS principles in their patient care, when other approaches are also adopted. Together, these strategies create a comprehensive framework for optimising antimicrobial use and reducing AMR, tailored to the specific needs and capacities of healthcare settings.

It's important to note that while bundled AMS interventions demonstrated effectiveness, disaggregating the individual contributions of each component can be challenging. This complexity makes it difficult to determine the specific impact of each approach within the bundle, highlighted in a few studies.[36,39,47]

Challenges in implementation of antimicrobial stewardship in resource-limited settings: A health system perspective

LMICs face significant challenges in implementing AMS programs, which can be assessed using the WHO health system building blocks framework for healthcare delivery.[53] This framework consists of six key components: leadership and governance, service delivery, human resources, medicines and technologies, financing, and information systems (Figure 1.5). The ability of LMICs to establish AMS programs varies widely, with some countries still in the early stages, requiring foundational investments, while others have systems in place that facilitate AMS integration into existing healthcare practices.[54] To effectively implement AMS programs, policymakers must address all six WHO building blocks.

Figure 1.5: WHO building blocks framework for healthcare delivery



(Source: Measuring the health systems impact of disease control programmes: A critical reflection on the WHO building blocks framework, 2014[55])

Leadership and governance

A lack of clear policies and national coordination can significantly impede AMS implementation. Weak regulatory frameworks for example, may fail to restrict the over-the-counter sale of antibiotics, leading to widespread self-medication and antibiotic misuse in communities.[56] In many LMICs, there is limited political commitment to AMS, with governance structures lacking enforcement mechanisms to regulate antibiotic distribution and prescribing.[57] Strengthening leadership at the national and facility levels, alongside multisectoral collaboration, is critical to advancing AMS policies.

Service delivery

Integrating AMS into routine patient care is challenging in resource-limited settings due to overburdened healthcare systems, workforce shortages, and inadequate infrastructure. Many LMICs face limited access to diagnostics, poor IPC, and inconsistent antimicrobial use monitoring. AMS interventions at the community level also pose a challenge. Addressing these barriers through capacity-building, integrated AMS policies in healthcare workflows, and community-focused

strategies, such as pharmacy-led interventions and patient education, is crucial for sustainable AMS implementation.

Human resources

A critical barrier to AMS in LMICs is the shortage of trained healthcare professionals with expertise in infectious diseases, clinical microbiology, and AMS principles.[58] Pharmacists, who play a key role in stewardship programs, also have varying levels of formal training and skills development in AMS, but even when trained, their skills are often underutilised. High patient load and limited time for AMS interventions further exacerbate the human resource challenges. Addressing these gaps require investment in AMS training programs and the integration of AMS in medical, nursing and pharmacy curricula at university-level education.[54]

Medicines and technologies

Access to quality-assured antibiotics remains a significant challenge in LMICs, with an estimated 17% of the global antibiotic supply being substandard or falsified, contributing to treatment failure and AMR.[59,60] Drug shortages further exacerbate the issue, as essential antibiotics are often insufficient to meet public health needs due to unpredictable demand, fragile supply chains, and poor economic incentives.[61] Limited access to microbiology services further hinders susceptibility-guided prescribing, often leading to inappropriate broad-spectrum antibiotic use. Strengthening supply chain systems, ensuring the availability of quality-assured medicines, and expanding access to affordable diagnostic tools are vital to improving AMS efforts in resource-limited settings.

Health financing

AMS programs in LMICs often face significant underfunding due to competing health priorities and a lack of dedicated budgetary support.[54] Many hospitals operate with limited financial resources, making it challenging to establish AMS teams, procure diagnostics, and implement stewardship interventions. In numerous settings, patients rely on out-of-pocket payments for healthcare, leading to self-medication and unrestricted antibiotic purchases. This practice has been strongly correlated with increased antimicrobial resistance in LMICs.[62] Addressing these financial barriers require integrating AMS into existing health budgets and promoting cost-effective stewardship interventions that align with resource constraints.

Information systems

Finally, effective AMS relies on robust health information systems to monitor antimicrobial use and resistance trends, but many LMICs lack electronic health records as well as integrated surveillance and reporting mechanisms, which hinder AMS implementation. Digitising patient records and integrating AMS metrics into routine hospital reporting systems are useful steps to enhance AMS implementation.

Individual barriers to AMR

Intrinsic factors amongst healthcare workers may also act as barriers to AMS practice. Several factors influence prescriber behaviour and contribute to inappropriate antibiotic use in LMICs. Some physicians underestimate AMR as an immediate threat, leading to complacency in prescribing practices.[63] Fear of patient deterioration can drive defensive prescribing, even in cases where bacterial infection is unconfirmed, increasing unnecessary antibiotic use.[63] Hierarchical influences also shape prescribing habits, as junior doctors tend to follow senior physicians' prescribing patterns,

which may not always align with AMS guidelines.[45] Additionally, physician autonomy and uncertainty in the absence of drug susceptibility data often lead to a preference for broad-spectrum antibiotics over narrow-spectrum alternatives.[63] Addressing these challenges require targeted interventions as described above.

Broader Determinants of AMR in Healthcare and Beyond

Infection prevention and control

Infection prevention and control (IPC) is crucial in combating AMR within healthcare facilities by reducing the spread of resistant pathogens between patients, healthcare workers and the facility environment, thus minimising the need for antibiotic use.[64] Effective IPC measures include hand hygiene, environmental cleaning, patient isolation, outbreak containment strategies and adherence to standard precautions. [65,66] These measures help prevent healthcare-associated infections (HAIs), which are often caused by multidrug-resistant organisms (MROs). By reducing infections, IPC decreases the demand for antibiotics, thereby lowering antibiotic selective pressure that drives resistance.[11] IPC and AMS have been likened to the two sides of the same coin, both striving to reduce AMR prevalence and improve healthcare quality.[33] Their interdependence has been demonstrated in studies showing that IPC and AMS programs, when implemented together, are more effective than AMS interventions alone.[67]

One Health and AMR

Another important consideration in this discussion is the contribution of extensive use of antimicrobials in agriculture, livestock, and aquaculture to AMR. Antimicrobials are not only used to treat infections, but also as growth promoters and preventative measures against disease.[68] This practice contributes to presence of antimicrobial residues in animal-derived products and the

environment, which then can transfer to humans through direct contact, consumption of contaminated food, or environmental pathways such as water and soil contamination.[69] Notably, bacteria can acquire resistance genes via horizontal gene transfer (HGT), a process where genetic material is exchanged between organisms that can subsequently be spread between human, animal, and environmental reservoirs.[70] This genetic exchange exacerbates the challenge of AMR across different sectors.

Given the complex and interconnected nature of AMR transmission, interventions limited to one sector alone are unlikely to be effective, necessitating a coordinated, multisectoral response. The "One Health" approach is an integrated, unifying approach that aims to sustainably balance and optimise the health of people, animals and ecosystems by recognising that they are all inherently linked and interdependent.[71] In the area of AMR, the "One Health" approach promotes responsible antimicrobial use, strengthen surveillance systems, and foster collaboration among stakeholders to reduce AMR transmission across all sectors at the same time.[10] This holistic strategy is essential to the long term preservation of antibiotics.

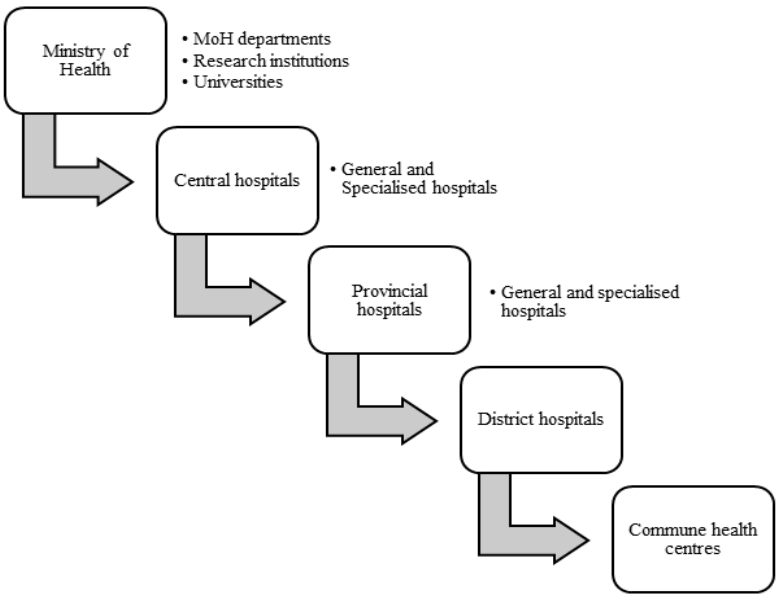
Antimicrobial Stewardship in Vietnam

Vietnam's National Action Plan against AMR

Vietnam was one of the first countries in the WHO Western Pacific Region to adopt a NAP to combat drug resistance in 2013.[72] Key strategies of the initial NAP focused on human health and included (a) improving policy and management, (b) promoting information, education and communication, (c) reinforcing technical expertise, (d) training the healthcare workforce, (e) financing, and (f) enhancing research and international cooperation. A central component of the NAP was AMS.[72]

Since 2013, subcommittees were set up to implement the NAP healthcare settings from national to district level. Drug and Treatment councils were set up to enforce management and use of drugs within the hospital.[73] Decision 4041/QD-BYT, an initiative to ensure all antibiotics are dispensed with a prescription was launched in 2017.[74] Tertiary courses and specialist training of healthcare professionals were introduced. National manuals about antibiotic use, diagnostic testing and infection control were developed. A technical guideline on setting up AMS for hospitals at all levels was released in 2016, titled "Decision 772/QD-BYT", requiring every hospital to establish a formal AMS team to oversee antibiotic monitoring and AMS activities.[75] AMS teams were formed, and AMR surveillance began in mainly tertiary sites, but not uniformly. In 2017, a specific NAP on AMR in livestock and aquaculture was released to provide guidance on antimicrobial use and AMR from a One Health perspective.[76] On December 31st, 2020, Decision 5631/QD-BYT replaced Decision 772 and built on guidance by providing more detailed instructions on setting up an AMS program and expanding the scope of activities to be implemented across all levels of hospitals.[77] Figure 1.6 demonstrates the organisational structures of hospitals in the Vietnamese healthcare system.

Figure 1.6 : Overview of the organisation of the Vietnamese health care system



(Source: Ha et al. 2015) [78]

While Vietnam's NAP on AMR provided a policy framework for AMS initiatives, its implementation has faced significant challenges, leaving many objectives unmet.[73] A 2024 scoping review identified barriers for implementation of the NAP using WHO's health system building blocks framework (Figure 1.7).[73] The latest iteration, titled "The National Strategy on the Prevention of Antimicrobial Resistance 2023–2030, with a vision to 2045"[79] adopts a broad One Health approach towards curbing AMR, integrating efforts between human health, agriculture and the environment. This updated strategy includes additional funding for AMS implementation, enhances education and training for healthcare and veterinary professionals, strengthens national surveillance of AMR and antimicrobial use in both healthcare and agriculture, and promotes AMS programs, including public awareness initiatives across human and animal health.[80]

Figure 1.7: Barriers for implementation of National Action Plan against AMR 2013-2020

Six blocks of activities	Implementation status	Barriers
Leadership/governance	Released the policy/action plan (NAPCA) Establish working groups Run project 4041	Cooperation among implementation bodies was not good Project objective was not feasible
Health workforce	National manual on antibiotic use, a manual on clinical microbiology testing techniques, and several guidelines on infection control were developed and used in short courses for practicing doctors and pharmacists at national and provincial hospitals	The doctor, pharmacist and other health professionals at the district and lower levels had less chance to get training on AMR topics compared to those working in provincial and national hospitals
Medications and technologies	Government agencies issued regulations indicate that antibiotics only sold under prescription	Antibiotics can still be bought and sold freely in almost all retail pharmacies throughout the country Imported drugs were preferred to locally-manufactured drugs because of the belief that the former are always of better quality
Service delivery	Up to 2019, half of hospitals from national to district levels in Vietnam had formed an AMS team A small number of Vietnamese hospitals have taken proactive steps in introducing AMS to implement the NAPCA in their facilities	The shortages in human resource at both higher- and lower-level hospitals
Health financing	Expenditure on antibiotics comprised one third of total drug costs	Perverse incentives exist that may drive inappropriate antibiotic use
Information	An AMR surveillance system extracting data from project hospitals was established and operated during the period of 2013 to 2016 Communication plan for AMR prevention is issued annually and its objectives are customised for each period	AMR surveillance system experienced delays in data submission from several hospitals to the MOH. Some hospitals did not find the feedback resulted in benefits to them

(Source: *Pham et.al* 2024)[73]

Implementation of AMS

Two studies examining the implementation of Vietnam's NAP against AMR revealed that, despite government mandates, AMS adoption across the country remains limited.[73,81] Three years after the introduction of "Decision 772/QD-BYT", only 50% of hospitals had established AMS teams.

Antimicrobial treatment guidelines varied vastly between hospitals and often compromised on stewardship principles.[73]

While some hospitals – particularly tertiary facilities – took proactive steps to integrate AMS, implementation has been inconsistent. In Ho Chi Minh city, a city-wide action plan was developed based on the NAP. This included the creation of an antibiotic guideline tailored to local antibiograms, which was distributed for use across hospitals in the region.[73,82] Several studies have explored AMS implementation in Vietnam, spanning situational analyses of hospitals, identification of AMS capacities and barriers, as well as the execution of AMS activities such as education and training, guideline development, audit and feedback, and the establishment of AMS committees.[83-86]

Additionally, research has evaluated the impact of AMS interventions in Vietnamese hospitals on various outcomes, including antimicrobial consumption, appropriateness of antimicrobial prescriptions, compliance with guidelines, costs, length of stay, and mortality rates.[87-89] However, significant evidence gaps remain. Most studies have focused on tertiary settings, leaving limited data on AMS effectiveness in district and commune-level facilities. Even less is known about AMS implementation in Vietnam's private healthcare sector. Furthermore, the quality of existing studies is often low, with very few randomised controlled trials (RCTs) on AMS interventions conducted in Vietnam. The implementation of AMS interventions in Vietnam will be further explored in the next chapter.

VRESIST program of research

Preliminary work contributing to this thesis was undertaken in Vietnam as a part of the VRESIST studies. This four-year program of research was funded by the Australian Department of Foreign

Affairs and Trade (DFAT). This included formative studies of clinical practice regarding antimicrobial use in private pharmacies across Vietnam.[73,90-92]

The sub-studies that were implemented preceding this thesis included: (1) Mapping access to pharmacy services in Vietnam which assessed the distribution of drug outlets and the sociodemographic characteristics of the communities they serve[90] (2) A qualitative study among different stakeholders to understand drivers of antibiotic use in Vietnam which helped in implications for designing community interventions[91] (3) Standardised patient surveys to assess antibiotic supply at the community pharmacies settings in Vietnam for different viral and bacterial infections[92] and (4)Assessing health system barriers to the implementation of the national action plan to combat antimicrobial resistance in Vietnam.[73] The studies comprised of 1,972 drug outlets, in four provinces in Vietnam, covering a total population of 1.96 million people.

Objectives of this thesis

Overall objective

The overall aim of this thesis was to assess the extent of AMR in district hospitals by evaluating antimicrobial consumption, the appropriateness of antimicrobial use, and the prevalence of multidrug-resistant organism (MRO) carriage among inpatients. Additionally, this research aimed to assess the effect of implementing an AMS program on these outcomes. Each chapter of this thesis presents research projects that examine these key measures and evaluate the effectiveness of AMS interventions in district hospitals in Vietnam.

Specific objectives

Specifically, the objectives of this thesis were:

Chapter 2: To determine the current landscape of AMS interventions in Vietnam by conducting a systematic review and meta-analysis synthesising evidence across three important key determinants of AMR in human health: antimicrobial consumption, appropriateness of antimicrobial use, as well as the presence and impact of AMS interventions on measured clinical outcomes.

Chapter 3(VRESIST B Study): To determine the feasibility and effectiveness of implementing an AMS intervention package in four district hospitals in a before-and-after study by analysing antimicrobial consumption and the appropriateness in antimicrobial prescribing before and after a six-month period of a bundled AMS intervention program.

Chapter 4: To evaluate the prevalence of multidrug-resistant (MRO) carriage and their antibiotic susceptibility profile in inpatients and assess if there was a change between before and after AMS interventions. This was conducted at the four district hospitals in Chapter 3.

Chapter 5 (VRESIST C Study): To assess the effect of an AMS program on antimicrobial consumption and appropriateness in antimicrobial prescribing in 16 district hospitals using a cluster randomised controlled trial design with a cross-over period at the end. We measured the “difference in differences” in these outcomes before and after the AMS intervention, between the intervention and control group hospitals.

Finally in **Chapter 6**, we summarise the findings from all the chapters on the impact of implementing AMS interventions in district hospitals, identify enablers and barriers to AMS implementation in Vietnam, and discussed policy implications of the findings of this research.

In the appendix, the abstract of a poster presentation on the difference in knowledge, attitudes and practices of healthcare workers on prescribing antibiotics before and after AMS interventions in the four district hospitals was included. Another poster presenting findings from Chapter 3 is also included in the appendix.

References for Chapter 1

1. Hutchings MI, Truman AW, Wilkinson B. Antibiotics: past, present and future. *Current Opinion in Microbiology* 2019; **51**: 72-80.

2. World Health Organisation. Antimicrobial resistance fact sheet. 2023. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance (accessed 15/7/2024).

3. Salam MA, Al-Amin MY, Salam MT, et al. Antimicrobial Resistance: A Growing Serious Threat for Global Public Health. *Healthcare (Basel)* 2023; **11**(13).

4. World Health Organization. Global Antimicrobial Resistance and Use Surveillance System(GLASS)/GLASS-AMR Module. 2020. https://www.who.int/initiatives/glass/glass-routine-data-surveillance (accessed 16/04/2023).

5. Reygaert WC. An overview of the antimicrobial resistance mechanisms of bacteria. *AIMS Microbiol* 2018; **4**(3): 482-501.

6. Darby EM, Trampari E, Siasat P, et al. Molecular mechanisms of antibiotic resistance revisited. *Nature Reviews Microbiology* 2023; **21**(5): 280-95.

7. World Health Organisation. WHO Bacterial Priority Pathogens List, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. . 2024. https://iris.who.int/bitstream/handle/10665/376776/9789240093461-eng.pdf?sequence=1 (accessed 20/02/2025).

8. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-Resistant Enterobacteriaceae: Epidemiology and Prevention. *Clinical Infectious Diseases* 2011; **53**(1): 60-7.

9. Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance--the need for global solutions. *The Lancet Infectious Diseases* 2013; **13**(12): 1057-98.

10. Food and Agriculture Organization of the United Nations. Antimicrobial resistance. 2024. https://www.fao.org/antimicrobial-resistance/en/ (accessed 10/11/2024).

11. World Health Organisation and UNICEF. Combatting Antimicrobial Resistance through Water, Sanitation and Hygiene and Infection Prevention and Control in Healthcare. 2020. https://www.washinhcf.org/resource/combatting-amr-through-wash-and-ipc-in-healthcare/ (accessed 21/01/2025).

12. Wang M, Xu X, Wu S, et al. Risk factors for ventilator-associated pneumonia due to multi-drug resistant organisms after cardiac surgery in adults. *BMC Cardiovascular Disorders* 2022; **22**(1): 465.

13. Bokhary H, Pangesti KNA, Rashid H, Abd El Ghany M, Hill-Cawthorne GA. Travel-Related Antimicrobial Resistance: A Systematic Review. *Trop Med Infect Dis* 2021; **6**(1).

14. Murray CJL, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet* 2022; **399**(10325): 629-55.

15. Naghavi M, Vollset SE, Ikuta KS, et al. Global burden of bacterial antimicrobial resistance 1990-2021: a systematic analysis with forecasts to 2050. *The Lancet* 2024; **404**(10459): 1199-226.

16. Jonas OB, Irwin A, Berthe FCJ, Le Gall FG, Marquez PV, Group) WB. Drug-resistant infections : a threat to our economic future (Vol. 1 of 2) : executive summary (English). 2017. http://documents.worldbank.org/curated/en/455311493396671601 (accessed.

17. Waddington C, Carey ME, Boinett CJ, Higginson E, Veeraraghavan B, Baker S. Exploiting genomics to mitigate the public health impact of antimicrobial resistance. *Genome Medicine* 2022; **14**(1): 15.

18. Sulis G, Sayood S, Gandra S. Antimicrobial resistance in low- and middle-income countries: current status and future directions. *Expert review of anti-infective therapy* 2022; **20**(2): 147-60.

19. World Health Organization. Antimicrobial resistance - Western Pacific -Viet Nam. 2024. https://www.who.int/vietnam/health-topics/antimicrobial-resistance (accessed 16/08/2022).

20. Global Research on Antimicrobial Resistance (GRAM) IfHMaEI, University of Oxford,. The burden of antimicrobial resistance (AMR) in Viet Nam: University of Oxford-IHME Strategic Partnership, 2022. https://www.healthdata.org/sites/default/files/2023-09/Viet_Nam.pdf (accessed 12/07/2024).

21. Torumkuney D, Kundu S, Vu GV, et al. Country data on AMR in Vietnam in the context of community-acquired respiratory tract infections: links between antibiotic susceptibility, local and international antibiotic prescribing guidelines, access to medicines and clinical outcome. *Journal of Antimicrobial Chemotherapy* 2022; **77**(Supplement_1): i26-i34.

22. World Health Organization. Antimicrobial resistance in the Western Pacific Region: a review of surveillance and health systems response: WHO Regional Office for the Western Pacific; 2015. (accessed 13/03/2023).

23. Mendiratta A. Vietnam Pharmacy Retail Market Outlook to 2025; by region: Ken Research, 2020. https://www.kenresearch.com/industry-reports/vietnam-pharmacy-retail-market (accessed.

24. Vu TVD, Choisy M, Do TTN, et al. Antimicrobial susceptibility testing results from 13 hospitals in Viet Nam: VINARES 2016–2017. *Antimicrobial Resistance & Infection Control* 2021; **10**(1): 78.

25. Larsson M, Nguyen HQ, Olson L, Tran TK, Nguyen TV, Nguyen CTK. Multi-drug resistance in Streptococcus pneumoniae among children in rural Vietnam more than doubled from 1999 to 2014. *Acta Paediatr* 2021; **110**(6): 1916-23.

26. Torumkuney D, Van P, Thinh L, et al. Results from the Survey of Antibiotic Resistance (SOAR) 2016–18 in Vietnam, Cambodia, Singapore and the Philippines: Data based on CLSI, EUCAST (dose-specific) and pharmacokinetic/pharmacodynamic (PK/PD) breakpoints. *Journal of Antimicrobial Chemotherapy* 2020; **75**(Supplement_1): i19-i42.

27. Tran DM, Larsson M, Olson L, et al. High prevalence of colonisation with carbapenem-resistant Enterobacteriaceae among patients admitted to Vietnamese hospitals: Risk factors and burden of disease. *Journal of Infection* 2019; **79**(2): 115-22.

28. Phu DH, Wongtawan T, Truong DB, Van Cuong N, Carrique-Mas J, Thomrongsuwannakij T. A systematic review and meta-analysis of integrated studies on antimicrobial resistance in Vietnam, with a focus on Enterobacteriaceae, from a One Health perspective. *One Health* 2022; **15**: 100465.

29. Pham MH, Hoi LT, Beale MA, et al. Evidence of widespread endemic populations of highly multidrug resistant Klebsiella pneumoniae in hospital settings in Hanoi, Vietnam: a prospective cohort study. *The Lancet Microbe* 2023; **4**(4): e255-e63.

30. World Health Organisation. Quadripartite Secretariat for One Health: One Health initiative. https://www.who.int/teams/one-health-initiative/quadripartite-secretariat-for-one-health (accessed 05/01/2025).

31. World Health Organization. Global Action Plan on Antimicrobial Resistance. 2015. https://www.who.int/publications/i/item/9789241509763 (accessed 15/07/2024).

32. World Health Organisation. WHO implementation handbook for national action plans on antimicrobial resistance: guidance for the human health sector. 2022. https://www.who.int/teams/surveillance-prevention-control-AMR/nap-amr-implementation-handbook?utm (accessed 01/12/2023).

33. World Health Organisation. Antimicrobial Stewardship programmes in health-care facilties in Low- and Middle-income countries - a WHO practical toolkit. 2019. https://www.who.int/publications/i/item/9789241515481 (accessed 10/01/2023).

34. Australian Commission on Safety and Quality in Health Care. Antimicrobial Stewardship in Australian Health Care. Sydney, Australia: ACSQHC, 202322/11/2024).

35. World Health Organisation. Status of antimicrobial resistance national action plan implementation 2022–2023 and specific human health considerations ahead of the High-level Meeting on AMR to be held at the 79th session of the United Nations General Assembly. 2023. https://cdn.who.int/media/docs/default-source/2021-dha-docs/dg_amr-status-report_wha77_unga_hlm_amr-2024.pdf?sfvrsn=979bcc1b_3&utm (accessed 120/07/2024).

36. Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017; **2**(2): Cd003543.

37. Schuts EC, Hulscher MEJL, Mouton JW, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. *The Lancet Infectious Diseases* 2016; **16**(7): 847-56.

38. Zay Ya K, Win PTN, Bielicki J, Lambiris M, Fink G. Association Between Antimicrobial Stewardship Programs and Antibiotic Use Globally: A Systematic Review and Meta-Analysis. *JAMA Network Open* 2023; **6**(2): e2253806-e.

39. Van Dijck C, Vlieghe E, Cox JA. Antibiotic stewardship interventions in hospitals in low- and middle-income countries: a systematic review. *Bulletin of the World Health Organization* 2018; **96**(4): 266-80.

40. Lam TT, Dang DA, Tran HH, et al. What are the most effective community-based antimicrobial stewardship interventions in low- and middle-income countries? A narrative review. *Journal of Antimicrobial Chemotherapy* 2021; **76**(5): 1117-29.

41. World Health Organisation. WHO policy guidance on integrated Antimicrobial Stewardship Activities. 2021. https://iris.who.int/bitstream/handle/10665/341432/9789240025530-eng.pdf? (accessed 12/11/2024).

42. World Health Organization. The WHO AWaRe (access, watch, reserve) antibiotic book. 2022. https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.04 (accessed 02/07/2024).

43. National Centre for Antimicrobial Stewardship. Antimicrobial Stewardship: Behaviour Change. https://www.ncas-australia.org/behaviour-change (accessed 10/10/2024).

44. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci* 2011; **6**: 42-.

45. Charani E, Smith I, Skodvin B, et al. Investigating the cultural and contextual determinants of antimicrobial stewardship programmes across low-, middle-and high-income countries—A qualitative study. *PloS one* 2019; **14**(1): e0209847.

46. Australian Commission on Safety and Quality in Health Care. Strategies and tools for antimicrobial stewardship - Antimicrobial Stewardship in Australian Health Care. 2018. https://www.safetyandquality.gov.au/sites/default/files/migrated/Chapter3-Strategies-and-tools-for-antimicrobial-stewardship.pdf (accessed 16/08/2024).

47. Mzumara GW, Mambiya M, Iroh Tam PY. Protocols, policies and practices for antimicrobial stewardship in hospitalized patients in least-developed and low-income countries: a systematic review. *Antimicrobial resistance and infection control* 2023; **12**(1): 131.

48. Forrest GN, Van Schooneveld TC, Kullar R, Schulz LT, Duong P, Postelnick M. Use of Electronic Health Records and Clinical Decision Support Systems for Antimicrobial Stewardship. *Clinical Infectious Diseases* 2014; **59**(suppl_3): S122-S33.

49. Xu AXT, Brown K, Schwartz KL, et al. Audit and Feedback Interventions for Antibiotic Prescribing in Primary Care: A Systematic Review and Meta-analysis. *Clinical Infectious Diseases* 2024.

50. Sadeq AA, Hasan SS, AbouKhater N, et al. Exploring Antimicrobial Stewardship Influential Interventions on Improving Antibiotic Utilization in Outpatient and Inpatient Settings: A Systematic Review and Meta-Analysis. *Antibiotics* 2022; **11**(10): 1306.

51. Otieno PA, Campbell S, Maley S, Obinju Arunga T, Otieno Okumu M. A Systematic Review of Pharmacist-Led Antimicrobial Stewardship Programs in Sub-Saharan Africa. *Int J Clin Pract* 2022; **2022**: 3639943.

52. Vicentini C, Blengini V, Libero G, Martella M, Zotti CM. Tailoring Antimicrobial Stewardship (AMS) Interventions to the Cultural Context: An Investigation of AMS Programs Operating in Northern Italian Acute-Care Hospitals. *Antibiotics (Basel, Switzerland)* 2022; **11**(9).

53. World Health Organisation. Monitoring the building blocks of health systems: a handbook of indicators and their measurement strategies. Geneva, Switzerland, 2010. https://iris.who.int/bitstream/handle/10665/258734/9789241564052-eng.pdf (accessed 21/01/2025).

54. Shamas N, Stokle E, Ashiru-Oredope D, Wesangula E. Challenges of implementing antimicrobial stewardship tools in Low to Middle Income Countries (LMICs). *Infection Prevention in Practice* 2023; **5**(4): 100315.

55. Mounier-Jack S, Griffiths U, Closser S, Burchett H, Marchal B. Measuring the health systems impact of disease control programmes: A critical reflection on the WHO building blocks framework. *BMC public health* 2014; **14**: 278.

56. Sachdev C, Anjankar A, Agrawal J. Self-Medication With Antibiotics: An Element Increasing Resistance. *Cureus* 2022; **14**(10): e30844.

57. Pokharel S, Raut S, Adhikari B. Tackling antimicrobial resistance in low-income and middle-income countries. *BMJ global health* 2019; **4**(6): e002104.

58. Pierce J, Apisarnthanarak A, Schellack N, et al. Global Antimicrobial Stewardship with a Focus on Low- and Middle-Income Countries. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2020; **96**: 621-9.

59. Guillermo AZ, Khonsavath B, Vayouly V, et al. Substandard and falsified antibiotics: neglected drivers of antimicrobial resistance? *BMJ global health* 2022; **7**(8): e008587.

60. Gullberg E, Cao S, Berg OG, et al. Selection of resistant bacteria at very low antibiotic concentrations. *PLoS pathogens* 2011; **7**(7): e1002158.

61. Pandey AK, Cohn J, Nampoothiri V, et al. A systematic review of antibiotic drug shortages and the strategies employed for managing these shortages. *Clinical Microbiology and Infection* 2024; **31**(3): 345-53.

62. Alsan M, Schoemaker L, Eggleston K, Kammili N, Kolli P, Bhattacharya J. Out-of-pocket health expenditures and antimicrobial resistance in low-income and middle-income countries: an economic analysis. *The Lancet Infectious diseases* 2015; **15**(10): 1203-10.

63. Mabaya G, Evans JM, Longo CJ, Morris AM. A Behavioral Analysis of Factors That Influence Antibiotic Prescribing in Hospitals: A Metasynthesis of Reviews. *Open forum infectious diseases* 2024; **12**(1).

64. World Health Organisation. Infection prevention and control. 2024. https://www.who.int/health-topics/infection-prevention-and-control (accessed 14/10/2024).

65. World Health Organisation. Evidence of hand hygiene to reduce transmission and infections by multidrug resistant organisms in health-care settings. 2017. https://www.who.int/publications/i/item/WHO-HIS-SDS-2017.7 (accessed 10/10/2024).

66. Knobler SL, Lemon SM, Najafi M, Burroughs T. Strategies to contain the development and consequences of resistance. The Resistance Phenomenon in Microbes and Infectious Disease Vectors: Implications for Human Health and Strategies for Containment: Workshop Summary; 2003: National Academies Press (US); 2003.

67. Septimus EJ. Antimicrobial Resistance: An Antimicrobial/Diagnostic Stewardship and Infection Prevention Approach. *Medical Clinics* 2018; **102**(5): 819-29.

68. Butaye P, Devriese LA, Haesebrouck F. Antimicrobial growth promoters used in animal feed: effects of less well known antibiotics on gram-positive bacteria. *Clin Microbiol Rev* 2003; **16**(2): 175-88.

69. Manyi-Loh C, Mamphweli S, Meyer E, Okoh A. Antibiotic Use in Agriculture and Its Consequential Resistance in Environmental Sources: Potential Public Health Implications. *Molecules* 2018; **23**(4).

70. Huddleston JR. Horizontal gene transfer in the human gastrointestinal tract: potential spread of antibiotic resistance genes. *Infection and drug resistance* 2014; **7**: 167-76.

71. World Health Organisation. Action against antimicrobial resistance requires a One Health approach. 2024. https://www.who.int/europe/publications/i/item/WHO-EURO-2024-9510-49282-73655 (accessed 11/12/2024).

72. Viet Nam Ministry of Health. National Action Plan on combatting drug resistance in period from 2013-2020 (Approved with Decision No.2174/QD-BYT). 2013. https://thuvienphapluat.vn/van-ban/The-thao-Y-te/Decision-2174-QD-BYT-2013-ratification-of-the-National-Action-Plan-to-Combat-Antimicrobial-Resistance-382068.aspx (accessed 16/08/2022).

73. Pham GN, Dang TTH, Nguyen T-A, et al. Health system barriers to the implementation of the national action plan to combat antimicrobial resistance in Vietnam: a scoping review. *Antimicrobial Resistance & Infection Control* 2024; **13**(1): 12.

74. Ministry of Health Vietnam. Decision 4041/QD-BYT:100% of Pharmacies Dispensing Antibiotics Must Have a Prescription. 2017.

75. Ministry of Health Vietnam. Decision No. 772/QD-BYT:Instructions on management of the antibiotic use in hospitals. 2016.

76. Vietnam Ministry of Agriculture and Rural Development. National Action Plan For Management Of Antibiotic Use And Control Of Antibiotic Resistance In Livestock Production And Aquaculture

(Issued in accordance with Decision No. 2625 /QĐ-BNN-TY), 2017. https://rr-asia.woah.org/app/uploads/2020/03/vietnam_ah_amr-nap-printed_en.pdf (accessed.

77. Vietnam Ministry of Health. Decision No. 5631/QD-BYT 2020: Guidance on management of the antibiotic use in hospitals. 2020. https://english.luatvietnam.vn/decision-no-5631-qd-byt-of-the-ministry-of-health-on-promulgating-the-guidance-on-management-of-the-antibiotic-use-in-hospit-196563-doc1.html (accessed 15/03/2022).

78. Ha B, Mirzoev T, Morgan R. Patient Complaints in healthcare services in Vietnam's Health system. *SAGE Open Medicine* 2015; **3**.

79. World Health Organisation. Everyone has a responsibility to prevent Antimicrobial Resistance in Viet Nam. 20 November 2023 2023. https://www.who.int/vietnam/news/detail/20-11-2023-everyone-has-a-responsibility-to-prevent-antimicrobial-resistance-in-viet-nam# (accessed 30/07/2024).

80. Ministry of Health Vietnam. Decision No. 1121/QD-TTg dated September 25, 2023 on approval of The national strategy for prevention and control of drug resistance in Vietnam for the period of 2023 - 2030 with a vision towards 2045. 2023. https://lawnet.vn/en/vb/Decision-1121-QD-TTg-2023-The-national-strategy-for-prevention-and-control-of-drug-resistance-8DDD4.html (accessed 10/01/2025).

81. Chua AQ, Verma M, Hsu LY, Legido-Quigley H. An analysis of national action plans on antimicrobial resistance in Southeast Asia using a governance framework approach. *The Lancet Regional Health – Western Pacific* 2021; **7**.

82. HCMC Department of Health. Implementing the action plan on AMR in Ho Chi Minh City Conference on Preliminary Results of Implementing National Action Plan to Combat AMR in Vietnam. 2017.

83. Huong VTL, Ngan TTD, Thao HP, et al. Improving antimicrobial use through antimicrobial stewardship in a lower-middle income setting: a mixed-methods study in a network of acute-care hospitals in Viet Nam. *Journal of global antimicrobial resistance* 2021; **27**: 212-21.

84. Huong VTL, Ngan TTD, Thao HP, et al. Assessing feasibility of establishing antimicrobial stewardship programmes in two provincial-level hospitals in Vietnam: an implementation research study. *BMJ open* 2021; **11**(10): e053343.

85. Lee TH, Lye DC, Chung DR, et al. Antimicrobial stewardship capacity and manpower needs in the Asia Pacific. *Journal of global antimicrobial resistance* 2021; **24**: 387-94.

86. Wertheim HF, Chandna A, Vu PD, et al. Providing impetus, tools, and guidance to strengthen national capacity for antimicrobial stewardship in Viet Nam. *PLoS Med* 2013; **10**(5): e1001429.

87. Nguyen HQ, Nguyen-Thi H, Huynh P, Le N, Nguyen N-Q, Hsia Y. Effectiveness of an enhanced antibiotic stewardship programme among paediatric patients in a tertiary hospital in Vietnam. *Journal of Hospital Infection* 2022; **127**: 121-8.

88. Nguyen TS, Ton TT, Pham TNT. Antimicrobial stewardship program at a tertiary teaching hospital in Vietnam: a longitudinal observational study. *Clin Microbiol Infect Dis* 2017; **2**(1): 1-5.

89. Vũ TTA, Nguyễn TH, Nguyễn MT, Lê VL, Bùi THQ. Đánh Giá Hiệu Quả Của Công Tác Dược Lâm Sàng Và Chương Trình Quản Lý Sử Dụng Kháng Sinh Trong Điều Trị Nhiễm Trùng Đường Tiết Niệu Tại Bệnh Viện Thống Nhất. *Tạp Chí Y Học Việt Nam* 2022; **511**(1).

90. Huy Tran H. Mapping access to drug outlets in Vietnam: distribution of drug outlets and the sociodemographic characteristics of the communities they serve. *The Lancet Regional Health - Western Pacific* 2022; **30**.

91. McKinn S, Trinh DH, Drabarek D, et al. Drivers of antibiotic use in Vietnam: implications for designing community interventions. *BMJ global health* 2021; **6**(7).

92. Zawahir S, Le HTT, Nguyen T-A, et al. Inappropriate supply of antibiotics for common viral infections by community pharmacies in Vietnam: A standardised patient survey. *The Lancet Regional Health – Western Pacific* 2022; **23**.

Chapter 2: Antimicrobial use and Antimicrobial Stewardship in the Vietnamese healthcare system: a Systematic Review and Meta-analysis

This chapter comprises a systematic review and meta-analysis has been submitted for publication.

Authors:

Jaslyn Doshi[1], Yen Pham Ngoc[2], Linh Thuy Duong[2], Tasnim Hasan[1], Quy Trinh Van[2], Justin Beardsley[3,4], Gregory J Fox[1,5]

Author contributions:

JD and GJF contributed to the conceptualisation of the review. JD came up with search teams and conducted the English language study search. TH conducted the English language study search and performed title and abstract reviews. YPN, LD, and QTV conducted the Vietnamese language study search manually, and performed title, abstract and text reviews, inputting translated data from Vietnamese to English into data collection forms. JD performed title, abstract and text reviews, filled out data collection forms for English language studies, performed and tabulated descriptive analyses of all included studies (English and Vietnamese), performed meta-analyses, and wrote all sections of the manuscript. LD, YPN and GJF performed data checking. GJF and JB provided supervision to JD. All authors reviewed and edited the manuscript.

Abstract

Background: Antimicrobial resistance (AMR) is a growing global health concern, driven by antimicrobial overuse and misuse. Antimicrobial stewardship (AMS) helps combat AMR by promoting judicious use of antimicrobials. Vietnam is a middle-income country that faces high levels of AMR and antimicrobial consumption, however evidence regarding the effectiveness of interventions to combat AMR in Vietnam remains limited. This systematic review aimed to (i) quantify antimicrobial consumption, (ii) determine the appropriateness of antimicrobial prescribing (iii) evaluate the feasibility and effectiveness of AMS interventions in the community and healthcare settings in Vietnam.

Methods: A systematic review and meta-analysis of the English and Vietnamese-language literature was conducted for publications between January 2010 to January 2023. Eligible studies were categorised into three domains: (1) studies quantifying antimicrobial consumption, (2) studies determining prescribing appropriateness, and (3) studies evaluating the effectiveness of AMS interventions. Two independent reviewers screened and extracted data in each language. Descriptive data were summarised from each study. Random-effects meta-analyses was used to establish pooled estimates, where applicable. (PROSPERO 398154)

Findings: Of 73 studies (41 English, 32 Vietnamese), 31 quantified antimicrobial consumption, 8 assessed prescribing appropriateness and 34 evaluated the outcomes of AMS interventions. The pooled estimate of hospital inpatient antimicrobial consumption was 90·8 DDD/100 bed-days (95% CI:54·4, 125·8 DDD/100 bed-days). Inappropriate prescribing against reference guidelines was estimated at 63% (95%CI: 49%,76%), while 74% (95%CI: 60%, 89%) of outpatient antimicrobials were dispensed without a prescription. Several AMS interventions reduced inappropriate prescribing but

did not reduce overall antimicrobial consumption. AMS implementation was largely evaluated in tertiary settings. Most studies were of low-quality with high heterogeneity.

Interpretation: High antimicrobial consumption and inappropriate prescribing were commonly reported in Vietnam. Increased regulatory enforcement and AMS expansion in healthcare facilities will be essential to mitigate AMR in Vietnam.

Introduction

Antimicrobial resistance (AMR) poses a significant threat to global public health.[1] Each year, around 5 million deaths are attributed to resistant bacterial infections, with low- and middle-income countries (LMICs) bearing the heaviest burden.[2] Inappropriate and excessive antimicrobial use in human health, agriculture and animal health are major drivers of AMR.[1] Vietnam, a Southeast Asian country with a population of 100 million people in 2024,[3] is among the highest antimicrobial users globally.[4] A high prevalence of "WHO Bacterial Priority Pathogens List"[5] resistant organisms such as carbapenem-resistant and third-generation cephalosporin-resistant Enterobacterales, methicillin-resistant *Staphylococcus aureus* and pathogens causing community-acquired pneumonia have been reported in Vietnam.[6-8] Sequential surveys between 2012 and 2017 indicate a significant rise in AMR prevalence.[9,10] For example, ampicillin-resistant *Haemophilus influenzae,* a common respiratory pathogen, increased from 51% in 2009, to 71% in 2012 and 88% in 2016.[10]

Healthcare in Vietnam is delivered by a mix of both public and private healthcare providers. Hospitals play the central role in service delivery from basic to complex medical conditions, consuming more than 95% of total health insurance spending.[11] The public system delivers care at multiple levels, encompassing central, provincial and local levels. Until 2025, local health facilities included district and commune level health facilities .[12] All levels of healthcare grapple with AMR, driven by factors such as the inappropriate use of antibiotics for viral infections, excessive reliance on broad-spectrum antimicrobials, and improper surgical prophylaxis.[8,13-16] In Vietnam, unregulated community pharmacies frequently serve as the first point of contact for individuals with infectious diseases seeking self-medication with antibiotics without prescriptions.[15,17,18]

Antimicrobial stewardship (AMS) plays a critical role in combating AMR. AMS is defined as a coordinated set of strategies to promote responsible use of antimicrobials by implementing

evidence-based interventions.[19] These are often delivered within healthcare facilities, but may also be implemented in the general community or agricultural sector.[19,20] AMS programs aim to maintain the effectiveness of commonly-used antimicrobials, reduce emergence of resistance, and lower healthcare costs.[19] Key strategies include education for prescribers, audit and feedback of antimicrobial appropriateness, development of local guidelines for antimicrobial use, and regular surveillance of antimicrobial consumption and AMR.[19]

While AMS has been well-studied and shown to be effective in high-income countries, its impact in LMICs remains not as extensively explored, where implementation often face challenges such as limited infrastructure, lack of consensus guidelines, weak regulatory enforcement, and insufficient access to resources such as manpower, education and diagnostics.[21,22] Nevertheless, a recent scoping review in 34 LMICs found that AMS programs demonstrated promising outcomes, including increased appropriateness of antibiotic prescriptions, reduced antimicrobial consumption, shorter hospital stays, reduced costs and lower mortality rates.[23]

AMS is an important national priority for Vietnam. In 2013, the Ministry of Health (MoH) introduced a National Action Plan (NAP) on AMR which outlined strategies for strengthening the control of AMR in the country, AMR surveillance and provision of training on appropriate antimicrobial use.[24,25] We conducted a review of published research to evaluate the current landscape of AMS in Vietnam.

This review explored three critical questions regarding AMS in human health in Vietnam: (i) what was the quantity of antimicrobials being used in healthcare facilities or the community in Vietnam? (ii) what proportion of antimicrobials were given inappropriately in healthcare facilities or the community in Vietnam and (iii) what are AMS interventions that have been implemented in healthcare facilities and in the community, and what are the effects of these interventions, if any.

These domains align with key components of AMS frameworks outlined by the WHO and Vietnam's NAP, which emphasize monitoring antimicrobial use, evaluating prescribing practices, implementing stewardship interventions, and assessing their effectiveness.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[26] A protocol was registered prospectively on PROSPERO (398154). We performed a review on studies pertaining to three key domains relevant to AMS in Vietnam, listed below. Search terms listed in Supplementary Table S2.1, and studies meeting eligibility criteria were categorised into three separate domains. Articles published in English or Vietnamese between 1 January 2010 and 31 January 2023 were included. Multi-country studies where disaggregated Vietnamese data were included, while non-human studies, unpublished literature, studies with less than 20 participants, studies reporting consumption of specific classes of antibiotics or single-organism diagnoses, and grey literature were excluded. Eligibility criteria, including predefined inclusion and exclusion parameters are presented in Supplementary Table S2.2.

Database searches for English language studies were conducted independently by two reviewers (JD and TH) in PubMed, EMBASE, Scopus and Medline. A third and fourth reviewer, (YPN and LTD) both fluent in Vietnamese, conducted a manual search for Vietnamese articles in 11 reputable Vietnamese medical journals using translated search terms (Supplementary Table S2.2). Included journals were those that had been recognised at a national level by government agencies, hospitals or universities, or were accessible through official websites. Any discrepancies regarding the inclusion of the articles by the reviewers were resolved by consensus of the four reviewers. Records were managed using EndNote and Microsoft Excel.

We categorised included studies in accordance with our three research questions: (i) antimicrobial consumption; using quantification of standardised metrics (see below) (ii) appropriateness of antimicrobial prescribing, assessed based on compliance with a reference guideline; and (iii) AMS interventions, including implementation of an AMS program, and its effect on predefined outcomes (Supplementary Table S2.2). The terms "antibiotic" and "antimicrobial" were used interchangeably, as most literature focused specifically on antibiotics, though this review encompasses all antimicrobials.

Antimicrobial consumption: We assessed antimicrobial consumption in Vietnam across healthcare facilities and community settings. Outcomes measured were quantified using standardised metrics such as defined daily dose (DDD) per 100 bed-days (inpatients) or per 1,000 inhabitants per day (outpatients/general population),[27] day of therapy (DOT), length of therapy (LOT) as well as other measures including total antimicrobial mass and cost. Proportions of antimicrobial use out of all medication use in a particular setting was also included. (Supplementary Table S2.2)

Appropriateness of prescribing: The second question addressed whether antimicrobial prescribing adhered to guidelines in healthcare and community settings. Appropriateness was assessed based on compliance with local, national, or international guidelines. Where possible, appropriateness was assessed against results of microbiological culture and drug susceptibility testing.. (Supplementary Table S2.2)

AMS interventions: For AMS interventions, we included studies from healthcare facilities and the community. The population included healthcare workers or patients exposed to AMS initiatives. Interventions included AMS teams, education programs, prescribing guidelines, restriction policies, audit and feedback, and microbiological decision tools. Comparators, where reported, included

standard care or pre-intervention data. Outcomes included the feasibility of AMS implementation and the effect of AMS interventions on prescribing appropriateness, antimicrobial consumption, healthcare costs, hospital stay, adherence to WHO AWaRe categories[28], mortality, hospital-acquired infections, and treatment success or failure. (Supplementary Table S2.2)

Data extraction and statistical analysis

A standardised data extraction form, adapted from the Cochrane data collection form for both intervention and non-intervention studies,[29] (Appendix) was used for data synthesis. Components from Vietnamese studies that were required for the data extraction form were translated by YPN and LTD to English and subsequently entered into the form. The first reviewer (JD) then analysed all forms for the final tabulation. Each study was systematically summarised and presented in a table. When three or more studies report the same outcome in a particular setting, we conducted a proportional random-effects meta-analysis for a pooled estimate using Jamovi 2·3.28 statistical platform.[30]

Risk of bias assessment

The risk of bias for each included study was assessed. For randomised controlled trials, the Cochrane risk of bias tool was used.[29] Non-RCTs were assessed for risk using templates from Newcastle-Ottawa scale.[31] (Supplementary Table S2.3 and S2.4)

Results

Characteristics of included studies

We identified 3064 studies in total in both English and Vietnamese, and with a series of screening by removal of duplicates, title and text review, the final count of studies included were 73 studies.

(Figure 2.1). Among 73 included studies, 31 addressed antimicrobial consumption, eight addressed prescribing appropriateness, and 34 addressed AMS interventions. 56 studies were performed on hospital inpatients, mainly comprising national and provincial hospitals. Six studies were performed on outpatients from health-care facilities and ten in the community including community pharmacies and drug counters. Four included studies were randomised controlled trials, 16 before-and-after studies, and the rest, observational studies. A breakdown of characteristics of studies is shown in Table 2.1.

Domain 1: Antimicrobial consumption

The search identified 21 English articles, and 10 Vietnamese on antimicrobial consumption (Figure 2.1). A summary of all studies related to antibiotic consumption included is displayed in Table 2.2. Antibiotic consumption, quantified using standardised Defined Daily Dose (DDD) per 100 bed-days (for inpatients) or 1000 inhabitants per day, were reported in six studies. A pooled estimate of hospital antibiotic consumption in Vietnam was 90·8 (95%CI 42, 139, I^2=99·8%) DDD/100 bed-days (Figure 2.2).

Secondly, we identified studies reporting antimicrobial consumption as proportions of total medications dispensed. Outcomes included (i) number of antimicrobials prescribed (ii) the antimicrobial classes used (iii)WHO AWaRe "Access", "Watch" and "Reserve" classification[28], (iv)antimicrobials dispensed without a prescription (v)antimicrobial use for surgical prophylaxis (vi)drug costs attributed to antimicrobials. Studies were conducted in both community and health care settings and were all observational. Despite heterogeneity in the outcome of the studies, a high proportion of antimicrobial use was reported across most studies.

Three studies reported the proportion of inpatients in intensive care(ICU) and coronary care unit (CCU) receiving antibiotics, with a pooled estimate of 77% (95% CI 64%, 90%, I^2=99·0%). (Figure 2.3a). Five studies examined the proportion of antibiotics dispensed in the community without a prescription, yielding a pooled estimate of 74% (95% CI 60%, 89%, I^2=99·5%) (Figure 2.3b) The proportion of total hospital drug expenditure attributed to antimicrobials was estimated at 32% (95%CI 26%, 37%, I^2=99·8%) (Figure 2.3c).

Domain 2: Appropriateness of antimicrobial prescribing

Three English and five Vietnamese studies assessing antimicrobial prescribing appropriateness across various healthcare settings were included (Figure 2.1). All were of observational design, evaluating prescribing practices against different reference standards, including local hospital, provincial hospital, national Ministry of Health, international, and pharmaceutical company guidelines, or even to microbiological culture results. None of the studies used a validated audit tool, but each outlined specific criteria for assessing antimicrobial appropriateness in their methods. Table 2.3 provides a detailed summary of healthcare settings, audit methods, reference standards, and key findings from these studies in Domain 2. From seven studies in this domain, we estimated that 63% (95% CI 47%, 79%, I^2= 99·2%) of antibiotics were inappropriately prescribed compared to reference guidelines (Figure 2.4).

Domain 3: Antimicrobial Stewardship

The search identified 17 English and 17 Vietnamese reports demonstrating the presence or implementation of an AMS program across various settings, (Table 2.4) and its effect on several outcomes (Table 2.5). In hospital settings, AMS interventions were generally bundled interventions, implementing several components together. These included AMS teams and committees, antimicrobial guidelines, audit of antimicrobial use and feedback, education and training of

healthcare workers as well as pre-authorisation for restricted antibiotics. Antimicrobial guidelines and education were central elements in more than half the studies. Other important aspects highlighted were leadership commitment with budget allocation for AMS, surveillance of antimicrobial use and antibiograms, access to microbiology services, information technology support and clinical pharmacists' involvement (Table 2.4).

The studies investigated the effect of AMS intervention upon antibiotic consumption, appropriateness of antibiotic prescribing, compliance to reference guidelines, proportion of patients who were prescribed antibiotics, and knowledge of healthcare providers (Table 2.5). Due to considerable differences in types of AMS interventions carried out as well as outcomes measured, meta-analyses could not be performed.

Four RCTs were included in this domain – two of which were on the same study population, reporting different outcomes. The first two RCTs studied the effect of C-reactive protein laboratory test on proportion of patients receiving antimicrobials and antimicrobial costs,[32,33] while the third, the effect of matrix-assisted laser desorption/ionization time-of-flight spectrometry (MALDI-TOF) on blood cultures for timely appropriate antimicrobial use.[34] The fourth RCT reported the impact of AMS education on healthcare workers' knowledge and prescribing practices in acute respiratory infections.[35] Notably, these studies targeted only single interventions and did not assess broader outcomes like antimicrobial consumption or prescribing appropriateness. The remaining studies were primarily before-and-after and observational designs.

Of the 26 published studies evaluating effect of AMS interventions, 19 demonstrated positive findings including an improvement in prescribing appropriateness (Figure 2.1). Additional benefits included increased compliance with guidelines, reduced antimicrobial costs, and no reported adverse

clinical outcomes post-intervention. Only three studies quantified the effect of AMS on total antimicrobial consumption using DDD and DOT, none of which showed a significant reduction following AMS implementation[36-38] (Table 2.5).

Risk of bias

For all three domains, most studies were judged to have a high risk of bias, with a smaller proportion classified as having some concerns (Supplementary Table S2.3). Most of the observational studies had a high risk of bias due to limitations in study design, population selection bias, the absence of justification for sample size, limited generalisability, and non-standardised data collection and reporting methods. Most studies did not adjust for potential confounders. Among the four RCTs reported, two were low risk,[32,34]one demonstrating some concern,[33] and one high risk[35] due to selection bias, using an unvalidated data collection tool, and providing insufficient detail on outcome measurements (Supplementary Table S2.4).

Discussion

This systematic review described the antimicrobial consumption and appropriateness of prescribing in Vietnam, as well as the presence and impact of antimicrobial stewardship interventions from 2010 to 2023. The review synthesised evidence from diverse healthcare settings, including district, provincial and national hospitals, pharmacies, drug counters, and community settings. We observed high antimicrobial consumption across Vietnam, with frequent inappropriate prescribing and widespread over-the-counter antibiotic dispensing without a prescription in community settings. Despite these challenges, we identified numerous AMS initiatives implemented across the country, reflecting efforts to promote responsible antibiotic use. Key interventions observed were antibiotic guidelines, forming AMS committees and teams, education and training, surveillance of antibiotic

use, and audit and feedback. Encouragingly, the growing number of scientific publications in recent years suggests an increasing national focus on AMR and AMS.

This review found a wide range of antimicrobial use among inpatients, ranging from 35 to 207 DDD per 100 bed-days. The meta-analysed usage of 90·8 /100 bed-days DDD (95% CI 42, 139) was comparable to hospital inpatients in other countries in the Asia-Pacific region - 134·8 DDD/100 bed-days in Indonesia[39], 93·9 DDD/100 bed-days in Malaysia[40] and 85·9 DDD/100-bed-days in Australia[41]. The literature presents higher annual per capita antibiotic consumption rate, taking into consideration the general population. In 2023, Vietnam had an estimated 19,706 DDD per 1000 inhabitants/day, far exceeding neighbouring countries such as Thailand (10,327 DDD/1000 inhabitants/day), Indonesia (4,573 DDD/1000 inhabitants/day), and India (5,531 DDD/1000 inhabitants/day).[42] In contrast, high-income countries reported lower per capita consumption, including the United States (8,307 DDD/1,000 inhabitants/day), the United Kingdom (7,000 DDD/1000 inhabitants/day) and Australia (7,866 DDD/1000 inhabitants/day).[42]

Whilst DDDs serve as a valuable tool for benchmarking antibiotic consumption across similar settings, it is essential acknowledge their limitations. DDDs are based on standard adult dosing, which can lead to inaccuracies in paediatric and geriatric populations, which vary across countries. Weight-based dosing or altered pharmacokinetics often necessitate adjustments, resulting in potential over- or underestimation in these metrics. [43] While DOT and LOT are valuable additional metrics that address these limitations, it is not reported widely.[44]

This review also identified a high proportion of hospital inpatients taking antibiotics, ranging from 67% to 77% of all inpatients,[13,45] with even higher usage in ICUs and CCUs at national and provincial hospitals (Figure 2.3a).[13,46,47] Similarly in the outpatient setting, a large study of 193, 010 children

with acute respiratory infections found that 97% were prescribed antibiotics.[48] Broad-spectrum beta-lactams were the predominant antibiotic class prescribed in hospital settings.[49-53] Two studies using the WHO "AWaRe" classification found that "Access" antibiotics were the most commonly used, exceeding the recommended 60% threshold.[36,48,54] However, another study reported that Vietnam had the largest increase in "Watch" antibiotic consumption among 75 countries, with usage rising by 10·6 DDD/1000 inhabitants per day between 2000 and 2015.[4]

Another major concern was the high proportion of antibiotics obtained without a prescription in the community, highlighting weak enforcement of Vietnam's prescription-only regulations.[55]. Our review estimated that among five studies, 74% (95% CI 60%, 89%) of antibiotics in the community were obtained without a script, higher than global (67%, 95% CI 55%, 79%) and Asian (65%, 95% CI 54%, 76%) estimates.[56] This finding accords with a study with a review of six LMICs in Asia and Africa, which ranked Vietnam the highest in self-medication without a prescription.[57]

A pooled estimate of 63% (95% CI 47%, 79%) of prescriptions were found to be inappropriate based on reference guidelines and microbiology culture results. Individual studies reported a large range of inappropriateness (between 30% to 90%) reflecting the heterogeneity in assessment methods and guidelines across settings.[13,58] A systematic review of 27 LMICs showed an even larger range of inappropriateness from 8% to 100%.[59] Multiple factors drive inappropriate antibiotic use, including diagnostic uncertainties, limited access to microbiologic and radiologic tests, antibiotic supply disruptions, insufficient AMS knowledge, and influences from pharmaceutical and insurance companies.[60-62] Additionally, community expectations reinforce antibiotics as a trusted remedy, contributing to widespread overuse without full awareness of the consequences.[17] Two studies reported unnecessary antimicrobial use in viral infections in outpatient and community settings.[15,48]

Another key finding was the high proportion of children being prescribed antibiotics for mild respiratory infections which were likely to be mostly inappropriate.[58,63]

While Vietnam's NAP against AMR mandates AMS implementation across all healthcare settings, progress remains in its early stages.[25] Shortages of human resources, a low degree of agreement between national and hospital guidelines on antibiotic use, limited access to microbiology and inadequate monitoring and reporting have been the biggest gaps identified in successful AMS implementation in Vietnam. AMS feasibility and implementation studies in this review primarily focused on tertiary hospital settings, revealing a gap at the district, commune, and community levels—where the majority of antibiotic use occurs.[8] A notable exception was a community-based education initiative in a rural community that stood out as a unique approach in improving public awareness on AMR and AMS.[64]

Improved antimicrobial prescribing appropriateness, lower healthcare costs, and increasing compliance to reference guidelines were the most common outcomes seen. Interestingly, total antimicrobial consumption did not reduce with AMS interventions,[36,37] but two studies reported a reduction in the DDDs of broad-spectrum antibiotics such as carbapenem and fosfomycin with AMS interventions.[65,66]

This review had several strengths. It was the first to synthesise data on human antibiotic use in Vietnam from 2010 onward, incorporating both English and Vietnamese-language studies. By including Vietnamese-language research, we captured locally relevant data and minimised publication bias that could result from relying solely on English-language studies. Our systematic approach, with a broad search strategy, ensured rigorous data collection and synthesis. Studies were categorised into three key domains provided a comprehensive overview of Vietnam's response to

AMR. Additionally, this review spanned diverse healthcare settings, from community and commune health centres to district, provincial, and national hospitals, offering valuable insights into antibiotic use across all levels of care. Covering studies from 2010 to 2023, it provides 13 years of longitudinal data, reflecting trends in antibiotic consumption and the evolution of AMS implementation. The evaluation of AMS studies further highlights successful strategies and areas needing improvement, guiding future stewardship efforts in Vietnam.

There were also some limitations to the study. The selection of Vietnamese-language journals manually and only including reputable and credible journals recognised by government agencies, excluded lower-tier journals which may have limited comprehensiveness of this review. Publication bias is another potential limitation, especially for studies on effect of AMS implementation, as studies with negative or inconclusive results may be less likely be published.

The data included in this review revealed significant evidence gaps. Most publications focused on major cities in northern and southern Vietnam, with limited studies from central Vietnam, leading to an overrepresentation of hospital and urban settings. There was also a notable lack of studies conducted in local healthcare settings and private healthcare facilities. This gap limits the ability to draw comprehensive nationwide conclusions on antibiotic use and AMS in Vietnam. Addressing these gaps should be a priority for future research. Randomised controlled trials implementing AMS initiatives will be useful to evaluate effectiveness in the different healthcare settings in Vietnam.

This review carries several important policy implications. It provides evidence that antimicrobial overuse and misuse remain major challenges in Vietnam, with AMS programs still in their early stages across human health. Key areas for future policy action include strengthening enforcement against over-the-counter antibiotic sales, reducing inappropriate antibiotic use for viral respiratory

infections, and expanding AMS implementation across all healthcare settings. The National AMR Strategy 2023–2030 aims to improve AMR surveillance, promote responsible antibiotic use in healthcare and agriculture, and raise public awareness.[67] Our review serves as a critical baseline to guide policymakers in addressing gaps and ensuring consistent AMS implementation across healthcare settings and the community. Sustaining impactful AMS programs will require ongoing support from national bodies and adequate resource allocation.

In conclusion, this systematic review offers a comprehensive summary of antimicrobial consumption, appropriateness of antimicrobial prescribing and AMS interventions in Vietnam between 2010 and 2023. While AMS has demonstrated effectiveness globally,[22] its implementation and effectiveness is not yet universal across Vietnam. Continued efforts in sustainable integration of AMS interventions and scale-up are essential to support national and global strategies to combat AMR.

Figure 2.1: PRISMA diagram of studies identified by this review.

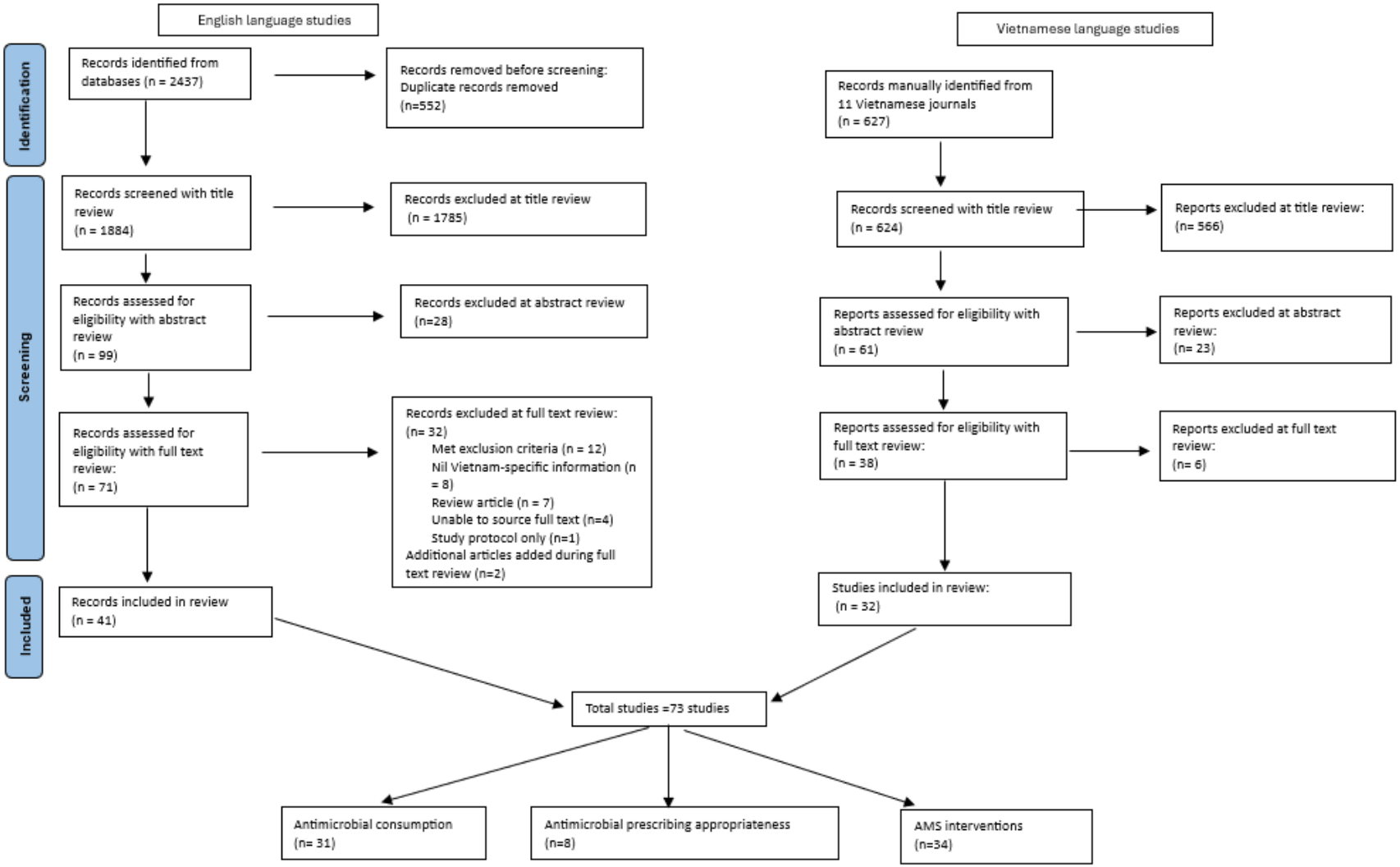
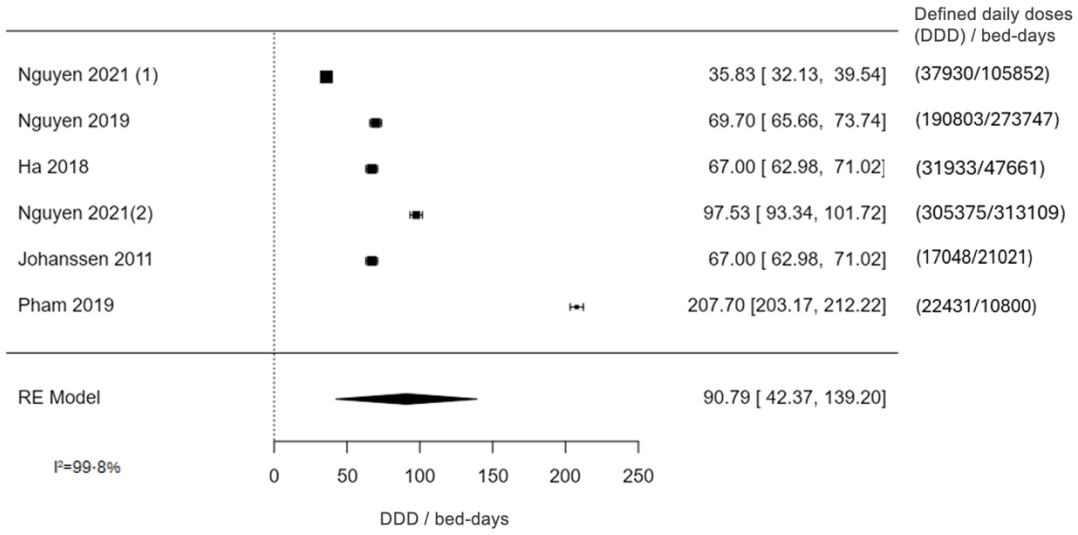


Table 2.1: Summary of the characteristics of included English and Vietnamese full text-reviewed studies

Characteristic	**Number (n)**	**Proportion (%)**
Total	73	100%
Domains		
Antimicrobial consumption	31	42·5%
Appropriateness in antimicrobial consumption	8	10·9%
Antimicrobial stewardship - Presence and implementation of AMS - Impact of AMS interventions	34 8 26	46·6%
Language		
English	41	56·2%
Vietnamese	32	43·8%
Study design		
Observational	50	68·5%
Before-and-after	19	26·0%
Randomised controlled trial	4	5·5%
Study population		
Hospital Patients - Inpatients - Outpatients	 56 5	 76·7% 6·8%
Community	10	13·7%
Healthcare providers	2	2·7%
Study region		
Across Vietnam/multiple regions	15	20·5%
Northern Vietnam	19	26·0%
Central Vietnam	3	4·1%
Southern Vietnam	33	45·2%
Multi-country including Vietnam	3	4·1%
Year study published		
2019-2023	30	41·1%
2015-2018	31	42·5%
2010-2014	12	16·4%
Healthcare level		
Provincial and national hospitals	52	71·2%
District and commune level hospitals	7	9·6%
Community	10	13·7%
Mixed	4	5·5%

Figure 2.2: Forest plot of Defined daily doses (DDD)/100 bed-days reported included studies using restricted maximum-likelihood random-effects model

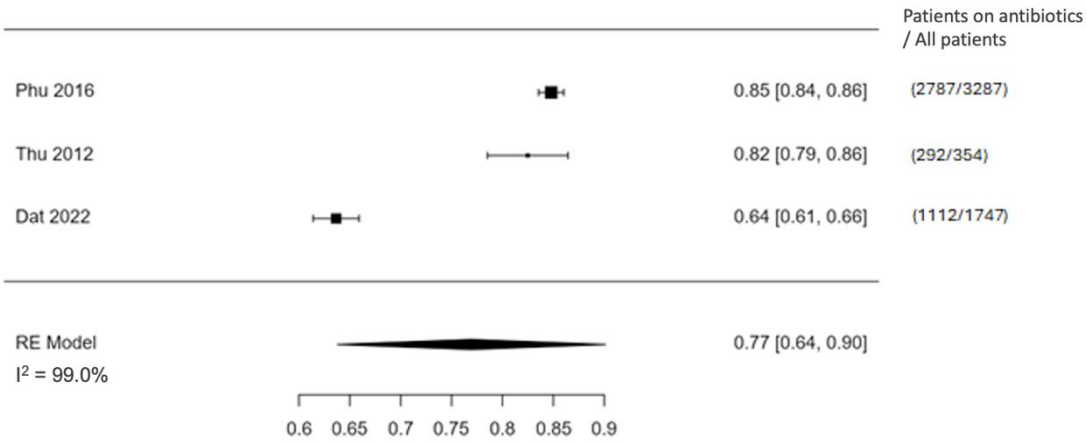


Nguyen 2021 (1)[68], Nguyen 2021(2)[52]

RE Model: Random effects model

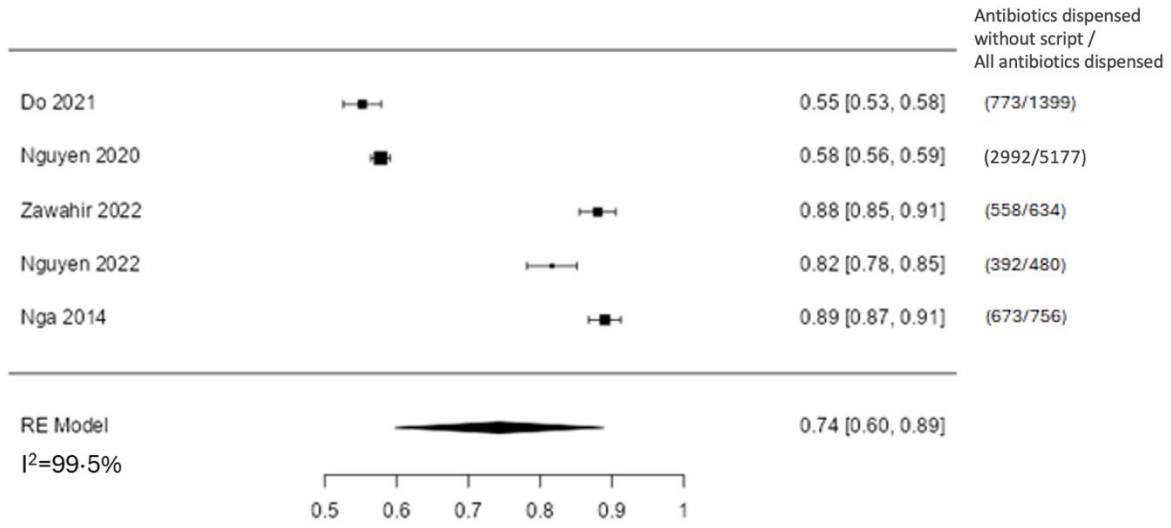
Figure 2.3: Summary forest plots of the proportions of antimicrobial consumption in various clinical settings using restricted maximum-likelihood random-effects model

Figure 2.3a: Proportion of inpatients in Intensive Care Unit (ICU) or Coronary Care Unit (CCU) on antibiotics



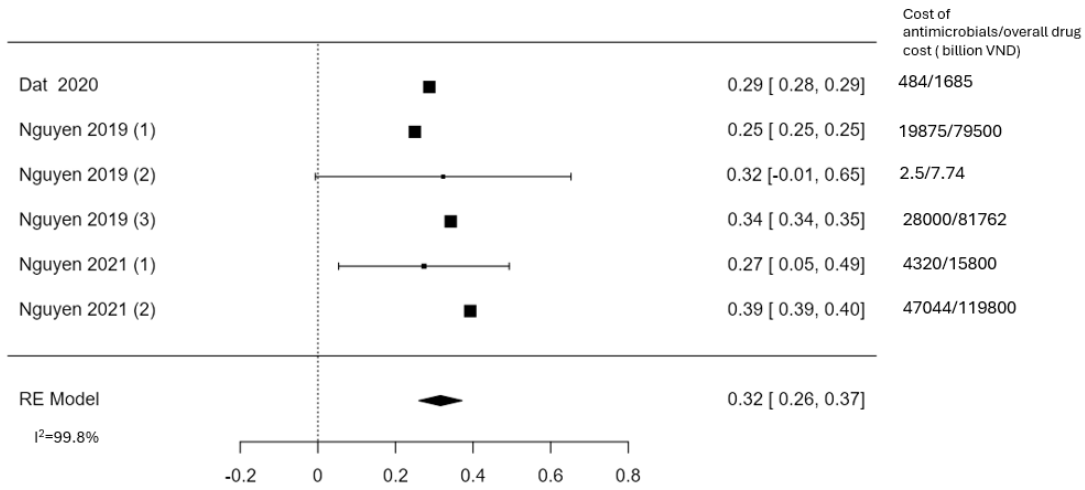
RE Model: Random effects model

Figure 2.3b: Proportion of antibiotics dispensed in the community without prescriptions



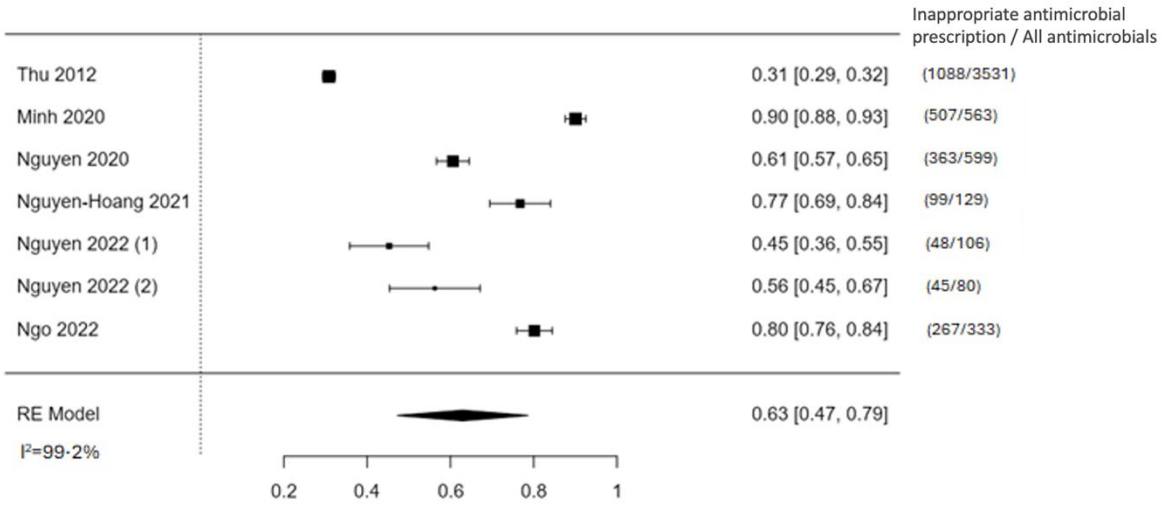
RE Model: Random effects model

Figure 2.3c: Proportion of costs of antimicrobials over all drugs purchased in hospitals



Nguyen 2019 (1)[69], Nguyen 2019 (2)[51], Nguyen 2019 (3)[50], Nguyen 2021 (1)[68] , Nguyen 2021 (2)[52]
RE model: Random-effects model
VND: Vietnamese Dong

Figure 2.4: Forest plot of the proportion of inappropriate antimicrobial prescribing according to reference guidelines using restricted maximum-likelihood random-effects model



Nguyen 2022 (1)[70], Nguyen 2022 (2)[71]

RE model: Random-effects model

Table 2.2 : Summary of included studies reporting antimicrobial consumption in healthcare facilities and the community in Vietnam

Table 2.2 : Summary of included studies reporting antimicrobial consumption in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Region	Year study conducted	Setting	Population	Study design	Sources of measurement	Outcome measure(s) relating to antimicrobial consumption	Main findings
Carrique-Mas et al [72] (2020)	English	Across Vietnam	2015	Community	2015 Vietnam population	Observational	Antimicrobial consumption: estimated in a multi-country survey using IQVIA MIDAS database for estimated Defined Daily Doses (DDD)[4] - converted to antimicrobial active ingredient (AAI). Daily consumption then extrapolated for a whole year. Human biomass: Vietnamese government population database and average mass	Mass of antimicrobials used per 1kg of human population in all of Vietnam	An estimated 261·7 mg (95%CI: 131·4–394·3 mg) of antimicrobial active ingredients (AAI) were administered per 1 kg of human. N/A
Cuong et al[73] (2021)	English	Dong Thap province in Mekong Delta region	2019	Community	Household farmers and their families (316 people)	Observational	Questionnaire about consumption of AAIs over the latest 90 days for humans present in the farm as well as medicines stored in their homes.	1. Antimicrobial use in the country = Antimicrobial active ingredients (AAI) as a ratio to estimated human biomass. Consumption (DDD/kg) measured either by reported consumption/number of days over 90 days or actual doctors' prescriptions where available 2. Proportion of study participants using antibiotics to estimate antibiotic use in the community 3. Estimated DDD per 1000 inhabitant-days.	1. Over 1 year, humans were estimated to have used 7·1DDD/kg, or 175·9mg of antimicrobial active ingredients (AAIs)per kg of standing body mass annually. 2. 34·7% of participants used antibiotics in the community in the last 90 days of the study. 3. Humans used 19·3 DDD of antibiotics/1000 inhabitant-day 4. Individuals <5 and >65 years consumed considerably more antimicrobials than people in other age categories.

Table 2.2 : Summary of included studies reporting antimicrobial consumption in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Region	Year study conducted	Setting	Population	Study design	Sources of measurement	Outcome measure(s) relating to antimicrobial consumption	Main findings
Dat et al[74] (2020)	English	Across Vietnam	2018	30 public hospitals (23 secondary hospitals and 7 primary) and 52 provincial departments of health in Vietnam	Public hospital inpatients	Observational	Dispensing quantity and costs of antimicrobial procurement from tender-winning bids	Total annual cost of antimicrobials (excluding those procured nationally for malaria, TB, influenza and HIV) - defined as monetary value of antimicrobial per DDD.	An estimated 28·6% of the total expenditure in pharmaceutical sales in 30 hospitals for antimicrobials. (US $5·85 billion) Oral antibacterials accounted for 91·4% of total DDDs across all sites. The most common oral antibacterials were the second generation cephalosporins. By AWaRe categories, the average price per DDD of Reserve group antibacterials was the highest (US $15·63 per DDD), followed by the Watch group antibacterials (US $0·86 per DDD), and Access group antibacterial (US $0·4 per DDD).
Dat et al[46] (2022)	English	Hanoi, Can Tho, Hanam, Thai Nguyen and Kontum	March - July 2019	51 primary and secondary hospitals - Coronary Care Units (CCU) in 5 provinces in Vietnam	Adult inpatients	Observational	Questionnaire-based survey of all patients admitted over a 7 consecutive day period in the 51 CCUs	Proportion of adult inpatients on empirical antibiotics in CCU.	Out of 1747 enrolled patients, empirical antibiotic treatments were initiated in 1112 (63·6%) patients. The most frequently prescribed antibiotics were cefotaxime (22·3%), levofloxacin (19%) and ceftazidime (10·8%). Antibiotics were given to 31·5% of patients without documented diagnosis of infection. Watch and/or Reserve group antibiotic were given in 87·3% of patients.
Do et al[57] (2021)	English	Multi-country study including Ba Vi district in Vietnam	2016-2018	Community and private pharmacies	Antibiotic suppliers - including drug suppliers, consumers, households and exit interviews amongst customers purchasing antibiotics	Observational	Questionnaire-based survey in six countries	1. Proportion of self-medication with antibiotics without scripts 2. Proportion of use of antibiotics by households 3. DDD supplied by antibiotic dispensers, AWaRe category, and indications	1. The proportion of antibiotics dispensed without prescription = 773/1399 [55·2%] in Vietnam 2. Vietnam had the second largest proportion of households amongst the 6 countries reporting use of antibiotics in the previous month (416/925) [45·0%] 3. "Access"-group antibiotics were predominant in almost all sites (3664/7222 DDDs) [50·7%] in Vietnam for mainly respiratory infections, followed by systemic infections

Table 2.2 : Summary of included studies reporting antimicrobial consumption in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Region	Year study conducted	Setting	Population	Study design	Sources of measurement	Outcome measure(s) relating to antimicrobial consumption	Main findings
Duong et al[75] (2018)	English	Ho Chi Minh city	2014-2016	3 tertiary paediatric hospitals	Paediatric inpatients	Observational	Questionnaire to paediatric participants with non-bloody, bloody and persistent diarrhoea, followed by clinical staff record of treatment and length of stay outcomes	Proportion of inpatients with paediatric diarrhoea that received antibiotics	85·2% of patients (2697/3166) received empirical antimicrobial treatment. 78·4% with non-bloody diarrhoea, 98·4% with bloody diarrhoea and 76·6% with persistent diarrhoea received antibiotics. Fluoroquinolones were the most used class of antimicrobials (1799/2697; 66·7%).
Johansson et al[76] (2011)	English	Uong Bi, Hanoi and Hai Phong	2007-2008	3 tertiary hospitals	N/A	Observational	Cross-sectional study of quantities of drugs delivered from the pharmacy to ICUs in 3 hospitals, measured in defined daily doses (DDD) per 1000 occupied bed days	1. DDD of antibiotics dispensed by pharmacies 2. Comparison of antibiotic use according to class	The mean antibiotic consumption was 811 DDD per 1000 occupied bed-days. The three most used antibiotics were third generation cephalosporins (351 DDD), followed by carbapenems (160 DDD) and ampicillin ⁄ amoxicillin (146 DDD)
Nga et al[14] (2014)	English	Ba Vi and Dong Da provinces	2010	Community pharmacies	N/A	Observational	Cross-sectional in-pharmacy observation of all information pertaining to drug sales - specifically related to antibiotic transactions	Proportion of drug transactions that include an antibiotic and proportion of antibiotics without a script	The proportion of drug sale transactions that included antibiotics was 24% (499/2083) in the urban sites and 30% (257/870) in the rural sites (p = 0·002). Most antibiotics were sold without a prescription: 88% (439/499) in urban and 91% (234/257) in rural pharmacies (p = 0·2), showing no significant difference between two areas.
Nguyen et al[77] (2019)	English	Can Tho	2016-2017	8 hospitals in Can Tho of various levels	Outpatients	Observational	Questionnaire-based survey on outpatient prescriptions in each hospital	1. Proportion of outpatient prescriptions that include an antibiotic 2. Class of antibiotics prescribed	37% of 2843 prescriptions had at least one antibiotic, out of which 94·6% had one antibiotic and 5·4% had more than one. All prescriptions that had more than one antibiotic prescribed were inappropriate. Cefuroxime accounted for more than 50% of total prescribed antibiotics
Nguyen et al[78] (2020)	English	Da Nang	2017-2018	Da Nang Hospital for Women and Children	Paediatric inpatients with CAP	Observational	Questionnaire-based survey on antibiotic use, clinical history, treatment course, pneumonia outcome and hospitalisation cost	1. Proportion of children started on antibiotics, and antibiotics use 2. Direct hospital cost	2853 (98·0%) children received antibiotics. 2360 (81·1%) received oral antibiotics only and 493(17·0%) received intravenous antibiotics. Intravenous antibiotics were given to 336 (12·3%) children with "non-severe" and 157/176 (89·2%) children with "severe" pneumonia. Hospital admission for oral antibiotics in "non-severe" pneumonia was a major cost driver - US$78·9 per patient, accounting for 54·0% of the total hospitalisation cost

Table 2.2 : Summary of included studies reporting antimicrobial consumption in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Region	Year study conducted	Setting	Population	Study design	Sources of measurement	Outcome measure(s) relating to antimicrobial consumption	Main findings
Nguyen et al[79] (2022)	English	9 provinces in Vietnam	2016-2018	Community	360 drug retailers	Observational	Observation and interview of participants from the community visiting drug retailers/pharmacies that fit inclusion and exclusion criteria	Proportion of individuals purchasing antibiotics without scripts	480/1626 surveyed participants purchased antibiotics, of which 81·7% of which did not have a prescription. In 86·4% of these, participants were prescribed antibiotics by drug sellers themselves. Most antibiotics were sold to treat respiratory tract infections (61·4%), with the 'Access' antibiotics (amoxicillin and cephalexin) being the most frequently sold.
Nguyen et al [49] (2020)	English	An Giang Province	2019	An Giang General hospital	Inpatients in Urology department with urinary tract infection (UTI)	Observational	Cross-sectional survey of medical records with UTI diagnosis	Number of prescriptions with antibiotics, class of antibiotics used. No DDD data available	In 552 patients, 2,992 prescriptions were issued with 5,177 antibiotics were used to treat UTIs. Beta-lactam the most frequently used antibiotic class, including penicillins and cephalosporins with or without beta-lactamase inhibitors.
Le et al[80] (2018)	English	District 8 in Ho Chi Minh city	2016	Community pharmacies in Ho Chi Minh	Simulated client method: Actors and self-reported caregivers	Observational	1. Simulated client method: Actors presenting to pharmacy to survey practice of retail pharmacies for paediatric diarrhoea 2.Self-reported caregiver community survey on the management and antimicrobial treatment of paediatric diarrhoea.	1. Antimicrobial recommendation by urban community pharmacies for childhood diarrhoea 2. Rate of sale of ciprofloxacin by actor without prescription 3. Self-reported purchase of antimicrobials from pharmacies, including in the last 30 days	8% (3/37) and 22% (8/37) of outlets sold antimicrobials for paediatric watery and mucoid diarrhoea, respectively to the actors. 100% of pharmacies sold Ciprofloxacin when asked by actor without explanation. 54% of parents/caregivers (213/394) reported they had at some time purchased antimicrobials from pharmacies, with 85% having done so within the 30 days prior
Phu et al[47] (2016)	English	Across Vietnam	2012-2013	Intensive care units in 14 national and provincial hospitals across Vietnam	Inpatients in Intensive care units	Observational	Repeated point prevalence survey (PPS) to assess antimicrobial use	Proportion of patients receiving antimicrobials in ICU and its indications, and according to class	The proportion of patients receiving antimicrobials at survey time ranged from 50·0% to 99·8% per ICU, with a pooled proportion of 84·8% (2787/3287). The main indications for antimicrobial use were community-acquired infections 41·8% (2386/5711) and HAIs 33·9% (1937/5711). Systemic antimicrobials accounted for 97·9% (5590/5711) of the total antimicrobials used. Third generation cephalosporins, fluoroquinolones, and carbapenems were used most common, accounting for 20·1% (1126/5590), 19·4% (1082/5590), and 14·1% (786/5590), respectively.

Table 2.2 : Summary of included studies reporting antimicrobial consumption in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Region	Year study conducted	Setting	Population	Study design	Sources of measurement	Outcome measure(s) relating to antimicrobial consumption	Main findings
Sohn et al[81] (2013)	English	Ho Chi Minh City	1999	11 surgical wards and 2 intensive care units in Cho Ray general hospital	Inpatients	Observational	Point prevalence survey of all patients who had surgery within 30 days on survey date	Proportion of patients who underwent surgery in the last 30 days who had preoperative, prophylactic and post-operative antimicrobials	Patients received antimicrobials preoperatively (n = 198; 51%), postoperatively (n = 390; 99·7%), or both. Of the 278 patients who appropriately had antimicrobial prophylaxis prior to surgery, 277 (99·6%) received postoperative antimicrobials for more than 24 hours after surgery.
Thu et al[13] (2012)	English	Across Vietnam	2008	36 hospitals - 2 national level hospitals, 18 provincial level hospitals and 16 district level hospitals across Vietnam	Inpatients in all wards on a selected day	Observational	Point-prevalence survey on a designated day	1. Prevalence of antibiotic prescription, stratified to ward 2. Appropriateness of indications for these prescriptions compared to standard published guidelines	67·4% (5,104/7,571 patients) received antibiotics, ranging from 48·2% (1,979/4,105) in medical ward patients to 93·2% (1,780/1,910) in surgery ward patients, with higher rates observed in surgical wards (adjusted odds ratio [aOR], 13·2; 95% CI 10·9-16·1), obstetrics and gynaecology wards (aOR, 5·0; 95% CI, 3·9-6·5), followed by paediatric and intensive care units. Patients in district and provincial hospitals were more likely to receive antibiotics compared to those in national hospitals. Antibiotics were less frequently prescribed in hospitals with laboratories. The indication was judged as appropriate in 3,531 patients (69·2%), including 2791 (54·7%) for empirical therapy, 546 (10·7%) for prophylaxis, and 194 (3·8%) for pathogen-directed therapy. Inappropriate antibiotic indication was associated with hospital ward (surgical and O&G wards), hospital type and regions, as well as hospital level.
Trinh et al[82] (2014)	English	Across Vietnam	2011	10 national and provincial hospitals in north, central, and south Vietnam	All inpatients with community-acquired pneumonia	Observational	Retrospective survey of patients admitted with community-acquired bacterial pneumonia and were prescribed at least one antibiotic	1. Proportion of inpatients with community acquired pneumonia on antibiotics 2. Class of antibiotic used	Most (93·4%) patients received antibiotics intravenously despite most cases being mild. A monotherapy regimen accounted for 42·4% (275) of all the antibiotic regimens, with third generation cephalosporins (C3G) being most prescribed. The odds of prescribing combined antibiotics as empiric therapy were significantly higher in the infectious disease wards and in the respiratory wards than in the general internal medicine ward

Table 2.2 : Summary of included studies reporting antimicrobial consumption in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Region	Year study conducted	Setting	Population	Study design	Sources of measurement	Outcome measure(s) relating to antimicrobial consumption	Main findings
Nguyen et al [83] (2020)	English	Ba Vi district	2017-2018	20 community antibiotic suppliers	Community – customers purchasing medications	Observational	Face-to-face customer exit surveys	1. Proportion of the community in rural Vietnam according accessing antibiotics from local pharmacies according to AWaRe classification, and the corresponding DOT 2. Number of antibiotics supplied without a prescription	1342/1404 antibiotic encounters were for humans, out of which 28·9% were for children. In the total of 1342 antibiotic encounters, access-group antibiotics were provided in 792 encounters (59·0%), watch-group antibiotics in 527 encounters (39·3%) and in 23 encounters where antibiotics were not recommended at all (1·7%). The total DOT with antibiotics was 5889, of which 59·2% were access-group, 38·9% were watch-group and 1·9% where antibiotics were not recommended. Antibiotics were purchased without prescription in 773 encounters (57·6%).
Nguyen et al[48] (2023)	English	Nam Dinh province	2019	112 commune health centres in 6 rural districts of Nam Dinh province	Outpatients with acute respiratory illnesses(ARI)	Observational	Cross-sectional study of health records for outpatients who were registered with the Vietnamese Health Insurance Scheme that were diagnosed with ARIs.	1. Proportion of outpatients consuming antibiotics for ARI 2. Antibiotic consumption by type of ARI 3. Antibiotic consumption by World Health Organization's Access-Watch-Reserve (WHO AWaRe) class for acute respiratory infections (ARIs)	1. Among 193,010 ARI visits, 187,144 (97·0%) were prescribed at least one systemic antibiotic. 2. Antibiotic prescription proportion was high in respiratory illnesses such as acute pharyngitis (97·2%) and acute bronchitis (97·3%) Even in patients diagnosed with influenza (viral) the proportion of patients prescribed an antibiotic was 77·3%. 3. Between WHO-AWaRe antibiotic groups, access-group antibiotics were the most frequently prescribed (172,976 visits [89·6% of the total visits for ARIs]). Watch-group antibiotics were less frequently prescribed, at 5·9%
Hoa et al[63] (2011)	English	Ba Vi district	2007	Community	Caregivers	Observational	Questionnaire-based survey and interview to caregivers on their attitudes with children <5 with mild acute respiratory infections	1. Proportion of children <5 years using an antibiotic for mild ARIs in the last 28days. 2. Antibiotic use in children <5 years old in a repeat survey after 28 days	1. In a 28-day period, 62% of children with mild ARIs had been given antibiotics. 63% of antibiotic courses were used for mild ARIs - most of which were recommended by healthcare providers (82%). At 28 day follow up, of the 823 children, 30% had used two or more antibiotic courses during the period. The average duration of the antibiotic courses was 3·54 days (range 1–22 days; median 3·0 days),

Table 2.2 : Summary of included studies reporting antimicrobial consumption in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Region	Year study conducted	Setting	Population	Study design	Sources of measurement	Outcome measure(s) relating to antimicrobial consumption	Main findings
Zawahir et al[15] (2022)	English	Hanoi, Thanh Hoa, Ca Mau and An Giang province	2019	Community pharmacies and drug counters in 40 districts	Actors playing members of the community	Observational	Standardised patient survey recording direct antibiotic request, symptoms-based antibiotic request and prescription-based request played by actors (acting as members of the community)	1. Proportion of antibiotics supplied without a prescription 2. Proportion of antibiotics supplied when directly requested	Antibiotics were supplied without a prescription in 558 [88% (95%CI 85–91%)] of interactions where symptoms of a viral URTI were reported. When antibiotics were directly requested, 135 (42%) interactions were fulfilled without a prescription. Sulphonamides were the most common class of antibiotics supplied. Female patient actors were more likely than males to obtain antibiotics for URTI for both symptom-based and direct product requests, however there was no difference for the actors reporting a child with acute watery diarrhoeal symptoms.
Nguyen et al[68] (2021)	Vietnamese	Kien Giang province	2018	Vinh Thuan General Hospital	N/A	Observational	Hospital pharmacy data of antibiotics	1. Proportion of drugs used that were antibiotics, and cost associated with it 2. DDD/100 bed-days in inpatient treatment	56 out of 419 drug items used were antibiotics with a cost of VND 4·32 billion,(US$ 170590)[84] accounting for 27·3% of the total cost of drugs used at the hospital. Antibiotics were calculated to account for 35·8 DDD/100-bed-days, in which the cephalosporins contributed the most with 27·6 DDD/100 bed-days
Pham et al[85] (2021)	Vietnamese	Bac Giang province	2020	Yen Dung medical centre	Inpatients	Observational	Medicine management software and 300 medical records that were randomly withdrawn	1. DDD of antibiotics used 3. Number of antibiotics used for each patient and antibiotic duration	74025 DDD of antibiotics were purchased in total and represented 65·2% of cost. No bed -days data available. Beta- lactams were the most used with 60·5 DDD (81·7%) and account for 78·6% of cost. 65·3% of patients were prescribed one antibiotic,30·3% prescribed two, and 4·3% prescribed three. 54·3% patients were prescribed antibiotics for 5-7 days; 43·3% extending to 7-10 days, and 2·3% of patients requiring antibiotics for more than 10 days.
Nguyen [50] 2019	Vietnamese	Hung Yen province	2016	Hung Yen General Hospital	N/A	Observational	The list of drugs used in the hospital released by pharmacy that year	1. Cost of antibiotics and its percentage of total drug cost 3. DDD/100 bed-days of antibiotic groups	The antibiotic costs accounted for 34·2% of the total drug costs. The main antibiotic route was parenteral (97·2% of total antimicrobial cost). Beta-lactam antibiotics were the most frequently used (56·5% of antimicrobials, 75% of cost). Total antibiotic consumption was 69·7 DDD/100 bed days. Ceftriaxone use was the highest with 12·1 DDD/100 bed- day

Table 2.2 : Summary of included studies reporting antimicrobial consumption in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Region	Year study conducted	Setting	Population	Study design	Sources of measurement	Outcome measure(s) relating to antimicrobial consumption	Main findings
Vu et al[86] (2022)	Vietnamese	Quang Ninh Province	2021	Vietnamese Swedish UongBi Hospital	Patients post-appendectomy, hernia repair and cholecystectomy on surgical antibiotic prophylaxis	Observational	Medical records	1. Proportion of surgeries using antibiotic prophylaxis 2. Length of hospital stay for patients on antibiotic prophylaxis	80·8% of patients who underwent appendectomy were on antibiotic prophylaxis, 14·4% for inguinal hernia surgery and 4·8% for cholecystectomy. The average hospital stay was 3·8 ± 21·3 days.
Nguyen et al[69] (2019)	Vietnamese	Hanoi	2017	354 Military Hospital	Inpatients	Observational	Inpatient pharmacy data	1. Proportion of antibiotics in the hospital's medication list 2. Antibiotic costs	Antibiotics accounted for 15·4% of items in hospital medication, costing VND 19·9 billion,(US$750,283)[84] equivalent to 25% of total value of all drugs used. The most used antibiotic were beta-lactams (40·7% of antibiotics, accounting for 56·5% of drug cost), notably 3rd generation cephalosporins.
Nguyen et al[51] (2019)	Vietnamese	Hanoi	2016	Vietnam-Cuba Friendship Hospital	Inpatients	Observational	Inpatient pharmacy data	1. Proportion of antibiotics in the hospital's medication list. 2. Antibiotic consumption according to type of antibiotics measured in DDD/100 bed-days 3. Antibiotic cost/DDD in the hospital	Antibiotics accounted for the highest portion of drug expenditure (32·3%) at 2·5 billion VND(US$98287)[84], out of which beta-lactams accounted for highest cost. (81·6%) Antibiotics with the highest consumption measured in DDD/100 bed-days were Augmentin, Cefazolin and Cefuroxime, while the highest antibiotic cost/DDD was Cefoperazole + sulbactam and Meropenem
Ha et al[45] (2018)	Vietnamese	Nghe An province	2016	Nghe An Trauma and Orthopaedic Hospital	Inpatients	Observational	Inpatient pharmacy data	1. DDD/100 bed-days for Nghe An Trauma and Orthopaedic (TOH) Hospital 2. Antibiotic cost/DDD in the hospital	Consumption of antibiotics in inpatient treatment at Nghe An TOH was 67 DDD/100 bed-day, with Amoxicillin clavulanic acid having the highest (11·2 DDD/100 bed-days). The highest antibiotic cost/DDD was Imipenem. IV antibiotics accounted for a high proportion - 76·9% of antibiotics and 97% of cost
Nguyen et al[52] (2021)	Vietnamese	Ho Chi Minh city	2018	Pham Ngoc Thach Hospital	Inpatients	Observational	Inpatient pharmacy data	1. DDD/1000 bed-days of total antibiotic use and according to class 2. Antibiotic costs in the hospital	The total antibiotic consumption for the hospital was 975·3 DDD/1000 bed-days, dominated by the beta-lactams. Beta-lactams accounted for 44·1% of antibiotics used, and 74% of cost. 39·3% of the total medicine costs were spent on antibiotics, out of which 85·7% were for intravenous antibiotics.

Table 2.2 : Summary of included studies reporting antimicrobial consumption in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Region	Year study conducted	Setting	Population	Study design	Sources of measurement	Outcome measure(s) relating to antimicrobial consumption	Main findings
Nguyen et al[53] (2016)	Vietnamese	Hanoi	2015	Thanh Nhan hospital	Surgical inpatients	Observational	Medical records of inpatients who had surgery, as well as reports from Pharmaceutical Department and General Surgery Department	1. Proportion of antibiotic use in surgical patients, and timing 2. Antibiotic classes most used	100% of patients used antibiotics post-operatively, and 26·3% of patients received antibiotics for pre-operatively. Beta-lactam antibiotics were the antibiotic class used the most at 52%, mainly consisting of second-generation cephalosporins.
Pham et al[87] (2019)	Vietnamese	Ho Chi Minh city	2017	General Medicine department at District 11 Hospital	Surgical inpatients	Observational	Inpatient medical records	1. Defined daily doses/100 bed-days in the hospital 2. Most common antibiotics used according to class	Total antibiotic consumption was 207·7 DDD/100 bed-days. The 5 most used antibiotics (89% of total DDD) were Cefuroxime, Ciprofloxacin, Cefixime, Ceftazidime, and Levofloxacin. Third-generation cephalosporins accounted for the highest consumption (76·4%) of antibiotics, predominated by Ceftazidime.

AWaRe classification is a tool used to consider the impact of different antibiotic classes on antimicrobial resistance. "Access" category antibiotics display low resistance potential, are narrow spectrum and of low cost, "Watch" antibiotics are broader-spectrum, higher cost and required in severe presentations, whereas "Reserve" category antibiotics are the last choice to treat multi-drug-resistant infections.

aOR: adjusted odds ratio

Table 2.3: Summary of included studies reporting appropriateness of antimicrobial prescribing against a reference guideline in Vietnam

Table 2.3: Summary of included studies reporting appropriateness of antimicrobial prescribing against a reference guideline in Vietnam

Study (Year published)	Language	Year study conducted	Region	Study design	Setting	Population	Source of measurement related to antibiotic appropriateness	Guidelines used to assess appropriateness	Outcome measure related to antibiotic use and its appropriateness	Main findings
Minh et al[58] (2020)	English	2009-2010	Ho Chi Minh city	Observational	Paediatric outpatient department in Children's Hospital (tertiary) in Ho Chi Minh city	Children with mild acute respiratory infections (ARI)	Medical records	Systematic reviews on ARIs (Cochrane reviews), local hospital guidelines and international guidelines (Infectious Diseases Society of America)	1. Proportion of antibiotics prescribed in children with ARI 2. Appropriateness of the antibiotic use based upon guidelines 3. Appropriateness of antibiotic based upon detected pathogens	Antibiotic use was considered inappropriate in 90·1% and 67·5% of the prescriptions, based on guidelines and detected pathogens, respectively Antibiotics were prescribed for 99·6% of patients, with a majority being 2nd and 3rd generation oral cephalosporins and amoxicillin +/-clavulanic acid.
Nguyen et al[71] (2022)	English	2020	Ho Chi Minh city	Observational	Department of Gastroenterology, Thong Nhat National Hospital.	Inpatients who underwent invasive gastrointestinal surgery	Medical records	2015 Vietnamese national antibiotic guideline	1. Appropriateness of prophylactic antibiotics before surgery 2. Appropriateness of post-operative antibiotic indication	The appropriateness of prophylactic antibiotics was 97·2%, however in 12·4% of patients, antibiotics were continued over 24 h postoperatively, making the overall appropriate rate of prophylactic antibiotics 54·7%. Post-operative antibiotic appropriateness was 38·5%. The median duration of postoperative antibiotic use was 9 (7–12) days; with the most prolonged duration of antibiotic use was 28 days. β-lactam and fluoroquinolone were the most used groups.
Nguyen-Hoang et al[88] (2021)	English	2018	Ho Chi Minh city	Observational	Thong Nhat National Hospital	Inpatients diagnosed with sepsis or septic shock	Medical records	1. Lexicomp Lexi-Drugs Multinational guideline 2. Micromedex Drug Reference 3. Sanford Guide to Antimicrobial Therapy	1. Appropriateness of empirical antibiotics in sepsis 2. Treatment outcome in those with appropriate antibiotics	Appropriate empirical antimicrobial agents were initiated in 56·6% (73/134) of all sepsis cases and/or septic shock. Of these patients, 31 cases (42·5%) and 61 cases (83·6%) received appropriate antimicrobials according to dosage and route of administration, respectively, bringing the overall rate of appropriate empirical antimicrobial therapy down to 23·3% of all cases. Success in treatment was markedly increased in patients receiving appropriate initial empirical antibiotics compared with those who did not (96·7% versus 75·8%, p=0·023).

Table 2.3: Summary of included studies reporting appropriateness of antimicrobial prescribing against a reference guideline in Vietnam

Study (Year published)	Language	Year study conducted	Region	Study design	Setting	Population	Source of measurement related to antibiotic appropriateness	Guidelines used to assess appropriateness	Outcome measure related to antibiotic use and its appropriateness	Main findings
Nguyen et al[70] (2022)	Vietnamese	2021	Ho Chi Minh city	Observational	Department of Infectious Diseases in Thong Nhat National Hospital	Inpatients with at least one antibiotic prescribed	Medical records	Decision 5631/QD-BYT or Sanford Guide 2021	1.Appropriateness in intravenous (IV) to per oral (PO) antibiotic de-escalation. 2. LOS in patients who had conversion to PO vs those who didn't	The overall appropriate rate of switching from IV to PO antibiotics was 43·8%. Appropriateness in timing of switching was 46·9%, oral antibiotic choice: 96·9% and dose: 96·9%. Median hospital stay was significantly lower in the converted patients group compared with the non-converted (6·7 days vs 11·1 days, $p < 0·001$)
Nguyen et al[89] (2020)	Vietnamese	2020	Hanoi	Observational	108 Military Central Hospital	Inpatients who had clean and clean surgery across all surgical specialties	Medical records	Local hospital guidelines	Appropriateness in use of antibiotic prophylaxis for surgical procedures according to local hospital guidelines	The overall proportion of using prophylaxis antibiotics is 65·93%. Based on local hospital guidelines, 100% of specialties complied with the timing of preoperative prophylactic antibiotics, 88·90% had the correct choice ,100% continued to use prophylactic antibiotics after surgery in accordance with the indications and duration of use as recommended. Only 77·78% of prophylactic antibiotic cases were changed to therapeutic antibiotics when indicated post-operatively
Ngo et al[90] (2022)	Vietnamese	2021	An Giang province, Vietnam	Observational	General Hospital of An Giang	Inpatients in Internal Medicine, Paediatrics and ICU departments with community-acquired pneumonia	Medical records	MoH 2015 antibiotic guidelines	Appropriateness of antibiotics used for CAP in terms of dose, duration and drug interactions	The proportion of appropriate use of antibiotics accounted for 19·8%. Appropriateness rate in dosing and duration was 71·5% and 61·6% respectively The rate of no drug interactions was 70·6%, and moderate and major interactions were 7·2% and 22·2%, respectively.

Table 2.3: Summary of included studies reporting appropriateness of antimicrobial prescribing against a reference guideline in Vietnam

Study (Year published)	Language	Year study conducted	Region	Study design	Setting	Population	Source of measurement related to antibiotic appropriateness	Guidelines used to assess appropriateness	Outcome measure related to antibiotic use and its appropriateness	Main findings
Nguyen et al[91] (2020)	Vietnamese	2017	Thai Binh and Nam Dinh province	Observational	Thai Binh and Nam Dinh general hospitals	Inpatients with respiratory, skin and soft tissue, urinary, and abdominal infections	Medical records	MoH decision 772/QD-BYT (specific guideline not mentioned)	1. Proportion of appropriate antibiotic use according to empiric choice and after having microbiology results for common infections 2. Proportion of antibiotics administered correctly in its preparation	Proportion of appropriate empiric antibiotic choice in Thai Binh General Hospital was 40·1%, whereas in Nam Dinh General Hospital it was 38·7%. On obtaining microbiology results, 71·6% of antibiotic prescriptions were appropriate in Thai Binh, however this was 40·3% at Nam Dinh hospital, showing a statistical difference between both hospitals (p<0·05) The proportion of antibiotics administered correctly at the two general hospitals of Thai Binh and Nam Dinh are 68·4% and 73·8%, respectively (p>0·05)
Ly et al[92] (2011)	Vietnamese	2011	Ho Chi Minh city	Observational	Blood Transfusion and Haematology Hospital	Inpatients with infections in ICU	Medical record	Assessed based on outcome of microbiology susceptibilities	1. Proportion of appropriate use of empiric antibiotic in the ICU	80% of empiric antibiotics started on inpatients in ICU were tested sensitive in antibiogram (microbiology susceptibility testing) later; however unclear if this was the best narrow-spectrum option

ARI: Acute respiratory infection

Table 2.4: Summary of studies reporting the implementation of an AMS program in healthcare facilities and the community in Vietnam

Table 2.4: Summary of studies reporting the implementation of an antimicrobial stewardship (AMS) program in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Year of study	Region	Study design	Setting	Population	Outcome measures related to presence of AMS	AMS program
Cai et al (2022)[64]	English	2020-2021	Nam Dinh province	Implementation study	Villages from communes in 2 districts	General community	Feasibility of implementation of participatory learning and action (PLA) intervention as a method of implementing AMS awareness in the community	Community (public) education about AMS and AMR - mass village meetings, photo capturing of real-life situations of antibiotic use followed by a community exhibition of pictures and raising awareness on AMR
Chang et al (2022)[93]	English	2020-2021	Vietnam (areas not specified)	Observational	2 secondary & 2 tertiary hospitals in Vietnam	Hospitals	Describe AMS programmes in the country that best reflect local AMS practice in each country	1. Hospital leadership support 2. Presence of AMS teams 3. AMS interventions - prospective audit feedback or pre-authorization and usage of treatment guidelines 4. Presence of AMS monitoring and reporting - DDD, antibiograms and publishing data about AMS and AMR 5. Hospital infrastructure - microbiology services
Huong et al (2021)[94]	English	2020 - 2021	Hai Phong and Cao Lanh	Implementation study	2 Provincial hospitals - Viet Tiep Hospital and Dong Thap General Hospital	Hospitals	Assess feasibility of AMS programme in the two hospitals using SWOT analysis, stakeholder meeting, baseline data, planning process as well as the actual implementation	1. Training and education 2. Prospective audit and feedback
Huong et al (2021)[95]	English	2018	All over Vietnam - VINARES network: 7 hospitals	Observational	2 national - (Hue Central General Hospital, Hue; Can Tho Central General Hospital, Can Tho), 2 specialised (National Hospital for Tropical Diseases, Ha Noi; Hospital for Tropical Diseases, Ho Chi Minh) and 3 provincial - Uong Bi Viet Nam-Sweden Hospital, Quang Ninh; Viet Tiep Hospital, Hai Phong; Da Nang Hospital, Da Nang)	Hospitals	Analyse the current state of AMS in hospitals in Vietnam to identify factors determining success in AMS implementation and associated challenges to inform planning and design of future programmes.	1. Antibiotic guidelines 2. Education activities 3. Building IT and data capacity for AMS activities 4. Pre-authorisation of antibiotic use 5. Audit and feedback 6. Documentation of treatment, monitoring and reporting. Gaps identified - microbiology services, drug supply, role of doctors
Lee et al (2021)[96]	English	2014	Vietnam (location of participating physicians not disclosed)	Observational	Hospitals across Vietnam	ID physicians	Survey to identify existing capacities and practices, and define the resources needed to establish antimicrobial stewardship where it is lacking.	1. Presence and number of Infectious Diseases Physicians (Adult and Paediatric) 2. Pre-authorisation of restricted antibiotics before dispensing 3. Audit and feedback 4. Automatic de-escalation of restricted antibiotics 5. Using technology for assistance with prescribing and educational activities

Table 2.4: Summary of studies reporting the implementation of an AMS program in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Year of study	Region	Study design	Setting	Population	Outcome measures related to presence of AMS	AMS program
Wertheim et al (2013)[97]	English	2012	Across Vietnam	Implementation study	VINARES network hospitals - National Hospital for Tropical Diseases, National Hospital for Paediatrics, Bach Mai Hospital, Viet Duc hospital, Saint Paul Hospital, Vietnam-Sweden Uong Bi Hospital, Viet Tiep Hospital, Hue Central General Hospital, Da Nang General Hospital, Binh Dinh General Hospital, Khanh Hoa Provincial Hospital, Dac Lac Provincial Hospital, Chio Ray Hospital, Children's Hospital Number 1, Hospital for Tropical Diseases, Can Tho Central Hospital	Hospitals	Study aimed to provide impetus and tools to support development of an effective antimicrobial stewardship programme for Viet Nam and thus bridge the "know–do" gap	1. Workshop for key stakeholders 2. Database for pharmacies to calculate monthly antibiotic consumption in defined daily dosages 3. Provision of computer to each lab for surveillance software, guidelines to Clinical and Laboratory Standards Institute (CLSI) translated into Vietnamese, and American Type Culture Collection(ATCC) reference strains for internal quality control. Training and materials provided by VINARES 4. Post-prescription surveys to collect information on route, dose and indication.
Nguyen et al (2021)[98]	Vietnamese	2020	Ho Chi Minh city	Observational	57 health facilities - 53 hospitals and 4 health centres (public and private) in Ho Chi Minh city	Healthcare workers	Survey to assess if antibiotic stewardship programme activities have been implemented	1. Monitoring of antibiotic prescribing 2. Participation of physicians in AMS activities (not specified) 3. Specific budget allocation for AMS activities Lack of important AMS interventions noted such as lack of microbiology support for reporting of antibiotic resistance and *Clostridium difficile* infection rates, monitoring of antibiotic consumption and human resources to enact AMS interventions
Bui et al (2022)[99]	Vietnamese	2021	Hanoi	Observational	Thanh Nhan General Hospital	Healthcare workers	Survey was carried to assess doctor's approval on AMS activities carried out by clinical pharmacists	1. Antibiotic request forms 2. Clinical pharmacist interventions including providing advice on antibiotic discontinuation, dosage changes, limiting approval time of restricted antibiotics and recommending supplement microbiology testing as required

SWOT analysis: A strategic planning tool that helps identify an organisation's strengths, weaknesses, opportunities, and threats

Table 2.5: Summary of studies reporting the effect of AMS interventions on various outcomes in healthcare facilities and the community in Vietnam

Table 2.5: Summary of studies reporting the effect of AMS interventions on various outcomes in healthcare facilities and the community in Vietnam

Study (Year published)	**Language**	**Year study conducted**	**Region**	**Study design**	**Setting**	**(P) Population**	**(I)AMS intervention**	**(C) Comparison**	**(O) Outcome measure related to AMS intervention**	**Main findings**
Do et al[32] (2016)	English	2014-2015	Hanoi	RCT	10 primary healthcare centres	Outpatients presenting with non-severe acute respiratory tract infection	C-reactive protein (CRP) point-of-care testing - laboratory biomarker	Routine care	1. Proportion of patients receiving antibiotics within 14 days of follow-up in the CRP-guided group vs routine care group 2. Antimicrobial activity in urine sample as a surrogate for antibiotic use in follow up patients between the two groups	581/902 (64%) patients were prescribed in CRP-guided group vs 738/947 (78%) patients in routine care (ITT analysis) within 14 days of follow-up (odds ratio [OR] 0·49, 95% CI 0·40–0·61; p<0·0001). Antimicrobial activity in a urine sample on day 3, 4, or 5 was significantly lower in the CRP group (30%) than in the routine treatment group (36%) (OR 0·78, 95% CI 0·63–0·95; p=0·015)
Lubell et al[33] (2018)	English	2016	Hanoi	RCT	10 primary healthcare centres (Based on Do et al[32] data)	Outpatients presenting with non-severe acute respiratory tract infection	C-reactive protein (CRP) point-of-care testing - laboratory biomarker	Routine care	Source of measurement: data from Do et al[32] Costs associated with CRP-guided group versus routine care	Similar costs in managing illness in both CRP-guided and routine care groups, in the context of low levels of adherence to test results. (p=0·28) Sensitivity analyses showed that higher adherence to test results would make the test cost-beneficial
Do et al [100] (2021)	English	2018-2019	Hanoi	Before-and-after study	Provincial general hospital	Hospital inpatients in Internal Medicine, Emergency and Outpatient department with community-acquired pneumonia (CAP)	A quality improvement process was divided into four phases (P1 to P4) over 10 months: (P1); plan—baseline data collection and mapping of existing care pathways (P2); do— training for new CAP quality standards and implementation including CURB-65 documentation, and radiology performance to confirm diagnosis within 4 hours (P3); study—mixed-method assessment (P4); act—re-training, recording quality	1. Comparison between P2 and P1 (baseline) 2. Comparison between P4 and P1 3. Comparison between P4 and P2	Effect of AMS intervention on 1. CURB65 documentation 2. Radiology performance to confirm diagnosis within 4 hours 3. Admission appropriateness 4. Use of antibiotic therapy	1. Documentation of the CURB-65 score improved significantly in P4(95·8%) compared to baseline (67·9%) (p<0·001) and against the P2 performance(80·0%) (p=0·008). 2. There was improvement in radiology performance to confirm a diagnosis within 4 hours in P4 compared to baseline (39·3% vs 76·4%, p=0·001) 3. There was no significant change in the admission appropriateness judged by the CURB-65 score or in the use of antibiotic therapy.

Table 2.5: Summary of studies reporting the effect of AMS interventions on various outcomes in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Year study conducted	Region	Study design	Setting	(P) Population	(I)AMS intervention	(C) Comparison	(O) Outcome measure related to AMS intervention	Main findings
							indications, re-implementation and re-assessment			
Hoa et al[35] (2017)	English	2010-2011	Ba Vi district	Randomised controlled trial	32 communes in Ba Vi district	Health care providers (HCPs)	Multi-faceted educational intervention on management of acute respiratory infections in children including education on appropriate antibiotic use, case-scenario discussion and poster distribution	Educational intervention on another topic - Sexually transmitted infections (to overcome Hawthorne effect)	1. Proportion of HCPs with improvement in knowledge (measured using a knowledge sum score of 8 questions based on knowledge and practical scenario components) on ARIs in intervention group compared to control group 2.Change in practice of antibiotic prescribing decisions in the intervention and control arms (measured by surveying prescribing/selling forms filled out by HCP) before and after intervention	1. Total knowledge score increased in the intervention group (by 1·17 points) compared to control group (by 0·48points) [p=0·054]. When stratified for healthy facility type and education level, the knowledge score improved in intervention group. 2. There was an improvement in decisions to prescribe antibiotics in mild ARIs in the intervention arm (28% improvement in intervention arm vs 3% improvement in control arm), though this was not statistically significant (aOR 1·0, p=0·99). The difference between both arms was significant with severe ARIs, where there was 14% more antibiotics in the control group post intervention, and 1% less in the intervention group, with an aOR of 30·1, p=0·048)
Nguyen et al[36] (2022)	English	2016-2018	Ho Chi Minh city	Before-After study	Hospital for Tropical Diseases in Ho Chi Minh City	Paediatric inpatients	2016 - 2018 Antibiotic stewardship programme (ASP): 1. Distribution of hospital antibiotic policy 2. Distribution of restricted antimicrobial list by MoH requiring approval 3. Establishment of treatment guidelines 4. Establishment of infection control practices 5. Antibiotic use monitoring 6. Educational activities 2018: Enhancement of programme + incorporation	Enhanced ASP (2018) compared to original ASP (2016-2018)	1. Defined daily doses (DDD) per 1000 patient-days 2. Days of therapy (DOT) per 1000 patient-days 3. Proportion of antibiotic use by the World Health Organization Access, Watch, and Reserve (AWaRe) system; Access-to-Watch ratio	The enhanced ASP did not improve antibiotic prescribing by DDDs per 1000 patient-days (RR: 1·05; 95% CI: 0·94-1·17) and DOT per 1000 patient-days (RR 1·11; 0·99-1·25) compared to the original ASP. The percentage of Access antibiotics prescribed, and the Access-to-Watch ratio increased after the enhanced ASP (RR 1·73; 1·38-2·17). There was no significant difference in adverse outcomes between the original and enhanced ASP (RR 1·25; 0·78-2·00).

Table 2.5: Summary of studies reporting the effect of AMS interventions on various outcomes in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Year study conducted	Region	Study design	Setting	(P) Population	(I)AMS intervention	(C) Comparison	(O) Outcome measure related to AMS intervention	Main findings
							of information technology (e-guidelines, remote antibiotic prescribing, real-time antibiotic monitoring)			
Nadjm et al [34] (2019)	English	2014-2016	Hanoi and Ho Chi Minh city	Randomised controlled trial	National Hospital of Tropical Diseases (NHTD) in Hanoi and Hospital for Tropical Diseases (HTD)	Blood culture samples from hospital inpatients	Use of matrix-assisted laser desorption/ionization time-of-flight spectrometry (MALDI-TOF) for identifying microorganisms in blood cultures and sterile samples	Conventional methods – Gram-staining, API test strips, VITEK$_2$ and other tests as per standard operating procedures	1. Timeliness to optimal antimicrobial therapy within 24 hours and 48 hours in the intervention and control arms 3. Reasons for non-optimal antibiotic prescription	No difference in timeliness to optimal antimicrobial therapy within 24 hours in intervention and control arms (aOR 1·17; 95% CI 0·82–1·67, p = 0·40) nor 48 hours [aOR 0·99 (95%CI 0·81–1·22) p = 0·937]. The predominant reason for a treatment to be considered non-optimal was because therapy was too broad (254/373, 68·1%). Subgroup of patients with Gram- positive organisms cultured showed a trend towards an increased proportion on optimal therapy at 24 h in the MALDITOF-MS arm (45/103, 43·7%) compared to the control arm (41/111, 36·9%; p = 0·1)
Nguyen-Thi et al[37] (2021)	English	2016-2020	Ho Chi Minh city	Before-After study	Hospital for Tropical Diseases	Hospital inpatients	New Antibiotic Stewardship Programme (n-ASP): 1. Increased blood collection into 2 bottles, using MALDI-TOF system 2. Restricting to a maximum of two antibiotics allowed in a prescription 3. All IV antibiotics and PO Linezolid get a consultation 3. Antibiotic approval process via hospital management software 4. Presence of 9 physicians and 4 clinical pharmacists 5. Compliance and reporting of results monthly	Previous-ASP (p-ASP): 1. Only limited antibiotics needed consultation 2. Presence of 2 physicians and 3 clinical pharmacists 3. One compliance report in 2017	1. Clinical outcomes on patients on Vancomycin 2. Differences in length of therapy (LOT) and day of therapy (DOT) of Vancomycin use in the two groups 3. Differences in Vancomycin cost in the two groups	The mortality rate reduced in new-ASP, compared to previous- ASP was higher than that in new-ASP (25·98%, vs 37·10% vs p <0·05). New-ASP had higher length of therapy (LOT), and day of therapy (DOT) compared to previous-ASP, but a lower cost USD$1775·5 (95% CI, 1576·22–1974·88) compared to USD$1891·22 (95% CI, 1713·46–2068·98) in previous-ASP.
Ory et al[101] (2022)	English	2016-2019	Hai Phong	Observational	Viet Tiep general hospital	Orthopaedic inpatients	Antimicrobial stewardship as well as infection control practices instituted. Once a year training in antibiotic prophylaxis and therapy for	Nil comparison	Prevalence of surgical site infection (SSI)	Prevalence of SSIs reduced without statistical significance from 7·8% (n=4/51) to 5·4% (n=2/37), p = 0·70. For antibiotic prophylaxis, a third-generation cephalosporin was given for longer than 48h after surgery in most cases. Of the SSI

Table 2.5: Summary of studies reporting the effect of AMS interventions on various outcomes in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Year study conducted	Region	Study design	Setting	(P) Population	(I)AMS intervention	(C) Comparison	(O) Outcome measure related to AMS intervention	Main findings
							surgeons was provided by an Infectious Diseases specialist in the orthopaedic ward, in accordance with CDC guidelines. Infection control hand hygiene training and posters on surgical preparation were carried out.			identified, the most frequently isolated microorganism was *Staphylococcus aureus*.
Phan et al[102] (2022)	English	2017-2020	Ho Chi Minh city	Before-After study	Thong Nhat general Hospital	Hospital inpatients who had undergone clean or clean-contaminated procedures in the following six departments of surgery: Trauma and Orthopaedics, Thoracic Vascular, Gastroenterology, Hepatobiliary, Urology, and Request- based	Period 1 (July 2017 - August 2019): Inauguration of AMS scheme. Period 2 (September 2019-February 2020): Implementation of antibiotic guidelines, formation of AMS teams/committees and restriction on antimicrobial use Period 3 (Feb 2020 - 2022): AMS activities as in Period 2 + strict monitoring of antibiotic prophylaxis, audit and feedback to doctors and surgeons.	Comparison between Periods 1,2 and 3	Appropriateness of antibiotic prophylaxis (AP) usage in clean and clean-contaminated surgical procedures	The overall appropriate rates of antibiotic prophylaxis (AP) usage improved from periods 1, 2, to 3 at 12·7%, 12·7%, and 39·0%, respectively ($p < 0·001$). Significant differences among the three study periods were detected with respect to the appropriateness of indications, dosage, intraoperative re- dosing, duration, and overall appropriateness ($p < 0·001$). [comparing period 3 to period 1] Significant reduction in postoperative prolonged AP and the average cost of antimicrobials per patient over the three intervention periods were seen. (both $p < 0·001$).
Vo et al[38] (2021)	English	2019	Ho Chi Minh city	Observational	Respiratory department in Nguyen Tri Phuong Hospital (NTPH)	Hospital inpatients with community-acquired pneumonia (CAP)	Use of antibiotic order form whenever initiating antibiotic regimen along with guidelines and training on how to use it for patients with CAP	Nil comparison	Initial empirical antibiotic therapy, clinical improvement after 72h, changing in antibiotic, de-escalation, day of therapy (DOT), length of therapy (LOT), Length of stay, treatment failure at discharge, obtaining microbiology before antibiotic administration	No difference in initial empirical antibiotic therapy, clinical improvement after 72h, change in antibiotic, de-escalation, DOT, LOT, Length of stay, treatment failure at discharge. Obtaining microbiology before antibiotic administration showed a difference before using form 14% vs 45% after ($p= 0·001$), allowing physicians to identify a causative organism to guide potential de-escalation.

Table 2.5: Summary of studies reporting the effect of AMS interventions on various outcomes in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Year study conducted	Region	Study design	Setting	(P) Population	(I)AMS intervention	(C) Comparison	(O) Outcome measure related to AMS intervention	Main findings
Nguyen et al [103] (2017)	English	2016	Ho Chi Minh city	Before-and-after study	Cho Ray general hospital	Hospital inpatients that received antibiotics across all wards	National AMS program as implemented by Vietnam MoH in 2016: - Antibiotic awareness week - Antibiotic national guidance committee - Preparation of best-practice antimicrobial guidelines	Comparison to before AMS programme	1. Compliance rate to hospital antibiotic guidelines 2. Difference in costs in antibiotic usage 3. Incidence of hospital acquired infection	Antibiotics used for treatment purposes increased compliance to the hospital antibiotic guideline by 14·5% to 77·5% post-intervention, compared to before (p<0·05). Antibiotics used for surgical prophylaxis had increased compliance by 48·6% compared to before intervention (p<0·05). There was no change to treatment response rate before and after intervention. The antibiotic cost was 17·2% of the total pharmaceutical budget, a reduction of 1·3% compared with 2015 (p<0·05). There was no significant difference in hospital infection rate before and after intervention (p>0·05).
Nguyen et al[104] (2021)	Vietnamese	2018-2020	Ho Chi Minh city	Before-and-after study	Thong Nhat general Hospital	Hospital inpatients with sepsis	Antimicrobial stewardship programme consisting of 1. Clinician education and training 2. Institution of antibiotic guidelines for management of common infections 3. Formation of antimicrobial stewardship teams or committees in hospital settings 4. Education on how to collect microbiological samples 5. Audit and feedback of antimicrobial prescriptions 6. Antibiotic use monitoring	Comparison to before AMS programme	1. Rationality of empiric antibiotics use according to treatment guidelines and antibiogram 2. Patient's treatment outcome at discharge	The proportion of patients receiving appropriate empiric antibiotic increased from 49·5% (stage 1) to 63·2% (stage 2), p = 0·044, but no improvement was seen in the appropriateness according to the antibiogram. The treatment success rate in the two stages were no different. Risk factors for treatment failure on discharge were respiratory infections (OR= 4·4; 95%CI=1·7 – 11·4), hospital-acquired infections (OR= 3·6; 95%CI=1·3 – 9·8) and inappropriate antibiotic use (OR= 3·4; 95%CI=1·27 – 9·1).
Vu et al[105] (2022)	Vietnamese	2018-2019	Ho Chi Minh city	Before-and-after study	Department of Surgery and Urology Thong Nhat Hospital	Hospital inpatients with UTI	Antimicrobial stewardship programme consisting of 1. Clinician education and training 2. Institution of antibiotic guidelines for management of common infections 3. Formation of antimicrobial stewardship teams or committees in	Comparison to before AMS programme	1. Appropriateness of antibiotic use - type, dose, and antibiotic combination. The assessment of the appropriateness was based on 3 different antibiotic guidelines. 2. Treatment outcome:	General appropriateness of antibiotics increased (from 52·5% before to 63·8% in the 2nd, p = 0·03). Antibiotic combination used, and dosing improved. Length of stay and treatment outcome (cure/discharge) did not change with the intervention. (p=0·12)

Table 2.5: Summary of studies reporting the effect of AMS interventions on various outcomes in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Year study conducted	Region	Study design	Setting	(P) Population	(I)AMS intervention	(C) Comparison	(O) Outcome measure related to AMS intervention	Main findings
							hospital settings 4. Education on how to collect microbiological samples 5. Audit and feedback of antimicrobial prescriptions 6. Antibiotic use monitoring		success or failure and length of stay	
Nguyen et al[106] (2021)	Vietnamese	2018-2020	Ho Chi Minh city	Before-and-after study	Respiratory Department in Thong Nhat Hospital	Hospital inpatients with Chronic obstructive pulmonary disease (COPD)	Antimicrobial stewardship programme consisting of 1. Clinician education and training 2. Institution of antibiotic guidelines for management of common infections 3. Formation of antimicrobial stewardship teams or committees in hospital settings 4. Education on how to collect microbiological samples 5. Audit and feedback of antimicrobial prescriptions 6. Antibiotic use monitoring 7. Clinical pharmacists collaborating with doctors	Comparison to before AMS programme	1. Appropriateness of antibiotic use - type, dose, and antibiotic combination. The assessment of the appropriateness was based on 3 different antibiotic guidelines. 2. Treatment success or failure and length of stay	Overall appropriateness rate of empiric antibiotics has increased (90·8% after vs 78·8% before, RR 1·15; CI 95% 1·02 – 1·31). There was no difference in length of stay before and after the intervention. (aOR 0·29; 95% CI -0·86 - 1·47) and treatment outcome (aOR -0·9; 95% CI -5·1, - 3·0)
Vo et al[107] (2021)	Vietnamese	2018-2020	Ho Chi Minh city	Before-and-after study	Department of Gastroenterology or Hepatobiliary, Unspecified hospital	Hospital inpatients with peritonitis	Implementation of an antimicrobial stewardship programme that included distribution of antibiotic guidelines and audit and feedback to prescribers	Comparison to before AMS programme	1.Appropriateness of antibiotic use - type, dose, and antibiotic combination. The assessment of the appropriateness was based on MoH guidelines, Surgical Infection Society (SIS) 2017 guideline 2. The rate of use of antibiotic combinations 3. Treatment success or failure and length of stay	Overall appropriateness rate increased from 62·5% to 68·2% with difference was not statistically significant (p = 0·47). However, the proportion of appropriate antibiotic use in empiric treatment increased from 9·6% to 43·9% (p < 0·001) based on the SIS 2017 guideline. The proportion of use of antibiotic combinations reduced, and single antibiotic use increased. (p=0·01). No difference was seen in the treatment outcome before and after the intervention.

Table 2.5: Summary of studies reporting the effect of AMS interventions on various outcomes in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Year study conducted	Region	Study design	Setting	(P) Population	(I)AMS intervention	(C) Comparison	(O) Outcome measure related to AMS intervention	Main findings
Vo et al[108] (2021)	Vietnamese	2018-2020	Ho Chi Minh city	Before-and-after study	Department of Gastroenterology or Hepatobiliary, Unspecified hospital	Hospital inpatients with cholecystitis	Antimicrobial stewardship programme instituted in 2019, and distribution and use of Antibiotic guidelines	Comparison to before AMS programme	1. Appropriateness of antibiotic use - type, dose, and antibiotic combination. The assessment of the appropriateness was based on MoH guidelines, Surgical Infection Society (SIS) 2017 guideline, Tokyo guidelines or drug leaflets for dosing 2. Treatment success or failure and length of stay	The rate of appropriate antibiotic use in empiric treatment increased from 66·3% to 80·7% (p = 0·04) The rate of inappropriate dosing also decreased significantly. All patients recovered after treatment before and after AMS programme.
Nguyen et al[109] (2019)	Vietnamese	2014-2015	Ho Chi Minh city	Before-After study	Six clinical departments at Cho Ray hospital	Hospital inpatients	AMS programme in Cho Ray Central Hospital - Institution of antibiotic guidelines for management of common infections - Formation of antimicrobial stewardship teams or committees in hospital settings - Audit and feedback of antimicrobial prescriptions	Comparison to before AMS programme	1. Proportion of compliance to antibiotic guidelines 2. Treatment outcome - length of stay, rate of acquisition of hospital-acquired infections and cost	1. The hospital's compliance with antibiotic guidelines in 2015 increased by 6% compared to 2014 and reached 63% in 2015 (p=0·001). Mean duration of hospital stay and overall hospital mortality remained unchanged in 2014 and 2015. (p=0·08). The proportion of expenses on antibiotics in 2014 decreased by 3·9% compared to 2013 (equivalent to about 42·5 billion VND).
Tran et al[110] (2022)	Vietnamese	2020-2021	Ninh Thuan province, Vietnam	Before-and-after study	Ninh Thuan Provincial General Hospital	Hospital inpatients in Intensive care and Poison Control Department	Intervention on carbapenem use including: 1. Situation report on current antimicrobial use 2. Development of guidelines for antibiotic use and approved by the Drugs - Treatment Council 3. Carbapenem approval and consultation system 4. Post-prescription review of carbapenem use and proposing interventions if	Before intervention	1. Antibiotic use appropriateness based on MoH 2015 guidelines, local hospital guidelines and the Sanford antimicrobial guideline 2. Prevalence of antimicrobial resistance	Appropriate use of antibiotic was 42·1% (118/280) pre-intervention and increased to 70·5% (134/190) at the intervention phase (p<0·001). No significant difference in antimicrobial resistant bacteria before and after the intervention.

Table 2.5: Summary of studies reporting the effect of AMS interventions on various outcomes in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Year study conducted	Region	Study design	Setting	(P) Population	(I)AMS intervention	(C) Comparison	(O) Outcome measure related to AMS intervention	Main findings
							antibiotic use is inappropriate.			
Vu et al[65] (2019)	Vietnamese	2017-2018	Hanoi, Vietnam	Before-and-after study	Thanh Nhan Hospital	Hospital inpatients	AMS interventions introduced in 2 stages 1. Issuance of "List of antibiotics to be approved before use" in Apr 2017 2. Issuance of "Guidelines on the use of IV Fosfomycin antibiotics in July 2018	Before intervention in 2013-2017 as well as comparison between Stage 1 and 2	1. Consumption of IV Fosfomycin 2. Appropriateness of IV Fosfomycin use	Average Fosfomycin consumption was reduced from 0·855DDD/100 patient-day at baseline to 0·278DDD/100 patient-day after the first stage of intervention and to 0·457 DDD/100 patient-day after the second stage of intervention. Appropriate use of Fosfomycin increased from 20% to above 80% after Stage 1 (p<0·001), and approaching 90% after Stage 2 (p=0·44)
Pham et al[66] (2017)	Vietnamese	2015-2016	Nghe An province, Vietnam	Before-and-after study	Department of Gastrointestinal Surgery (DGS) and Surgical Intensive Care Unit (SICU) of Nghe An Friendship General Hospital	Hospital inpatients using carbapenem	In both departments: Phase 1: Development of criteria for antibiotic use (guidelines) Phase 2/3: Criteria set was distributed to hospital Phase 3: Clinical pharmacy activities including audit and feedback	Before intervention	Carbapenem consumption - average number of days of antibiotic and carbapenem treatment, amount in DDD/1000 bed-days, average carbapenem cost, carbapenem cost/total antibiotic cost ratio	In General Surgery Department, the total consumption of carbapenem remained nearly unchanged after the intervention phase (73·2 vs 86 DDD/1000bed-days); meanwhile, the cost significantly reduced (from 10·6 to 6·2 million VND per patient, US418 to $245[84] p<0·001) In Surgical ICU, the consumption and cost decreased dramatically from 511·6 to 141·1 DDD/1000bed-days and from 10·1 to 4·0 million VND,(US$399 to $158)[84] per patient (p<0·001) Nil
Nguyen et al [111] (2020)	Vietnamese	2017-2019	Thai Binh Province, Vietnam	Before-and-after study	Thai Binh provincial general hospital	Hospital inpatients with respiratory infection skin soft tissue infection, urinary infection or	Interventions were implemented from 2017 to 2019: · Establish AMS committee at hospital · Develop guidelines for the treatment of some infections	Before intervention	1. Proportion of appropriate empiric antibiotic use based on MoH guidelines 2. Proportion of appropriate antibiotic choice after having results of antibiogram	The proportion of appropriate initial antibiotic use at baseline was 41·1%, and 56·7% after intervention, but the increase was not statistically significant. Proportion of antibiotic appropriateness based on antibiogram results were also not statistically significant (71·6% before and 80·2% after)

Table 2.5: Summary of studies reporting the effect of AMS interventions on various outcomes in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Year study conducted	Region	Study design	Setting	(P) Population	(I)AMS intervention	(C) Comparison	(O) Outcome measure related to AMS intervention	Main findings
						abdominal infection	· Training and education · Audit and feedback · Monitoring, analysis & reporting			
Nguyen et al[112] (2017)	Vietnamese	2016	Ho Chi Minh city	Before-and-after study	Cho Ray hospital	Hospital inpatients on antibiotics	AMS programme had been in place since 2010. In 2016, there was an introduction of - Antibiotic usage surveillance - Updated antibiotic guidelines - Pilot monitoring and feedback to prescribers	Comparison between early 2016 and late 2016 as well as prior to intervention (2015)	Proportion of antibiotic guideline compliance and antibiotic usage cost	In early 2016, antibiotic compliance increased from 60% to over 80% in late 2016. (no statistics provided) Average guideline compliance rate increased by 14·5% compared to 2015 (p<0·05) for antibiotics used for treatment purposes. The antibiotic usage cost was 17·2%, which decreased by 1·3% compared to 2015. (p<0·05).
Nguyen et al[113] (2018)	Vietnamese	2016-2017	Ho Chi Minh city	Before-and-after study	Urology and General Surgery ward in Binh Dan hospital	Hospital inpatients undergoing clean or clean-contaminated surgical procedures	Surveillance of antibiotic use (no details provided)	Comparison to before AMS interventions	Appropriateness of surgical antibiotic prophylaxis - indication, choice, dose, route, timing and duration based on local hospital guidelines, and two international guidelines	Proportion of surgical antibiotic prophylaxis compliant to guidelines increased from 27·5% to 63·8% after the intervention (p<0·001). The proportion of antibiotic prophylaxis at a reasonable dose (95·1% to 99·4%, p=0·046), timing (94·9% vs 81·0%) (p=0·001), choice (p<0·001) and duration (2·9 ± 1·7 to 2·0 ± 1·2 days (p<.001) improved significantly post- intervention
Do et al[114] (2019)	Vietnamese	2016-2018	Ho Chi Minh city	Before-and-after study	University Medical Centre HCMC	Hospital inpatients undergoing gastrointestinal and hepatobiliary operations	Clinical pharmacist activities (details not specified)	Comparison to before AMS interventions	1. Antibiotic choices before and after intervention 2. Appropriateness of antibiotic usage according to choice, dose, timing and duration based on MoH guidelines 2015 and 2 international guidelines	After clinical pharmacy intervention, the overall proportion of antibiotics appropriately used increased significantly (from 13% to 74%, p < 0·05 for antibiotic prophylaxis and from 25·3% to 50%, p < 0·05 for post-surgery antibiotics. Duration of antibiotic therapy reduced from 2 (95%CI: 1,5) days to 1 (1,1) day for prophylactic antibiotics (p < 0·05) and from 5 (3,7) days to 3 (0,5) days for therapeutic antibiotics (p < 0·05). Length of stay after surgery reduced from 7 (5,9) days to 6 (4,8) days (p < 0·05). Inappropriate antibiotic choice (Ceftazidime used as example) significantly reduced post-intervention (from 58·7% to 2·6%) and replaced by Cephazolin (57·1%)

Table 2.5: Summary of studies reporting the effect of AMS interventions on various outcomes in healthcare facilities and the community in Vietnam

Study (Year published)	Language	Year study conducted	Region	Study design	Setting	(P) Population	(I)AMS intervention	(C) Comparison	(O) Outcome measure related to AMS intervention	Main findings
Nguyen et al[115] 2019	Vietnamese	2013-2015	Ho Chi Minh city	Before-and-after study	Children Hospital 1	Paediatric ICU inpatients	1. Approval of antibiotic requests, ensuring appropriateness before use on patients. 2. AMS Team of doctors, clinical pharmacists and nurses perform dose corrections as needed 3. De-escalation of antibiotics from IV to PO 4. Education and training activities 5. Reporting of adverse reactions (ADRs) 6. In cooperation with the microbiology department, antibiogram reports released to ICU department	Comparison to before AMS interventions	Appropriateness of antibiotic use according to choice, route and duration	No significant differences were seen in appropriateness before and after intervention in overall antibiotic usage (37·3% versus 34·0%), antibiotic selection (69·8 % versus 54·7%), and antibiotic duration (96·1% versus 94·3%). However, there was an improvement in proportion of appropriate antibiotic route of administration pre- and post-intervention (no proportions provided, p =0·04)
Vu et al[116] 2021	Vietnamese	2017-2020	Ho Chi Minh city	Before-and-after study	HCMC University of Medicine and Pharmacy Hospital	Inpatients undergoing clean or clean-contaminated surgical procedures	1. Issuance of antibiotic guidelines for the use of antibiotic prophylaxis with the participation of clinical pharmacists in monitoring compliance 2. Clinical pharmacists providing audit and feedback to prescribers	Comparison to before AMS interventions	Features of the AP use in surgery · Assessing the rationality in using AP · AP cost assessment · Clinical pharmacist intervention	The total compliance rate of surgical antibiotic prophylaxis was 47·4% and 44·3% before and after intervention respectively (p = 0·512) The proportion of antibiotic prophylaxis increased significantly in terms of appropriateness in dose (80·2% to 90·7%, p=0·003) and timing (86·5% to 93·1%, p=0·028) No significant changes were seen in antibiotic choice, route and duration of antibiotics.

AMS: Antimicrobial stewardship, aOR: Adjusted odds ratio, HCP: healthcare providers, CI: confidence intervals, RCT: randomised controlled trials

CURB-65: Pneumonia severity score that estimates mortality of community-acquired pneumonia to help determine inpatient vs. outpatient treatment

Supplementary material for Chapter 2

Table 2.1: Search terms

	Antimicrobial Use & Resistance Concepts (Lines 1–16)	
1	antibiot$.mp. or exp antibiotics	Searches for any word beginning with "antibiot" (e.g., antibiotic, antibiotics) in multiple fields (.mp.), or retrieves all articles indexed under the "antibiotics" MeSH heading (exp = exploded subject heading)
2	antimicrob$.mp.	Searches for any word starting with "antimicrob" (e.g., antimicrobial, antimicrobials) across multiple fields
3	exp Anti-Bacterial Agents	Explores the subject heading for "Anti-Bacterial Agents" and all narrower terms under it
4	exp Anti-Infective Agents	Explodes the broader term "Anti-Infective Agents" (includes antibacterial, antifungal, antiviral, etc.)
5	exp Cross Infection/	Retrieves studies indexed under healthcare-associated or nosocomial infections
6	exp Community-Acquired Infections/	Captures literature specifically on community-acquired infections
7	exp Respiratory Tract Infections/	Searches for studies on respiratory infections (common targets of antibiotic use)
8	exp Wound Infection/	Captures wound infections, another major antibiotic indication
9	exp Catheter-Related Infections/	Focuses on infections related to catheter use, often hospital-acquired
10	exp Vancomycin Resistance/ or exp Vancomycin/ or vancomycin.mp.	Captures literature on vancomycin and vancomycin resistance
11	aminoglycosides.mp. or exp Aminoglycosides/	Focuses on this antibiotic class
12	fluoroquinolones.mp. or exp Fluoroquinolones/	Focuses on this antibiotic class
13	broad spectrum antibiotics.mp.	Direct phrase search for broad-spectrum antibiotics
14	carbapenems.mp. or exp Carbapenems/	Focuses on this antibiotic class
15	exp Cephalosporins/ or broad spectrum cephalosporins.mp.	Includes cephalosporins, another key broad-spectrum class.

16	exp Drug resistance, Bacterial/	Captures bacterial resistance more generally.
17	or/1–16	Combines all the above terms with OR – pulling in any article relevant to antimicrobial use, classes, resistance, or infections that lead to use.
AMS Intervention Concepts (Lines 18–29)		
18	antimicrobial stewardship/	Index term for stewardship activities
19	antibiotic stewardship.mp	Free-text search for the phrase
20	exp Education/ or education.mp.	Captures educational interventions or mentions.
21	information campaign.mp.	Searches for public or institutional information campaigns.
22	audit.mp.	Captures the concept of auditing practices.
23	feedback.mp. or exp Feedback/	Looks at feedback as part of AMS interventions.
24	dissemination.mp. or exp Information Dissemination/	Captures guideline or information spread.
25	guidance.mp.	General search for the term “guidance.”
26	guideline implementation.mp.	Searches for studies on how guidelines are put into practice.
27	guideline adherence.mp. or exp Guideline Adherence/	Looks for studies on how well prescribers follow guidelines.
28	exp Quality Assurance, Health Care/ or quality assurance.mp.	Looks at broader quality improvement activities in health care.
29	exp Practice Guideline/	Captures articles tagged with clinical guidelines.
30	(hospital? Or clinic?)ab.ti	Searches for these terms in the abstract or title to limit to facility-based settings.
31	(primary care? Or community? Or health centre? Or health service)	Captures other settings like primary care and community health.
Setting Filters and Combinations (Lines 30–40)		
32	or/18-31	Combines AMS-related terms and interventions with OR.
33	17 and 32	Combines antimicrobial use/resistance terms, healthcare facility and AMS interventions
34	Viet?nam.mp	Searches for Vietnam, allowing for spelling variation.
35	33 and 34	Narrows the search to Vietnam-related studies.
36	limit 35 to english language and Vietnamese	Includes only studies in English or Vietnamese.

37	limit 36 to humans	Ensures results are human studies.
38	limit 37 to yr= "2010 -Current"	Limits studies to the past 14 years.
39	(influenza$ or antimalar$ or malaria$ or prophylax$).mp.	Searches for terms related to conditions or drugs not relevant to AMS
40	38 not 39	Excludes studies focused on malaria, influenza, or prophylaxis.

Table S2.2: PICO for research questions

Domain	**Antimicrobial consumption**	**Antimicrobial appropriateness**	**Antimicrobial stewardship (AMS)**
Research Question	What quantity of antimicrobials are being used in healthcare facilities or in the community in Vietnam?	What proportion of antimicrobials are given inappropriately within healthcare facilities or the community in Vietnam?	- What antimicrobial stewardship interventions have been implemented within healthcare facilities or in the community in Vietnam? - What are the effects of these AMS interventions and what are its effects, if any?
Population (P)	- Health care facilities - Pharmacies/drug counters - Individuals in healthcare facilities - Community	- Health care facilities - Pharmacies/drug counters - Individuals in healthcare facilities - Community	- Health care facilities - Pharmacies/drug counters - Individuals in healthcare facilities - Community
Intervention (I)	- N/A	N/A	- Formation of antimicrobial stewardship teams or committees - Healthcare worker education and training - Patient and/or public education - Institution of antimicrobial guidelines for management of common infections - Appointment of antimicrobial champions - Restrictions/ pre-authorisation on broad-spectrum antimicrobials - Audit and feedback of antimicrobial prescriptions - Antibiotic dosing and de-escalation strategies - Use of laboratory-based markers or microbiological techniques - Other activities aimed to reduce the inappropriate or excessive use of antimicrobials

Domain	**Antimicrobial consumption**	**Antimicrobial appropriateness**	**Antimicrobial stewardship (AMS)**
Comparator (C)	- N/A	- N/A	- Standard care, without an AMS intervention
Outcome (O)	Antimicrobial consumption reported as - Defined daily dose (DDD) - Days of therapy (DOT) - Mass of antimicrobials (kg) - Cost of antimicrobials - Proportion of antimicrobials over all medications - Proportion of antimicrobials prescribed without a prescription	Antimicrobial appropriateness assessed by - Compliance to guidelines - Microbiological results on susceptibilities	Presence of an AMS programme Feasibility of AMS intervention Changes in - Appropriateness of antimicrobial prescribing - Antimicrobial consumption reported as DDD, DOT, or particular classes of antimicrobials - Healthcare-associated costs - Length of stay in hospital - Proportion of antimicrobials used - Knowledge, attitudes and practices around antimicrobial prescribing - Proportion of antibiotic use according to WHO Access, Watch, Reserve (AWaRe) categories - Mortality rates - Prevalence of hospital-acquired infections - Carriage of multi-resistant organisms in individuals

AMS: Antimicrobial stewardship, DDD: Defined daily doses, DOT: Days of therapy

WHO AWaRe classification is a tool used to consider the impact of different antibiotic classes on antimicrobial resistance. "Access" category antibiotics display low resistance potential, are narrow spectrum and of low cost, "Watch" antibiotics are broader-spectrum, higher cost and required in severe presentations, whereas "Reserve" category antibiotics are the last choice to treat multi-drug resistant infections.[28]

Table S2.3: Risk of bias assessments for non-randomised controlled trial studies

Study	Study type	Selection (5 stars)	Comparability (1 star)	Outcome (3 stars)	Overall score	Risk of bias
Carrique-Mas et al [72] (2020)	Observational	★	-	★	2	High
Cuong et al[73] (2021)	Observational	★	-	★	2	High
Dat et al[74] (2020)	Observational	★	-	★	2	High
Dat et al[46] (2022)	Observational	★★	-	★★	4	High
Do et al[57] (2021)	Observational	★★★	-	★★	5	High
Duong et al[75] (2018)	Observational	★★★	★	★★	6	Some concerns
Johansson et al[76] (2011)	Observational	★★	-	★★	4	High
Nga et al[14] (2014)	Observational	★★★★	★	★★★	8	Low
Nguyen et al[77] (2019)	Observational	★★★	-	★★★	6	Some concerns
Nguyen et al[78] (2020)	Observational	★★★	-	★★	5	High
Nguyen et al[79] (2022)	Observational	★	-	★★	3	High
Nguyen et al [49] (2020)	Observational	★★	-	★★	4	High
Le et al[80] (2018)	Observational	★	★	★★	4	High
Phu et al[47] (2016)	Observational	★★	-	★★★	5	High
Sohn et al[81] (2013)	Observational	★★	-	★★	4	High
Thu et al[13] (2012)	Observational	★★★★★	★	★★★	9	Low

Study	Study type	Selection (5 stars)	Comparability (1 star)	Outcome (3 stars)	Overall score	Risk of bias
Trinh et al[82] (2014)	Observational	★★★	★	★★	6	Some concerns
Nguyen et al [83] (2020)	Observational	★★	-	★★	4	High
Nguyen et al[48] (2023)	Observational	★★★★	★	★★★	8	Low
Hoa et al[63] (2011)	Observational	★★★	★	★★	6	Some concerns
Zawahir et al[15] (2022)	Observational	★★★★	★	★★	7	Low
Nguyen et al[68] (2021)	Observational	★★	-	★★	4	High
Pham et al[85] (2021)	Observational	★★	-	★★	4	High
Nguyen[50] 2019	Observational	★★	-	★★	4	High
Vu et al[86] (2022)	Observational	★★	-	★★	4	High
Nguyen et al[69] (2019)	Observational	★★	-	★★	4	High
Nguyen et al[51] (2019)	Observational	★★	-	★★	4	High
Ha et al[45] (2018)	Observational	★★★	-	★★	5	High
Nguyen et al[52] (2021)	Observational	★★	-	★★	4	High
Nguyen et al[53] (2016)	Observational	★★	-	★★	4	High
Pham et al[87] (2019)	Observational	★★	-	★★	4	High

Study	Study type	Selection (5 stars)	Comparability (1 star)	Outcome (3 stars)	Overall score	Risk of bias
Minh et al[58] (2020)	Observational	★★★	-	★★	5	High
Nguyen et al[71] (2022)	Observational	★★	-	★★★	5	High
Nguyen-Hoang et al[88] (2021)	Observational	★★	-	★★★	5	High
Nguyen et al[70] (2022)	Observational	★★★	-	★★	5	High
Nguyen et al[89] (2020)	Observational	★★	-	★★★	5	High
Ngo et al[90] (2022)	Observational	★	-	★★	3	High
Nguyen et al[91] (2020)	Observational	★★	-	★★	4	High
Ly et al[92] (2011)	Observational	★★	-	★★	4	High
Cai et al (2022)[64]	Observational	★	-	★	2	High
Chang (2022)[93]	Observational	★	-	★★	3	High
Huong et al (2021)[94]	Observational	★	-	★	2	High
Huong et al (2021)[95]	Observational	★	-	★	2	High
Lee et al (2021)[96]	Observational	★	-	★★	3	High
Wertheim et al (2013)[97]	Observational	★	-	★	2	High
Nguyen et al (2021)[98]	Observational	★★	-	★	3	High
Bui et al (2022)[99]	Observational	★	-	★	2	High
Do et al [100] (2021)	Before-and-After study	★★	-	★★★	5	High
Nguyen et al[36]	Before-and-After study	★★★	★	★★★	7	Low

Study	Study type	Selection (5 stars)	Comparability (1 star)	Outcome (3 stars)	Overall score	Risk of bias
(2022)						
Nguyen-Thi et al[37] (2021)	Before-and-After study	★★★	-	★★★	6	Some concerns
Ory et al[101] (2022)	Observational	★★	-	★★★	5	High
Phan et al[102] (2022)	Before-and-After study	★★★★★	-	★★★	8	Low
Vo et al[38] (2021)	Observational	★★	-	★★★	5	High
Nguyen et al [103] (2017)	Before-and-After study	★★	-	★★	4	High
Nguyen et al[104] (2021)	Before-and-After study	★★	-	★★★	5	High
Vu et al[105] (2022)	Before-and-After study	★	-	★★	3	High
Nguyen et al[106] (2021)	Before-and-After study	★★	-	★★★	5	High
Vo et al[107] (2021)	Before-and-After study	★★	-	★★★	5	High
Vo et al[108] (2021)	Before-and-After study	★★	-	★★	4	High
Nguyen et al[109] (2019)	Before-and-After study	★★	-	★★★	5	High
Tran et al[110] (2022)	Before-and-After study	★★	-	★★★	5	High
Vu et al[65] (2019)	Before-and-After study	★★	-	★★★	5	High
Pham et al[66] (2017)	Before-and-After study	★★	-	★★★	5	High
Nguyen et al [111] (2020)	Before-and-After study	★★	-	★★	4	High

Study	Study type	Selection (5 stars)	Comparability (1 star)	Outcome (3 stars)	Overall score	Risk of bias
Nguyen et al[112] (2017)	Before-and-After study	★★	-	★★	4	High
Nguyen et al[113] (2018)	Before-and-After study	★★	-	★★	4	High
Do et al[114] (2019)	Before-and-After study	★★	-	★★	4	High
Nguyen et al[115] 2019	Before-and-After study	★★	-	★★★	5	High
Vu et al[116] 2021	Before-and-After study	★★★	★	★★★	6	Some concerns

See appendix for Newcastle Ottawa Quality Assessment scale for explanation of each risk of bias column[31]

Table S2.4: Cochrane tool for risk of bias assessments for randomised controlled trials

Study	Bias arising from randomisation/ selection process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of outcome	Bias in selection of the reported result	Overall risk of bias
Do et al[32] (2016)	Low	Low	Low	Low	Low	Low
Lubell et al[33] (2018)	Low	Low	Low	Some concerns	High	Some concerns
Hoa et al[35] (2017)	High	High	High	High	Some concerns	High
Nadjm[34] et al (2019)	Low	Low	Low	Low	Low	Low

RCT: Randomised controlled trial

References for Chapter 2

1. World Health Organisation. Antimicrobial resistance fact sheet. 2023. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance (accessed 15/7/2024).

2. Murray CJL, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet* 2022; **399**(10325): 629-55.

3. Worldometers.info. Countries in the world by population. https://www.worldometers.info/world-population/population-by-country/ (accessed 09/07/2024).

4. Klein EY, Van Boeckel TP, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proceedings of the National Academy of Sciences* 2018; **115**(15): E3463-E70.

5. World Health Organisation. WHO Bacterial Priority Pathogens List, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. . 2024. https://iris.who.int/bitstream/handle/10665/376776/9789240093461-eng.pdf?sequence=1 (accessed 20/02/2025).

6. Minh NNQ, Toi PV, Qui LM, et al. Antibiotic use and prescription and its effects on Enterobacteriaceae in the gut in children with mild respiratory infections in Ho Chi Minh City, Vietnam. A prospective observational outpatient study. *PloS one* 2020; **15**(11): e0241760.

7. Van Khien V, Thang DM, Hai TM, et al. Management of antibiotic-resistant Helicobacter pylori infection: perspectives from Vietnam. *Gut and Liver* 2019; **13**(5): 483.

8. Torumkuney D, Kundu S, Vu GV, et al. Country data on AMR in Vietnam in the context of community-acquired respiratory tract infections: links between antibiotic susceptibility, local and international antibiotic prescribing guidelines, access to medicines and clinical outcome. *Journal of Antimicrobial Chemotherapy* 2022; **77**(Supplement_1): i26-i34.

9. Vu TVD, Do TTN, Rydell U, et al. Antimicrobial susceptibility testing and antibiotic consumption results from 16 hospitals in Viet Nam: The VINARES project 2012–2013. *Journal of global antimicrobial resistance* 2019; **18**: 269-78.

10. Vu TVD, Choisy M, Do TTN, et al. Antimicrobial susceptibility testing results from 13 hospitals in Viet Nam: VINARES 2016–2017. *Antimicrobial Resistance & Infection Control* 2021; **10**(1): 78.

11. World Health Organisation. Hospitals in Viet Nam. https://www.who.int/vietnam/health-topics/hospitals (accessed 04/08/2023).

12. Hoa NT, Tam NM, Derese A, Markuns JF, Peersman W. Patient experiences of primary care quality amongst different types of health care facilities in central Vietnam. *BMC health services research* 2019; **19**(1): 275.

13. Thu TA, Rahman M, Coffin S, Harun-Or-Rashid M, Sakamoto J, Hung NV. Antibiotic use in Vietnamese hospitals: a multicenter point-prevalence study. *American journal of infection control* 2012; **40**(9): 840-4.

14. Nga DTT, Chuc NTK, Hoa NP, et al. Antibiotic sales in rural and urban pharmacies in northern Vietnam: an observational study. *BMC Pharmacology and Toxicology* 2014; **15**(1): 1-10.

15. Zawahir S, Le HTT, Nguyen T-A, et al. Inappropriate supply of antibiotics for common viral infections by community pharmacies in Vietnam: A standardised patient survey. *The Lancet Regional Health – Western Pacific* 2022; **23**.

16. Huynh C, Tram T, Nguyen, et al. Trends in the Use of Surgical Antibiotic Prophylaxis at a Provincial Hospital in Vietnam. 2020; **11**: 32-9.

17. McKinn S, Trinh DH, Drabarek D, et al. Drivers of antibiotic use in Vietnam: implications for designing community interventions. *BMJ global health* 2021; **6**(7).

18. Zellweger RM, Carrique-Mas J, Limmathurotsakul D, Day NPJ, Thwaites GE, Baker S. A current perspective on antimicrobial resistance in Southeast Asia. *The Journal of antimicrobial chemotherapy* 2017; **72**(11): 2963-72.

19. World Health Organisation. Antimicrobial Stewardship programmes in health-care facilties in Low- and Middle-income countries - a WHO practical toolkit. 2019. https://www.who.int/publications/i/item/9789241515481 (accessed 10/01/2023).

20. Dyar OJ, Huttner B, Schouten J, Pulcini C. What is antimicrobial stewardship? *Clinical Microbiology and Infection* 2017; **23**(11): 793-8.

21. Abbas S. The challenges of implementing infection prevention and antimicrobial stewardship programs in resource-constrained settings. *Antimicrobial Stewardship & Healthcare Epidemiology* 2024; **4**(1): e45.

22. Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017; **2**(2): Cd003543.

23. Harun MGD, Sumon SA, Hasan I, Akther FM, Islam MS, Anwar MMU. Barriers, facilitators, perceptions and impact of interventions in implementing antimicrobial stewardship programs in hospitals of low-middle and middle countries: a scoping review. *Antimicrobial Resistance & Infection Control* 2024; **13**(1): 8.

24. Ministry of Health Vietnam. National Action Plan on Combatting Drug Resistance in the period from 2013-2020 (Decision No. 2174/QD-BYT). Hanoi, Vietnam, 2013. https://www.who.int/publications/m/item/vietnam-national-action-plan-for-combating-drug-resistance (accessed 16/08/2022).

25. Pham GN, Dang TTH, Nguyen T-A, et al. Health system barriers to the implementation of the national action plan to combat antimicrobial resistance in Vietnam: a scoping review. *Antimicrobial Resistance & Infection Control* 2024; **13**(1): 12.

26. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372**: n71.

27. World Health Organisation. ATC/DDD Toolkit. 2024. https://www.who.int/tools/atc-ddd-toolkit (accessed 23/02/2022).

28. World Health Organization. The WHO AWaRe (access, watch, reserve) antibiotic book. 2022. https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.04 (accessed 02/07/2024).

29. Data collection form for intervention reviews: RCTs and non-RCTs. 2014. https://dplp.cochrane.org/data-extraction-forms.

30. *jamovi*. The jamovi project. Sydney, Australia; 2024.

31. GA Wells BS, D O'Connell, J Peterson, V Welch, M Losos, P Tugwell,. Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2021. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

32. Do NT, Ta NT, Tran NT, et al. Point-of-care C-reactive protein testing to reduce inappropriate use of antibiotics for non-severe acute respiratory infections in Vietnamese primary health care: a randomised controlled trial. *The Lancet Global Health* 2016; **4**(9): e633-e41.

33. Lubell Y, Do NT, Nguyen KV, et al. C-reactive protein point of care testing in the management of acute respiratory infections in the Vietnamese primary healthcare setting–a cost benefit analysis. *Antimicrobial Resistance & Infection Control* 2018; **7**: 1-6.

34. Nadjm B, Dat VQ, Campbell JI, et al. A randomised controlled trial of matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDITOF-MS) versus conventional microbiological methods for identifying pathogens: Impact on optimal antimicrobial therapy of invasive bacterial and fungal infections in Vietnam. *J Infect* 2019; **78**(6): 454-60.

35. Hoa NQ, Thi Lan P, Phuc HD, Chuc NTK, Stalsby Lundborg C. Antibiotic prescribing and dispensing for acute respiratory infections in children: effectiveness of a multi-faceted intervention for health-care providers in Vietnam. *Global Health Action* 2017; **10**(1): 1327638.

36. Nguyen HQ, Nguyen-Thi H, Huynh P, Le N, Nguyen N-Q, Hsia Y. Effectiveness of an enhanced antibiotic stewardship programme among paediatric patients in a tertiary hospital in Vietnam. *Journal of Hospital Infection* 2022; **127**: 121-8.

37. Nguyen-Thi H-Y, Nguyen D-A, Huynh P-T, Le NDT. Impact of antimicrobial stewardship program on vancomycin usage: costs and outcomes at hospital for tropical diseases in Ho Chi Minh City, Vietnam. *Risk Management and Healthcare Policy* 2021: 2637-46.

38. Vo DC, Mai TA, Nguyen TT, Nguyen DT, Vo TH. The use of an antibiotic order form in a tertiary hospital: Influence on physicians' prescribing patterns. *Journal of Pharmacy & Pharmacognosy Research* 2021; **9**(4): 474-83.

39. Limato R, Lazarus G, Dernison P, et al. Optimizing antibiotic use in Indonesia: A systematic review and evidence synthesis to inform opportunities for intervention. *The Lancet Regional Health - Southeast Asia* 2022; **2**.

40. Pharmacy Practice and Development Division. The Report on Antibiotic Utilisation in Malaysian Hospitals 2008-2017. 2020. https://pharmacy.moh.gov.my/en/documents/report-antibiotic-utilisation-malaysian-hospitals-2008-2017.html (accessed 04/072023).

41. SA Health. Antimicrobial use in Australian Hospitals: National Antimicrobial Utilisation Surveillance Program 2020 Annual Report. 2022. www.sahealth.sa.gov.au/nausp (accessed 22/12/2023).

42. The Center for Disease Dynamics EP. ResistanceMap: Antibiotic use. 2018. https://resistancemap.onehealthtrust.org/AntibioticUse.php (accessed 03/02/2025).

43. Kuster SP, Ruef C, Ledergerber B, et al. Quantitative Antibiotic Use in Hospitals: Comparison of Measurements, Literature Review, and Recommendations for a Standard of Reporting. *Infection* 2008; **36**(6): 549-59.

44. Stanić Benić M, Milanič R, Monnier AA, et al. Metrics for quantifying antibiotic use in the hospital setting: results from a systematic review and international multidisciplinary consensus procedure. *Journal of Antimicrobial Chemotherapy* 2018; **73**(suppl_6): vi50-vi8.

45. Hà VT, Hoàng TK. Thực trạng tiêu thụ kháng sinh trong điều trị nội trú tại Bệnh viện Chấn thương - Chỉnh hình Nghệ An năm 2016. *Tạp chí dược học (BYT)* 2018; **58**(5).

46. Dat VQ, Dat TT, Hieu VQ, Giang KB, Otsu S. Antibiotic use for empirical therapy in the critical care units in primary and secondary hospitals in Vietnam: a multicenter cross-sectional study. *The Lancet Regional Health–Western Pacific* 2022; **18**.

47. Phu VD, Wertheim HF, Larsson M, et al. Burden of hospital acquired infections and antimicrobial use in Vietnamese adult intensive care units. *PloS one* 2016; **11**(1): e0147544.

48. Nguyen NV, Do NTT, Vu DTV, et al. Outpatient antibiotic prescribing for acute respiratory infections in Vietnamese primary care settings by the WHO AWaRe (Access, Watch and Reserve) classification: An analysis using routinely collected electronic prescription data. *The Lancet Regional Health–Western Pacific* 2023; **30**.

49. Nguyen DV, Nguyen TTH, Nguyen TD, et al. Antibiotic Use in a Local Hospital in Vietnam: A Cross-Sectional Study Based on Medical Records among Urinary Tract Infection Patients. *Systematic Reviews in Pharmacy* 2020; **11**(3).

50. Nguyễn TTH, Đặng VH. Phân tích cơ cấu thuốc kháng sinh sử dụng tại Bệnh viện Đa khoa tỉnh Hưng Yên năm 2016. *Tạp chí y học việt nam* 2019; **477**(1&2).

51. Nguyễn QH, Phạm TPN. Phân tích danh mục thuốc kháng sinh sử dụng tại Bệnh viện Hữu Nghị Việt Nam Cu Ba năm 2016. *Tạp chí dược học (BYT)* 2019; **59**(8).

52. Nguyễn TTH, Nguyễn TMT. Phân tích danh mục thuốc kháng sinh sử dụng tại Bệnh viện Phạm Ngọc Thạch năm 2018. *Tạp chí dược học (BYT)* 2021; **15**: 93-6.

53. Nguyễn THT, Bùi KT, Phùng TH, Phạm QA. Thực trạng sử dụng kháng sinh trên người bệnh phẫu thuật và một số yếu tố ảnh hưởng tại khoa ngoại tổng hợp bệnh viện Thanh Nhàn, Hà Nội năm 2015. *Tạp chí y tế công cộng* 2016; **13**(40).

54. Mudenda S, Daka V, Matafwali SK. World Health Organization AWaRe framework for antibiotic stewardship: Where are we now and where do we need to go? An expert viewpoint. *Antimicrob Steward Healthc Epidemiol* 2023; **3**(1): e84.

55. Kinh LN. Decision No. 04/2008/QD-BYT - Guidelines for the implementation of the regulation on prescription drugs in outpatient treatment. 2008. https://thuvienphapluat.vn/cong-van/The-thao-Y-te/Cong-van-1517-BYT-KCB-Huong-dan-thuc-hien-Quy-che-ke-don-thuoc-trong-dieu-tri-ngoai-tru-82396.aspx (accessed 22/07/2024).

56. Auta A, Hadi MA, Oga E, et al. Global access to antibiotics without prescription in community pharmacies: a systematic review and meta-analysis. *Journal of Infection* 2019; **78**(1): 8-18.

57. Do NTT, Vu HTL, Nguyen CTK, et al. Community-based antibiotic access and use in six low-income and middle-income countries: a mixed-method approach. *The Lancet Global Health* 2021; **9**(5): e610-e9.

58. Minh NNQ, Toi PV, Qui LM, et al. Antibiotic use and prescription and its effects on Enterobacteriaceae in the gut in children with mild respiratory infections in Ho Chi Minh City, Vietnam. A prospective observational outpatient study. *PloS one* 2020; **15**(11): e0241760.

59. Sulis G, Adam P, Nafade V, et al. Antibiotic prescription practices in primary care in low- and middle-income countries: a systematic review and meta-analysis. *PLoS medicine* 2020; **17**(6): e1003139.

60. Chaw P, Höpner J, Mikolajczyk R. The knowledge, attitude and practice of health practitioners towards antibiotic prescribing and resistance in developing countries—A systematic review. *Journal of clinical pharmacy and therapeutics* 2018; **43**(5): 606-13.

61. Md Rezal RS, Hassali MA, Alrasheedy AA, Saleem F, Md Yusof FA, Godman B. Physicians' knowledge, perceptions and behaviour towards antibiotic prescribing: a systematic review of the literature. *Expert review of anti-infective therapy* 2015; **13**(5): 665-80.

62. Di KN, Tay ST, Sri La Sri Ponnampalavanar S, Pham DT, Wong LP. Physician's Perspectives on Factors Influencing Antibiotic Resistance: A Qualitative Study in Vietnam. *Healthcare (Basel)* 2022; **11**(1).

63. Hoa NQ, Chuc NTK, Phuc HD, Larsson M, Eriksson B, Lundborg CS. Unnecessary antibiotic use for mild acute respiratory infections during 28-day follow-up of 823 children under five in rural Vietnam. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2011; **105**(11): 628-36.

64. Cai HTN, Tran HT, Nguyen YHT, et al. Challenges and lessons learned in the development of a participatory learning and action intervention to tackle antibiotic resistance: experiences from northern Vietnam. *Frontiers in public health* 2022; **10**: 822873.

65. Vũ ĐH, Đặng TLA, Nguyễn HAB, et al. Đánh giá hiệu quả can thiệp của chương trình quản lý kháng sinh với fosfomycin truyền tĩnh mạch tại Bệnh viện Thanh Nhàn. *Tạp chí dược học (BYT)* 2019; **59**.

66. Phạm TTV, Dương TT. Tác động của các can thiệp dược lâm sàng trên kê đơn kháng sinh nhóm carbapenem tại một bệnh viện đa khoa tuyến tỉnh. *Tạp chí dược học (BYT)* 2017; **57**.

67. Ministry of Health Vietnam. Decision No. 1121/QD-TTg dated September 25, 2023 on approval of The national strategy for prevention and control of drug resistance in Vietnam for the period of 2023 - 2030 with a vision towards 2045. 2023. https://lawnet.vn/en/vb/Decision-1121-QD-TTg-2023-The-national-strategy-for-prevention-and-control-of-drug-resistance-8DDD4.html (accessed 10/01/2025).

68. Nguyễn Tth, Trần Tt. Phân Tích Thuốc Kháng Sinh Sử Dụng Tại Bệnh Viện Đa Khoa Huyện Vĩnh Thuận, Tỉnh Kiên Giang Năm 2018. *Tạp Chí Y Học Việt Nam* 2021; **499**(1-2).

69. Nguyễn TTH, Nguyễn XT. Phân tích danh mục thuốc kháng sinh sử dụng tại Bệnh viện Quân y 354 năm 2017. *Tạp chí dược học (BYT)* 2019; **59**(4).

70. Nguyễn NTT, Trần TVA, Nguyễn TH, et al. Khảo Sát Tình Hình Chuyển Đổi Kháng Sinh Từ Đường Tiêm/Truyền Sang Đường Uống Tại Bệnh Viện Thống Nhất. *Tạp Chí Y Học Việt Nam* 2022; **518**(2).

71. Nguyen HT, Bui QTH, Vo TV, Pham HTT, Vo TD. Antibiotic use in gastrointestinal surgery patients at a Vietnamese national hospital. *BMC Gastroenterol* 2022; **22**(1): 480.

72. Carrique-Mas JJ, Choisy M, Van Cuong N, Thwaites G, Baker S. An estimation of total antimicrobial usage in humans and animals in Vietnam. *Antimicrobial Resistance & Infection Control* 2020; **9**: 1-6.

73. Cuong NV, Ly NPC, Van NTB, et al. Feasibility study of a field survey to measure antimicrobial usage in humans and animals in the Mekong Delta region of Vietnam. *JAC-antimicrobial resistance* 2021; **3**(3): dlab107.

74. Dat VQ, Toan PK, van Doorn HR, Thwaites CL, Nadjm B. Purchase and use of antimicrobials in the hospital sector of Vietnam, a lower middle-income country with an emerging pharmaceuticals market. *PloS one* 2020; **15**(10): e0240830.

75. Duong VT, Tuyen HT, Van Minh P, et al. No clinical benefit of empirical antimicrobial therapy for pediatric diarrhea in a high-usage, high-resistance setting. *Clinical Infectious Diseases* 2018; **66**(4): 504-11.

76. Johansson M, Phuong D, Walther S, Hanberger H. Need for improved antimicrobial and infection control stewardship in Vietnamese intensive care units. *Tropical Medicine & International Health* 2011; **16**(6): 737-43.

77. Nguyen PH, Nguyen MC, Tran CKH, Pham DT. Assessment of outpatient drug prescription at eight local hospitals in Can Tho city during the period of 2016-2017.

78. Nguyen PT, Tran HT, Fitzgerald DA, Graham SM, Marais BJ. Antibiotic use in children hospitalised with pneumonia in Central Vietnam. *Archives of Disease in Childhood* 2020; **105**(8): 713-9.

79. Nguyen TTP, Do TX, Nguyen HA, et al. A national survey of dispensing practice and customer knowledge on antibiotic use in Vietnam and the implications. *Antibiotics* 2022; **11**(8): 1091.

80. Le TQN, de Alwis R, Khanh Lam P, et al. Quantifying antimicrobial access and usage for paediatric diarrhoeal disease in an urban community setting in Asia. *Journal of Antimicrobial Chemotherapy* 2018; **73**(9): 2546-54.

81. Sohn AH, Parvez FM, Vu T, et al. Prevalence of surgical-site infections and patterns of antimicrobial use in a large tertiary-care hospital in Ho Chi Minh City, Vietnam. *Infection Control & Hospital Epidemiology* 2002; **23**(7): 382-7.

82. Trinh HT, Hoang PH, Cardona-Morrell M, et al. Antibiotic therapy for inpatients with community-acquired pneumonia in a developing country. *Pharmacoepidemiology and drug safety* 2015; **24**(2): 129-36.

83. Nguyen NV, Do NTT, Nguyen CTK, et al. Community-level consumption of antibiotics according to the AWaRe (Access, Watch, Reserve) classification in rural Vietnam. *JAC-antimicrobial resistance* 2020; **2**(3): dlaa048.

84. OANDA. Historical currency converter. 2024. https://www.oanda.com/currency-converter/en/?from=VND&to=USD&amount=1 (accessed 24/10/2024) 2024).

85. Phạm Pl. Thực Trạng Sử Dụng Kháng Sinh Trong Điều Trị Nội Trú Tại Trung Tâm Y Tế Huyện Yên Dũng, Tỉnh Bắc Giang Năm 2020. *Tạp Chí Y Học Việt Nam* 2022; **509**(1).

86. Vũ Đt, Trần Vđ, Vũ Th. Kết Quả Điều Trị Kháng Sinh Dự Phòng Trong Phẫu Thuật Một Số Bệnh Tiêu Hóa. *Tạp Chí Y Học Việt Nam* 2022; **512**(2).

87. Phạm ĐL, Đào DKN, Ngô NB. Đánh giá tình hình sử dụng kháng sinh theo ngày điều trị và liều dùng theo ngày tại bệnh viện Quận 11 năm 2017. *Tạp chí y học TP Hồ Chí Minh* 2019; **23**(3).

88. Nguyen-Hoang N, Bui QTH. Assessing the appropriateness of antimicrobial therapy in patients with sepsis at a Vietnamese national hospital. *JAC-antimicrobial resistance* 2021; **3**(2): dlab048.

89. Nguyễn NT, Nguyễn QT, Bùi TCL, et al. Đánh Giá tuân thủ hướng dẫn sử dụng kháng Sinh dự phòng Trong phẫu thuật tại Bệnh viện Trung ương Quân đội 108. *Tạp chí y dược học lâm sàng (BV 108)* 2020; **15**(11).

90. Ngô Tkh, Phạm Ttl, Lê Tt, Trần Htp. Tình Hình Sử Dụng Kháng Sinh Hợp Lý Và Một Số Yếu Tố Liên Quan Trong Điều Trị Viêm Phổi Cộng Đồng Tại Một Bệnh Viện Đa Khoa Thuộc Tỉnh An Giang Năm 2021. *Tạp Chí Y Dược Học Cần Thơ* 2022; (55): 160-5.

91. Nguyễn TK, Lương NK, Hương PLT. Thực Trạng Sử Dụng Kháng Sinh Hợp Lý Tại Bệnh Viện Đa Khoa Tỉnh Thái Bình Và Nam Định Năm 2017. *Tạp Chí Y Học Dự Phòng* 2020; **30**.

92. Lý AB, Lê TC, Cồ NPD. Đánh giá tình hình sử dụng kháng sinh kinh nghiệm trên bệnh nhân sốt nhiễm khuẩn tại khoa hồi sức cấp cứu Bệnh viện Truyền máu Huyết học từ 01/04/2011 đến 30/06/2011. *Tạp chí y học TP Hồ Chí Minh* 2011; **15**.

93. Chang F-Y, Chuang YC, Veeraraghavan B, et al. Gaps in antimicrobial stewardship programmes in Asia: a survey of 10 countries. *JAC-antimicrobial resistance* 2022; **4**(6): dlac117.

94. Huong VTL, Ngan TTD, Thao HP, et al. Assessing feasibility of establishing antimicrobial stewardship programmes in two provincial-level hospitals in Vietnam: an implementation research study. *BMJ open* 2021; **11**(10): e053343.

95. Huong VTL, Ngan TTD, Thao HP, et al. Improving antimicrobial use through antimicrobial stewardship in a lower-middle income setting: a mixed-methods study in a network of acute-care hospitals in Viet Nam. *Journal of global antimicrobial resistance* 2021; **27**: 212-21.

96. Lee TH, Lye DC, Chung DR, et al. Antimicrobial stewardship capacity and manpower needs in the Asia Pacific. *Journal of global antimicrobial resistance* 2021; **24**: 387-94.

97. Wertheim HF, Chandna A, Vu PD, et al. Providing impetus, tools, and guidance to strengthen national capacity for antimicrobial stewardship in Viet Nam. *PLoS Med* 2013; **10**(5): e1001429.

98. Nguyễn Thy, Huỳnh Pt, Lê Đtn, Et Al. Tình Hình Triển Khai Hướng Dẫn Chương Trình Quản Lý Kháng Sinh Của Bộ Y Tế Ở Các Cơ Sở Y Tế Tại Tp. Hồ Chí Minh. *Tạp Chí Y Học Việt Nam* 2021; **507**(1).

99. Bùi TKD, Nguyễn TT, Ngô TTU, et al. Phân tích đặc điểm can thiệp dược lâm sàng với các kháng sinh ưu tiên quản lý tại bệnh viện Thanh Nhàn. *Tạp chí y học việt nam* 2022; **517**(Special edition).

100. Do NT, Li R, Dinh HT, et al. Improving antibiotic prescribing for community-acquired pneumonia in a provincial hospital in Northern Vietnam. *JAC-antimicrobial resistance* 2021; **3**(2): dlab040.

101. Ory J, Le Minh Q, Tien HP, et al. Impact of antibiotic stewardship and implementation of infection control on prevalence of surgical site infections in a large tertiary-care hospital in Haiphong city. 2022.

102. Phan QTN, Le TD, Do QK, et al. Impact of antimicrobial stewardship intervention in clean and clean-contaminated surgical procedures at a Vietnamese national hospital. *Tropical Medicine & International Health* 2022; **27**(4): 454-62.

103. Nguyen TS, Ton TT, Pham TNT. Antimicrobial stewardship program at a tertiary teaching hospital in Vietnam: a longitudinal observational study. *Clin Microbiol Infect Dis* 2017; **2**(1): 1-5.

104. Nguyễn Pd, Võ Th, Trần Qn, Nguyễn Tnt, Bùi Thq. Đánh Giá Hiệu Quả Của Chương Trình Quản Lý Sử Dụng Kháng Sinh Trong Điều Trị Nhiễm Khuẩn Huyết Tại Bệnh Viện Thống Nhất. *Tạp Chí Y Học Việt Nam* 2022; **510**(2).

105. Vũ Tta, Nguyễn Th, Nguyễn Mt, Lê Vl, Bùi Thq. Đánh Giá Hiệu Quả Của Công Tác Dược Lâm Sàng Và Chương Trình Quản Lý Sử Dụng Kháng Sinh Trong Điều Trị Nhiễm Trùng Đường Tiết Niệu Tại Bệnh Viện Thống Nhất. *Tạp Chí Y Học Việt Nam* 2022; **511**(1).

106. Nguyễn Mt, Trần Tpm, Nguyễn Týn, Bùi Thq. Đánh Giá Hiệu Quả Của Chương Trình Quản Lý Sử Dụng Kháng Sinh Và Hoạt Động Dược Lâm Sàng Trong Việc Sử Dụng Kháng Sinh Điều Trị Đợt Cấp Bệnh Phổi Tắc Nghẽn Mạn Tính Tại Bệnh Viện Thống Nhất. *Tạp Chí Y Học Việt Nam* 2022; **510**(2).

107. Võ Dt, Trần Tt. Vai Trò Của Chương Trình Quản Lý Sử Dụng Kháng Sinh Trong Điều Trị Viêm Phúc Mạc Tại Một Bệnh Viện Thành Phố Hồ Chí Minh. *Tạp Chí Y Học Việt Nam* 2021; **500**(1).

108. Võ Dt, Trần Tt. Khảo Sát Hiệu Quả Của Chương Trình Quản Lý Sử Dụng Kháng Sinh Trong Điều Trị Viêm Túi Mật Tại Một Bệnh Viện Thành Phố Hồ Chí Minh. *Tạp Chí Y Học Việt Nam* 2021; **498**(2).

109. Nguyễn Vt, Nguyễn Qb. Hiệu Quả Ban Đầu Của Chương Trình Giám Sát Sử Dụng Kháng Sinh Tại Bệnh Viện Chợ Rẫy. *Tạp Chí Y Học Việt Nam* 2019; **484**.

110. Trần Md, Nguyễn Nk, Nguyễn Nh. Đánh Giá Hiệu Quả Can Thiệp Của Hoạt Động Dược Lâm Sàng Trong Việc Sử Dụng Nhóm Kháng Sinh Carbapenem Tại Khoa Hồi Sức Tích Cực - Chống Độc Bệnh Viện Đa Khoa Tỉnh Ninh Thuận. *Tạp Chí Y Học Việt Nam* 2022; **515**(1).

111. Nguyễn TK, Lương NK, Phan LTH. Hiệu quả một số biện pháp can thiệp tăng cường sử dụng kháng sinh hợp lý tại bệnh viện đa khoa tỉnh Thái Bình từ năm 2017 đến 2019. *Tạp chí Y học Dự phòng* 2021; **30**(7): 179-86.

112. Nguyễn TS, Phạm TNT, Tôn TT. Hiệu quả chương trình giám sát sử dụng kháng sinh năm 2016 tại bệnh viện Chợ Rẫy. *Tạp chí y học TP Hồ Chí Minh* 2017; **21**.

113. Nguyễn PCH, Huỳnh LH, Bùi HN. Đánh giá hiệu quả chương trình quản lý kháng sinh trong sử dụng kháng sinh dự phòng ở các khoa ngoại tại bệnh viện Bình Dân. *Tạp chí y học TP Hồ Chí Minh* 2018; **22**.

114. Đỗ BN, Đặng NĐT. Hiệu quả can thiệp của dược sĩ lâm sàng trong việc sử dụng kháng sinh trên bệnh nhân phẫu thuật tiêu hóa, gan mật tụy tại bệnh viện Đại học Y dược Tp. Hồ Chí Minh. *Tạp chí y học TP Hồ Chí Minh* 2019; **23**.

115. Nguyễn TBN, Nguyễn NK. Can thiệp của dược sĩ lâm sàng đối với sử dụng kháng sinh trên bệnh nhi nhiễm khuẩn đa kháng tại khoa Hồi sức tích cực, bệnh viện Nhi đồng 1. *Tạp chí y học TP Hồ Chí Minh* 2019; **23**.

116. Vũ TTT, Đặng NĐT. Đánh giá hiệu quả can thiệp của dược sĩ lâm sàng trong việc sử dụng kháng sinh dự phòng tại bệnh viện Đại học Y dược Thành phố Hồ Chí Minh. *Tạp chí y học TP Hồ Chí Minh* 2021; **25**.

Chapter 3: Feasibility of an antimicrobial stewardship programme to reduce inappropriate antimicrobial use in four district hospitals in Vietnam

This chapter contains an article that has been submitted for publication.

Jaslyn Doshi[1] Yen Ngoc Pham[2], Thuy Thu Ma[2], Linh Thuy Duong[2], Van Thi Thuy Pham[3], Rodney James[4,5], Qingbin Li[1], Thuy Thi Thu Nguyen[3], Tuan Anh Huynh[6], Thu Minh Pham Vo[7], Anh Duc Hoang[8,9], Matthew Watts[10,11], Justin Beardsley[11,12], Thu Anh Nguyen[1,2], Greg J. Fox[1,13]

Author contributions

GJF and TAN contributed to funding acquisition and conceptualisation of the trial. GJF, TAN, and YPN contributed to the trial design and provided scientific input. GJF, TAN, YPN, JD and TTM led the trial implementation. LTD, VTTP, RJ, TTTN, TAH, TMPV, ADH and MW implemented the study, providing scientific input. JD, JB, YPN and GJF contributed to the data checking and analysis. QL and JD conducted the data and statistical analysis. JD drafted the manuscript. All authors contributed to manuscript review and editing.

Abstract

Objectives: Excessive and improper use of antimicrobials is a major driver of antimicrobial resistance. Antimicrobial stewardship (AMS) addresses this by promoting judicious use of antimicrobials. This study evaluated the feasibility and effectiveness of an AMS programme in district hospitals in Vietnam.

Methods: A before-and-after study was undertaken in four district hospitals in Vietnam over 6 months. Interventions included (i) establishing AMS committees and teams, (ii) distribution of antimicrobial guidelines, (iii) healthcare worker training, and (iv) conducting periodic standardised audits of appropriateness of antimicrobial prescriptions, followed by tailored feedback. The co-primary outcomes were (i) monthly antimicrobial consumption in the hospital and (ii) appropriateness of antimicrobial prescribing according to standardized guidelines, before and after the AMS programme. Secondary outcomes included changes in antimicrobial costs and all-cause mortality.

Results: The AMS program was successfully implemented with strong stakeholder engagement and high staff participation across all four hospitals. At baseline, 79% (95% CI: 74.9%, 83.7%) of 454 antimicrobial prescriptions were inappropriate, primarily due to prolonged duration, overly broad-spectrum agents or incorrect dosing. No improvement was observed post-intervention with 80.3% (95%CI:77.4%, 83.1%) of 992 prescriptions assessed as inappropriate. A modest reduction in antimicrobial consumption was seen post-intervention, with a decrease of 4.2 Defined Daily Doses (DDD)/100-bed days per month (95% CI: -6.2, -2.3). Antimicrobial costs were unchanged. All-cause mortality reduced post-intervention. [RR=0.32 (95%CI 0.09, 0.92)].

Conclusion: AMS interventions were feasible to implement in district hospitals in Vietnam and resulted in modest reductions in total antimicrobial consumption and all-cause mortality. However, the persistently high rates of inappropriate prescribing highlight the need for broader implementation and strengthening of stewardship efforts to more effectively address key drivers of antimicrobial resistance at the district level.

Introduction

Antimicrobial resistance (AMR) occurs when bacteria, viruses, fungi, or parasites acquire the capacity to survive in the presence of antimicrobials, making infections harder to treat.[1] The global increase in drug resistance over the past two decades has prompted the World Health Organisation (WHO) to classify AMR as one of the foremost threats to public health.[2] The overuse and misuse of antimicrobials in healthcare and agriculture are among the main drivers of AMR.

Vietnam, a lower middle-income country in Southeast Asia, is a hotspot for AMR. Surveillance data have shown many of the highest burden settings for AMR occur in Southeast Asia.[3,4] In Vietnam in 2019, 14,300 deaths were attributable to AMR, making it the third greatest cause of death in the country.[5] Vietnamese regulators have yet to contain the excessive and improper use of antimicrobials, with sales of antibiotics without a prescription widespread, and doctors frequently prescribing inappropriate regimens.[6-8] Recognising the significant burden of AMR in the country, the Vietnamese Ministry of Health (MoH) developed a National Action Plan on combating AMR; which included the introduction of antimicrobial stewardship (AMS) in healthcare settings.[9]

AMS is a systematic approach to promote responsible use of antimicrobials by using key strategies such as educating health professionals, using evidence-based guidelines, audit and feedback as well as performing regular surveillance of antimicrobial usage activities.[10] There is an expanding body of research showing that it is both impactful and cost-effective in healthcare settings worldwide, lowering antimicrobial consumption, without negative effects on clinical outcomes.[11] However, most of these studies have focused upon better-resourced tertiary hospitals. Few studies have evaluated the implementation of AMS in local health care facilities in low- and middle-income countries (LMICs).[12]

In Vietnam, healthcare is delivered by a mix of both public and private providers. Public hospitals remain the main setting for health service delivery, including the provision of primary healthcare.[13] The public health care system is divided into four tiers: national, provincial, district and commune levels. According to a national survey there were 13,544 healthcare facilities – 47 central, 462 provincial, 952 district hospitals and 11,100 commune health facilities in 2020.[14] Most local communities are serviced by district hospitals and commune health centres. They deliver basic and preventative acute and chronic care for most medical conditions.[15] As the availability of primary care services is limited, district hospitals are frequently the first point of contact for the community seeking medical care. These hospitals have insufficient resources to implement the National Action Plan against AMR effectively.

This study aimed to investigate the feasibility and effectiveness of an integrated AMS programme at district level health care facilities in Vietnam.

Methods

Study design and setting

A prospective before-and-after intervention study was conducted in four public district hospitals in Hanoi and Ca Mau provinces in Vietnam over six months. The AMS interventions were developed based on the WHO practical toolkit for AMS in LMICs and the Australian AMS programme, aligned to Vietnam Ministry of Health (MoH) policy.[9,10,16] All four district hospitals received the same package of AMS interventions, tailored to the local context.

Pre-implementation phase

The intervention began with a pre-implementation phase. The research team first engaged with the hospital administrators, obtained consent and carried out a survey of existing facilities and AMS activities (Table 3.1). Study booklets outlining the planned AMS activities were distributed across the hospitals for staff.

The AMS interventions consisted of four components:

(i)AMS committees and teams

An AMS committee was appointed at each facility, including a senior hospital leader, heads of clinical departments, and head of the pharmacy. Committees' roles were to endorse antimicrobial guidelines, adapt the AMS interventions to their hospital's needs, oversee its implementation, and supervise AMS teams. The AMS committee met every one to two months to discuss the progress of implementation of activities in their hospitals (Table 3.2).

AMS teams were also established at each facility to deliver the AMS interventions. Teams comprised at least one doctor (with Infectious Diseases training where possible) and one pharmacist. Teams were responsible for distributing and promoting guidelines and conducting periodic audits of antimicrobial use followed by feedback sessions (described below). Teams were trained using a standard manual by experienced physicians and pharmacists both in-person and online. A second training session was held in Hanoi for all four AMS teams to reinforce the use of the audit tool and encourage its continued application beyond the intervention period (Table 3.2).

(ii) Development and distribution of antimicrobial guidelines

Antimicrobial guidelines for common conditions in district hospitals were developed with input from Infectious Diseases physicians in Australia and Vietnam, based on MoH guidelines[17] and local antibiograms from Vietnamese tertiary healthcare settings. Guidelines covered respiratory, skin and soft tissue, urinary tract infections and surgical prophylaxis for adults and children. These were translated and printed in Vietnamese; and distributed in paper form to each participating ward.

(iii) Healthcare worker education and training

Two workshops were held for all doctors and pharmacists at all facilities, delivered by experienced AMS clinicians (Table 3.2). Workshops covered AMS rationale, appropriate prescribing, diagnosis of common conditions, guideline use, antimicrobial dosing, de-escalation, surgical prophylaxis, and included practice case scenarios.

(iv) Audit and feedback

Periodic audits of patient records were conducted by AMS teams and study staff during the six-month intervention period using the Australian Hospital National Antimicrobial Prescribing Survey (Hospital NAPS)[18] template to assess appropriateness of antimicrobial use against guidelines. A baseline audit preceded the intervention, followed by a feedback session presenting prescribing trends, suboptimal practices and improvement recommendations to the entire hospital staff upon commencement of the intervention. This audit and feedback process was repeated in one to three major hospital departments, depending on the hospital's capacity over the six-month intervention period (Table 3.2). In these sessions, feedback was performed immediately after each audit, allowing real-time changes to be incorporated. Feedback was respectful, non-judgmental and encouraged constructive dialogue to foster staff engagement on improving prescribing practices. Audit and feedback reports were shared with the respective departments and AMS committees. Departments

demonstrating the greatest commitment to improving prescribing practices were recognized as “AMS champions” at the conclusion of the intervention.

Outcomes

Two co-primary outcomes were evaluated: antimicrobial consumption and the appropriateness of antimicrobial prescription, as defined below.

Antimicrobial consumption

Antimicrobial consumption was measured in Defined Daily Dose (DDD) per 100 occupied bed-days, a standardised measurement endorsed by WHO,[19] and compared before and after the intervention. DDD is derived from the overall antimicrobial usage during a fixed period. The dose was based upon the average maintenance dose of a drug used for its main indication in an adult. Quantification of antimicrobials was based upon inventory records of antimicrobials that were dispensed by Pharmacy departments to the wards each month, as data about individual antimicrobial administration were not routinely collected. The number of bed-days was defined as the number of days a patient occupied a bed overnight in hospital, collected from the hospital information systems. Paediatric-specific antimicrobial consumption information, frequently calculated using Days of Therapy (DOT),[20] was not available in participating hospitals. Therefore, comparison of antimicrobial consumption was presented as DDD.[21]

Antimicrobial appropriateness

The appropriateness of antimicrobial prescriptions was assessed using the Australian Hospital NAPS audit tool,[18] proven feasible and translatable across diverse healthcare settings in several countries.[22] Audits were carried out by research study staff.

Healthcare records of all inpatients at 8am on a designated day were collected and reviewed. A form captured information on name of antimicrobial, dose, route, clinical indication, start and end date, as well as patients' age, weight, serum creatinine, allergies, and surgical procedures, if any. The clinical indication for each prescribed antimicrobial was determined using documented symptoms, vital signs, examination findings, and clinical investigations. If the documented clinical information did not support the recorded diagnosis, the study team physicians used clinical judgment to establish the diagnosis. Each prescription was assessed against either the study or MoH guidelines. For conditions where guidelines were unavailable, physicians again used clinical judgement.

The appropriateness of each prescription was categorised based on pre-defined definitions, (1) Optimal (2) Adequate (3) Suboptimal (4) Inadequate (5) Not assessable (Supplementary Figure S3.1). Discrepancies were resolved by discussion amongst the AMS team and study staff or referred to an independent assessor blinded to the hospital if no consensus was reached. The audit process was repeated in all inpatients on another designated day at the end of the six-month intervention period across all sites (Table 3.2). Assessments were transcribed from paper forms to an online database and checked by the blinded independent assessor to reduce analysis bias.

Secondary outcomes

Secondary outcomes included (i) all-cause mortality rate and, (ii) the monthly cost of antimicrobial drugs dispensed by the pharmacy, measured during the month before and the month after the intervention. Mortality was defined as the number of deaths reported to occur in hospital, plus critically ill patients discharged home with a documented disposition of "expected death", over a one-month period. The mortality rate per inpatient was then calculated for the month before the intervention and the final month of the intervention. Antimicrobial formulary cost information was derived from hospital pharmacy records.

Data collection & analysis

Data were collected on paper records and entered in an online database by research staff. The Hospital NAPS database was used to document the assessment of appropriateness. Descriptive statistics were calculated to summarize the main characteristics of the data, while statistical analyses were conducted using STATA-18.[23]

For antimicrobial consumption, the median monthly DDD/100 bed-days was first calculated for the four sites from before the intervention (February 2022) to after the intervention (September 2022). Then, a Wilcoxon Signed-Rank test compared the difference of median DDD/100-bed days between February and September 2022, with point estimates and 95% confidence intervals calculated. A linear mixed-effects model analysed monthly DDD/100 bed-days data per site, and robust linear regression assessed the difference in consumption over time, using monthly aggregates. Antimicrobial costs were analysed using the same approach as consumption.

Appropriateness was presented as the proportion of antimicrobials prescribed inappropriately over all prescriptions, and the difference between groups were compared using chi-squared testing. Pre-specified subgroup analyses were conducted by study site, age (≤15 years vs. >15 years), specialty, reasons prescriptions were inappropriate, and proportion of antimicrobials according to class and to WHO Access, Watch and Reserve (AWaRe) classifications.[24] The same test and assumption checks applied to the main analysis were also used in each subgroup.[24] Mortality rates were analysed using exact logistic regression, expressed as risk ratios with 95% confidence intervals.

Ethical issues

Approval for this study was obtained from the National Institute of Hygiene and Epidemiology (NIHE) in Vietnam (IRB – VN01057/IORG 0008555), University of Sydney (Project no:2021/193) and Royal Melbourne Hospital for Hospital NAPS (HREC/74195/MH-2022). Each hospital director provided approval for the study on behalf of their facility, and a waiver for individual consent was granted, consistent with standard audit and feedback practices. Data were collected in a de-identified manner.

Results

The intervention was implemented concurrently in four district hospitals between March and August 2022. The number of participants in each hospital, over the study period, is shown in Figure 3.1, and in Supplementary Table S3.1. Two hospitals were in Hanoi province (northern Vietnam) and another two in Ca Mau province (southern Vietnam). Table 3.1 presents hospital characteristics and AMS interventions in place prior to the AMS campaign. Table 3.3 shows AMS activities carried out and number of staff participating in each activity.

Antimicrobial consumption

The median antimicrobial consumption was 65.7 DDD/100 bed-days prior to the intervention period, and 54.9 DDD/100 bed days after the intervention period. There was no significant change in overall antimicrobial consumption, with 10.7 (95% CI: -91.0, 69.7) DDD/100-bed days fewer antimicrobials used before compared to after the intervention. Using linear regression, there was an overall reduction of 4.2 (95% CI: -6.2,-2.3) DDD/100-bed days per month over the study period. Antimicrobial consumption in each hospital is displayed in Figure 3.2. There was no difference in the proportion of inpatients on antimicrobials on days of audit (Table S3.3).

Ca Mau hospitals showed a reduction in average antimicrobial consumption of 17.3 (95% CI: 9.8, 24.8) DDD/100 bed-days per month and 3.2 (95% CI: 0.5, 7.0) DDD/100 bed-days per month. No difference was seen in antimicrobial consumption at the hospitals in Hanoi (Supplementary Table S3.2).

Appropriateness of antimicrobial prescribing

The proportion of inappropriate antimicrobial prescriptions was 79.3% (95% CI: 74.9%, 83.7%) prior to the intervention, and 80.3% (95%CI: 77.4%, 83.1%) after the intervention. The 1% (95%CI: -4.3%, 6.2%) difference was not statistically significant.

Subgroup analyses

Results of further subgroup analyses from the audit data are displayed in Table 3.4. In the post-intervention period, the proportion of inappropriate paediatric antimicrobial prescriptions [94% (95%CI:91%, 97%)] was 21% (95%CI: 16%, 26%) higher compared to adults [73%, (95%CI: 69%, 77%)]. Doctors on general surgical wards were also more likely to prescribe antimicrobials inappropriately at 84% (95%CI: 79%, 90%) compared to doctors on general medical wards, [72% (95%CI: 66%, 79%)], with a risk difference of 12% (95%CI: 4%, 21%).

Broad-spectrum antimicrobials, especially third-generation cephalosporins and beta-lactam/beta-lactam inhibitors were used in high proportions in all hospitals. (Table 3.4) WHO “Watch” antibiotics were the predominant category of prescribed antimicrobials pre- intervention. Post-intervention, use of third-generation cephalosporins reduced and WHO “Access” antibiotics became the predominant category of antimicrobials prescribed (Table 3.4).

Prolonged surgical prophylaxis, defined as administration of antimicrobials beyond 24 hours post-surgery was observed in 96% (95%CI: 92%,100%) of surgical patients. This decreased by 23% (95%CI: 15%,32%) to 73% (95%CI: 65%, 80%) post-intervention. When stratified by ward, Obstetrics and Gynaecology and Infectious Diseases wards reduced their inappropriate prescribing over the intervention period, while the paediatric ward saw increased inappropriateness. (Table 3.4) However, the proportion of oral antimicrobials prescriptions reduced, while non-compliance to guidelines and incorrect dosing increased (Table 3.4).

Secondary outcomes

The median antimicrobial costs in all four hospitals increased from USD $6200 equivalent in Vietnamese Dong[25] in the month before the intervention to USD $16,100[25] in the month after intervention, a non-significant difference of $10,025(95%CI: -$6530, $24,600). The robust linear regression on monthly average costs increased by $2300 (95%CI: -$400, $4450) per month. The relative risk of mortality reduced significantly post-intervention compared to pre-intervention, with a relative risk (RR) of 0.32 (95%CI: 0.09, 0.92) (Table S3.4).

Discussion

This before-and-after intervention study demonstrated that implementing an AMS program in district hospitals in Vietnam is feasible, even in settings with limited resources and infrastructure, when supported by hands-on guidance. High levels of healthcare worker participation and positive feedback throughout the implementation period indicate that the program was successfully delivered. Although only a modest reduction in antimicrobial consumption was observed and the extremely high rates of inappropriate antimicrobial prescribing remained unchanged, the findings highlight the critical importance of introducing AMS programs at lower-level healthcare facilities and underscore the need to sustain and strengthen stewardship activities in these settings.

In particular, hospitals in Ca Mau province demonstrated both an increase in antimicrobial appropriateness and a reduction in consumption following the intervention period.. The observed reduction in all-cause mortality should be interpreted cautiously, as the study design does not account for seasonal variation or allow causal attribution.

The proportion of inappropriate antimicrobial use was highest among surgical and obstetric wards, of which a high proportion of prescriptions were for surgical and procedural prophylaxis. Deficient operating theatre facilities and poor infection control practices in Vietnam have been blamed for this.[26] Other studies on antibiotics use around surgery in Vietnam have also shown high levels of inappropriateness at around 55% in two separate studies, lower than our study, although different definitions were used.[27,28] As for obstetric use, both the MoH and a WHO guideline offer evidence on using a single dose of intravenous (IV) antibiotics for operative vaginal deliveries requiring instrumentation.[29] In this study however, we saw widespread antibiotic use even in normal vaginal deliveries.

We observed excessive use of WHO “Watch” category antibiotics before the intervention, aligning with previous studies in Vietnam that highlight their widespread use, particularly in children and community settings.[30] Our intervention had a significant impact on this marker, with a striking reduction from 62% to 36%. Use shifted to “Access” antibiotics, which increased from 35% to 57%, approaching the WHO target of 60% of all prescribed antibiotics to come from this “Access” group.[31]

We found that IV antimicrobials were preferred locally compared to oral antimicrobials, contrary to study and national MoH guidelines. Unnecessary or prolonged IV antimicrobial administration were associated with increased costs, more complications from venous access, and higher hospital lengths of stay, without evidence for better clinical outcomes.[32]

Compliance with study and national MoH guidelines was low, with prescribers habitually using other unpublished guidelines such as those established locally within the hospital or adapted from a tertiary hospital. Significant discrepancies in drug choice, duration, and dose recommendations across guidelines led to considerable variation in prescribing practices. Furthermore, the 2015 MoH guideline,[17] had not been updated to reflect global recommendations or evolving local resistance patterns. WHO recommends updated, standardised treatment guidelines based upon local antibiotic resistance and abiding to stewardship principles,[10] but this is potentially challenging in Vietnam due to resource limitations. Physicians also reported frequent drug shortages driven by changes in national drug procurement policies impacting antimicrobial selection,[33] often resulting in inappropriate substitute antimicrobial choices despite the availability of effective alternatives.

Another concerning observation was the high rates of inappropriate prescribing in paediatric wards. Antimicrobials were frequently prescribed for children, even those presenting with viral illnesses such as upper respiratory tract infections and gastroenteritis which require only supportive treatment. This has been widely reported in other studies conducted in Vietnam, which showed that children are disproportionately affected by non-discretionary prescribing,[34,35] as well as the need to justify hospital admissions in children.[34]

AMS teams and committees are crucial for successful hospital-based AMS programmes.[10] Our findings confirm their importance at a district level. A 2019 Vietnamese MoH review revealed that only 51% of 655 hospitals studied had AMS committees, of which 72% were inactive.[36] Leaders within the four hospitals in the present study expressed strong enthusiasm for advancing AMS activities, recognizing their value in improving hospital practice.[10]

Real-time department-specific audit and feedback were key components of this intervention. A Cochrane review found AMS campaigns that included a feedback process to be more effective than those without.[37] Although WHO recommends audit and feedback as a core element of an AMS programme in LMICs,[10] its implementation is limited to only a few tertiary hospitals in Vietnam, due to resource constraints.

This study demonstrated that with hands-on guidance, implementing an AMS campaign at district hospitals was feasible, effective and aligned with Vietnam MoH guidance on AMS implementation. It provided a sustainable model for hospital staff and showcased the value of collaboration between local and international clinicians and researchers.

However, the study had limitations. The six-month intervention period was likely too short to assess long-term changes in prescribing behaviour, which typically requires more time.[38] While few studies in the Cochrane review address long-term AMS effects, those that do show lasting improvements after years of consistent implementation.[37,39] Additionally, the lack of control sites in this before-after study limited the ability to account for confounding factors, such as seasonality, drug stock-outs, and reduced patient numbers during COVID-19 restrictions at the beginning of the study. A randomised controlled trial would better evaluate the effectiveness of AMS campaigns in district hospitals in Vietnam.

This study has significant policy implications, highlighting the urgent need for implementation of AMS interventions across all district hospitals to address the high rates of inappropriate antimicrobial use. While restrictive prescribing or pre-authorisation of antibiotic prescriptions have been shown to be more effective ,[37] they are challenging to implement in district hospital settings due to limited access to trained doctors and pharmacists to provide advice on a daily basis. Strengthening of

infection prevention and control measures also reduce antimicrobial consumption by lowering healthcare-associated infections.[40] Further research is required to identify if adding these strategies will prove to be more effective in this setting.

In conclusion, inappropriate antimicrobial use was widespread in all wards in the four district hospitals studied. This study demonstrated the feasibility of implementing an AMS program at the district level in Vietnam, despite only modest improvements seen. It is crucial to scale up these interventions and explore more effective approaches to promote judicious antimicrobial use in Vietnam and other similar settings in LMICs.

References for Chapter 3

1. World Health Organisation. Antimicrobial resistance fact sheet. 2023. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance (accessed 15/7/2024).

2. Mendelson M, Matsoso MP. Guest Editorial: The World Health Organization Global Action Plan for antimicrobial resistance. *South African medical journal* 2015; **105**(5): 325-.

3. Torumkuney D, Kundu S, Vu GV, et al. Country data on AMR in Vietnam in the context of community-acquired respiratory tract infections: links between antibiotic susceptibility, local and international antibiotic prescribing guidelines, access to medicines and clinical outcome. *Journal of Antimicrobial Chemotherapy* 2022; **77**(Supplement_1): i26-i34.

4. Duong TN, Le TV, Tran KH, et al. Azole-resistant Aspergillus fumigatus is highly prevalent in the environment of Vietnam, with marked variability by land use type. *Environ Microbiol* 2021; **23**(12): 7632-42.

5. Global Research on Antimicrobial Resistance (GRAM) IfHMaEI, University of Oxford,. The burden of antimicrobial resistance (AMR) in Viet Nam: University of Oxford-IHME Strategic Partnership, 2022. https://www.healthdata.org/sites/default/files/2023-09/Viet_Nam.pdf (accessed 12/07/2024).

6. Nguyen KV, Thi Do NT, Chandna A, et al. Antibiotic use and resistance in emerging economies: a situation analysis for Viet Nam. *BMC Public Health* 2013; **13**(1): 1158.

7. World Health Organisation. Everyone has a responsibility to prevent Antimicrobial Resistance in Viet Nam. 20 November 2023 2023. https://www.who.int/vietnam/news/detail/20-11-2023-everyone-has-a-responsibility-to-prevent-antimicrobial-resistance-in-viet-nam# (accessed 30/07/2024).

8. Zawahir S, Le HTT, Nguyen T-A, et al. Inappropriate supply of antibiotics for common viral infections by community pharmacies in Vietnam: A standardised patient survey. *The Lancet Regional Health – Western Pacific* 2022; **23**.

9. Son NT. Decision No. 5631/QD-BYT 2020 Guidance on management of the antibiotic use in hospitals. 2020. https://english.luatvietnam.vn/decision-no-5631-qd-byt-of-the-ministry-of-health-on-promulgating-the-guidance-on-management-of-the-antibiotic-use-in-hospit-196563-doc1.html (accessed 15/03/2022).

10. World Health Organisation. Antimicrobial Stewardship programmes in health-care facilties in Low- and Middle-income countries - a WHO practical toolkit. 2019. https://www.who.int/publications/i/item/9789241515481 (accessed 10/01/2023).

11. Pierce J, Apisarnthanarak A, Schellack N, et al. Global Antimicrobial Stewardship with a Focus on Low- and Middle-Income Countries. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2020; **96**: 621-9.

12. Van Dijck C, Vlieghe E, Cox JA. Antibiotic stewardship interventions in hospitals in low- and middle-income countries: a systematic review. *Bulletin of the World Health Organization* 2018; **96**(4): 266-80.

13. World Health Organisation. Hospitals in Viet Nam. https://www.who.int/vietnam/health-topics/hospitals (accessed 04/08/2023).

14. Ministry of Health Vietnam. Annual Health Statistics Report 2019-2020. 2020.

15. Hoa NT, Tam NM, Derese A, Markuns JF, Peersman W. Patient experiences of primary care quality amongst different types of health care facilities in central Vietnam. *BMC health services research* 2019; **19**(1): 275.

16. Australian Commission on Safety and Quality in Health Care. Antimicrobial Stewardship in Australian Health Care. Sydney, Australia: ACSQHC, 202322/11/2024).

17. Ministry of Health Vietnam. Instructions for Use of Antibiotics - Decision No. 708/QD-BYT. Hanoi, Vietnam, 2015. https://kcb.vn/thu-vien-tai-lieu/tai-lieu-huong-dan-su-dung-khang-sinh.html (accessed 31/03/2022).

18. National Centre for Antimicrobial Stewardship. The National Antimicrobial Prescribing Survey. 2024. https://www.ncas-australia.org/National_Antimicrobial_Prescribing_Survey (accessed 08/04/2022).

19. World Health Organisation. ATC/DDD Toolkit. 2024. https://www.who.int/tools/atc-ddd-toolkit (accessed 23/02/2022).

20. Baier J, Höpner J, Haase R, et al. Monitoring antibiotic consumption in pediatrics. How close to reality are days of therapy and recommended daily dose methods? *The Pediatric Infectious Disease Journal* 2022; **41**(4): e126-e32.

21. Nguyen NP-t, Truong QT, Huynh TP, et al. Measurement of DDD and DOT metrics for optimizing antimicrobial surveillance in two tertiary hospitals in Viet Nam: A four-year retrospective study. *Pharmaceutical Sciences Asia* 2024; **51**: 301-13.

22. James R, Nakamachi Y, Morris A, et al. The feasibility and generalizability of assessing the appropriateness of antimicrobial prescribing in hospitals: a review of the Australian National Antimicrobial Prescribing Survey. *JAC-antimicrobial resistance* 2022; **4**(1).

23. StataCorp. Stata Statistical Software: Release 18. College Station, TX:StataCorp LLC; 2023.

24. World Health Organization. The WHO AWaRe (access, watch, reserve) antibiotic book. 2022. https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.04 (accessed 02/07/2024).

25. OANDA. Historical currency converter. 2024. https://www.oanda.com/currency-converter/en/?from=VND&to=USD&amount=1 (accessed 24/10/2024) 2024).

26. Nguyen D, MacLeod WB, Phung DC, et al. Incidence and Predictors of Surgical-Site Infections in Vietnam. *Infection Control & Hospital Epidemiology* 2001; **22**(8): 485-92.

27. Nguyen HT, Bui QTH, Vo TV, Pham HTT, Vo TD. Antibiotic use in gastrointestinal surgery patients at a Vietnamese national hospital. *BMC Gastroenterol* 2022; **22**(1): 480.

28. Van Tuong P, Xiem CH, Anh NC, Quang LN. Assessment of Antibiotic Prophylaxis in Surgical Patients and Association Factors at Thu Duc District Hospital, Ho Chi Minh City, Vietnam in 2018. *Health Services Insights* 2021; **14**: 11786329211029354.

29. World Health Organisation. WHO recommendation on routine antibiotic prophylaxis for women undergoing operative vaginal birth. 2021. https://www.who.int/publications/i/item/9789240027992 (accessed 01/11/2023).

30. Nguyen NV, Do NTT, Nguyen CTK, et al. Community-level consumption of antibiotics according to the AWaRe (Access, Watch, Reserve) classification in rural Vietnam. *JAC-antimicrobial resistance* 2020; **2**(3): dlaa048.

31. World Health Organisation. WHO Thirteenth General Programme of Work 2019-2023 : Target ≥60% of total antibiotic consumption being Access group antibiotics. https://www.who.int/data/gho/indicator-metadata-registry (accessed 03/07/2024).

32. Béïque L, Zvonar R. Addressing Concerns about Changing the Route of Antimicrobial Administration from Intravenous to Oral in Adult Inpatients. *Can J Hosp Pharm* 2015; **68**(4): 318-26.

33. Viet Nam Ministry of Health. Circular No. 15/2019/TT-BYT dated July 11, 2019 providing guidance on bidding for supply of drugs for public health facilities. 2019. https://thuvienphapluat.vn/van-ban/EN/Dau-tu/Circular-15-2019-TT-BYT-providing-guidance-on-bidding-for-supply-of-drugs-for-public-health-facilities/421945/tieng-anh.aspx#google_vignette (accessed 10/12/2023).

34. Nguyen PT, Tran HT, Fitzgerald DA, Graham SM, Marais BJ. Antibiotic use in children hospitalised with pneumonia in Central Vietnam. *Archives of Disease in Childhood* 2020; **105**(8): 713-9.

35. Larsson M, Kronvall G, Thi Kim Chuc N, et al. Antibiotic medication and bacterial resistance to antibiotics: a survey of children in a Vietnamese community. *Tropical Medicine & International Health* 2000; **5**(10): 711-21.

36. Hanoi Hospital Pharmacy Association. Thực trạng triển khai chương trình quản lý sử dụng kháng sinh tại các bệnh viện trên to n quốc [Status of implementing antimicrobial stewardship programs in hospitals across Vietnam]. Open Hanoi Hospital Pharmacy Scientific Conference; 2019; Hanoi; 2019.

37. National Centre for Antimicrobial Stewardship. Antimicrobial Stewardship: Behaviour Change. https://www.ncas-australia.org/behaviour-change (accessed 10/10/2024).

38. Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017; **2**(2): Cd003543.

39. Del Fabro G, Venturini S, Avolio M, et al. Time is running out. No excuses to delay implementation of antimicrobial stewardship programmes: impact, sustainability, resilience and efficiency through an interrupted time series analysis (2017–2022). *JAC-antimicrobial resistance* 2024; **6**(3).

40. World Health Organisation. Infection Prevention and Control and Antimicrobial Resistance. 2024. https://www.who.int/teams/integrated-health-services/infection-prevention-control/ipc-and-antimicrobial-resistance (accessed 15/10/2024).

Tables and Figures

Table 3.1: Pre-existing facilities and antimicrobial stewardship interventions prior to the study

Province	**Hanoi**		**Ca Mau Province**	
Hospital	Hospital A	Hospital B	Hospital C	Hospital D
Population of the province	8 million people		1.2 million people	
Number of inpatient wards	13	9	8	7
Number of inpatient beds	638	290	160	220
Number of inpatients in the month prior to the intervention	3590	988	227	339
Total number of healthcare workers - Doctors - Nurses - Pharmacists	113 224 19	46 119 11	37 31 10	79 20 11
Access to imaging	Yes – Xray, CT scan, Mammogram, and Ultrasound	Yes – Xray and Ultrasound	Yes – Xray and Ultrasound	Yes – Xray and Ultrasound
Presence of health information system	Yes – for inpatient and outpatient information	Yes – for inpatient information	Yes – for inpatient and outpatient information	No – in development
Antibiotic use record	DDD, DOT and costs recorded	Nil data on antibiotic use	Nil data on antibiotic use	Nil data on antibiotic use
Microbiology testing	Basic microbiology tests available e.g. - Microscopy and bacterial culture - Drug susceptibility testing	Access to send-away microbiology tests to an external laboratory unit.	Only microscopy available	Only microscopy available
Antibiotic guidelines used routinely	Hospital and MoH guidelines	MoH guidelines	MoH and Provincial health guidelines	MoH guidelines
Existing AMS activities, prior to the intervention period	Some training and education activities Guidelines available	Nil	AMS committee had been recently constructed	Nil

AMS: Antimicrobial Stewardship MoH: Ministry of Health, DDD: Defined Daily Dose, DOT: Days of therapy

Table 3.2: Timeline of monthly AMS interventions carried out in hospitals

AMS Intervention	Pre-intervention	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Post-intervention
Antimicrobial consumption data collection	X	X	X	X	X	X	X	X
AMS Committee and team formation	X							
Training AMS teams to use Hospital NAPS audit tool	X						X (Refresher session)	
AMS Committee meeting		X		X		X	X	
Distribution of antimicrobial guidelines	X							
Education workshops			X			X		
Audit of antimicrobial appropriateness	X		X (1 ward)		X (1 ward)			X
Feedback session to prescribers		X	X (1 ward)		X (1 ward)			

AMS: Antimicrobial stewardship, NAPS: National Antimicrobial Prescribing Survey - audit tool adapted from Australia

Table 3.3: Activities undertaken as a part of the AMS interventions at each hospital

Activities	Number of staff participating (n)				
Hospital	Hospital A (11 wards)	Hospital B (7 wards)	Hospital C (5 wards)	Hospital D (7 wards)	Total
Training of AMS team staff on AMS and the use of Hospital NAPS audit tool	4	5	2	2	13
Stakeholder meetings with AMS committee and research staff	13	15	18	17	63
Internal AMS committee meetings					
- Meeting 1	8	8	9	9	34
- Meeting 2	8	8	9	9	34
- Meeting 3	8	8	18	9	43
- Meeting 4	8	8	18	9	43
Healthcare worker training and education sessions					
- Workshop 1	32	18	28	41	119
- Workshop 2	40	48	37	44	169
Audit and feedback sessions					
- Feedback session 1	8	8	28	41	85
- Feedback session 2	14	6	8	5	33
- Feedback session 3	8	7	10	6	31
Refresher training for AMS teams	4	4	3	4	15

AMS: Antimicrobial Stewardship, NAPS: National Antimicrobial Prescribing Survey - audit tool adapted from Australia

Table 3.4: Descriptive analyses of patients analysed using Hospital National Antimicrobial Prescribing Survey (Hospital NAPS) audit tool before and after intervention.

Descriptors	BEFORE intervention n (%)	AFTER intervention n (%)	Risk difference (95%CI)
Number of patients on day of audit in all participating hospital wards			
Total inpatients at 8am on the day of audit (n)	454	992	NA
Total inpatients prescribed antimicrobials (n)	240 (52.9)	570 (57.5)	NA
Total antimicrobial prescriptions (n)	324	751	NA
Overall proportion of inappropriate prescriptions (%)	79.3%	80.3%	NA
Number of antimicrobial prescriptions assessed on day of audit in all hospitals, n (%)			
Total	324	751	NA
Adult (>17 years)	265 (81.8)	478 (63.7)	
Paediatric (≤16 years)	59 (18.2)	273 (36.3)	
Usage of broad-spectrum antimicrobials according to class, n (%)			
2nd CEP	9 (2.8)	1 (0.1)	**-2.7% (-4.5%, -0.9%)**
3rd CEP	153 (47.2)	213 (28.4)	**-18.8% (-25.1%, -12.5%)**
Fluoroquinolones	33 (10.2)	73 (9.7)	-0.5% (-4.4%, 3.4%)
Aminoglycosides	18 (5.6)	53 (7.1)	1.5% (-1.6%, 4.6%)
Carbapenems	1 (0.3)	2 (0.3)	0 (0)
Beta-lactam/BLI	48 (14.8)	151(20.1)	**5.3% (0.5%, 10.1%)**
Usage of antimicrobials according to WHO AWaRe Classification (Watch, Access, Reserve)*, n (%)			
Access	113 (34.9)	425 (56.6)	**21.7% (15.4%, 28.0%)**
Watch	202 (62.4)	268 (35.7)	**-26.7% (-33.0%, -20.4%)**
Reserve	0 (0)	0 (0)	0 (0)
Uncategorised/Other	9 (2.8)	58 (7.7)	**4.9% (2.3%, 7.5%)**
Route of administration of antimicrobials, n(%)			
Intravenous	223 (68.8)	577 (76.8)	**8.0% (2.1%, 13.9%)**
Oral	93 (28.7)	160 (21.3)	**-7.4% (-13.1%, -1.7%)**
Antimicrobial prescription compliance to study/MoH guidelines, n(%)			
Compliant with guidelines	67 (20.7)	98 (13.1)	**-7.6 (-12.6%, -2.6%)**
Non-compliant with guidelines	244 (75.3)	600 (79.9)	4.6% (-0.9%, 10.1%)
No guidelines available	11 (3.4)	51 (6.8)	**3.4% (0.7%, 6.1%)**
Not assessable	0 (0)	1 (0.1)	0.1% (-0.1%, 0.3%)
Reasons for inappropriateness, n(%)			
Incorrect Dosing*	50 (15.4)	163 (21.7)	**6.3% (1.4%, 11.2%)**
Spectrum too broad	147 (45.4)	282 (37.6)	**-7.8% (-14.2, -1.4%)**
Spectrum too narrow	15 (4.6)	31 (4.1)	-0.5% (-3.2%, 2.2%)
Incorrect route	22 (6.8)	185 (24.6)	**17.8% (13.7%, 21.9%)**
Duration too long	117 (36.1)	143 (19.0)	**-17.1% (-23.0%, -11.2%)**
Antibiotics not required for condition	39 (12.0)	153 (20.4)	8.4% (3.8%, 13.0%)
Percentage of inappropriate prescriptions by age group, n (%)			

Descriptors	BEFORE intervention n (%)	AFTER intervention n (%)	Risk difference (95%CI)
Adult	206/265 (77.7)	347/477 (72.7)	**-5.0% (-11.4%, 1.4%)**
Paediatric	51/59 (86.4)	256/273 (93.8)	7.3% (-1.9%, 16.5%)
Percentage of inappropriateness by specialty, n(%)			
General Medicine	57/83 (68.7)	130/180 (72.2)	3.5% (-8.4%, 15.5%)
General Surgery	49/58 (84.5)	146/173 (84.4)	-0.1% (-10.9%, 10.7%)
Cardiology	6/8 (75.0)	7/9 (77.8)	2.8% (-37.7%, 43.3%)
Obstetrics & Gynaecology	43/46 (93.5)	58/73 (79.5)	**-14.0% (-25.7%, -2.3%)**
Paediatrics	34/42 (81.0)	194/205 (94.6)	13.7% (1.4%, 26.0%)
Infectious Diseases	10/12 (83.3)	0/6 (0)	**-83.3% (-104.4%, -62.2%)**
Others**	58/75 (77.3)	68/104 (65.4)	-11.9% (-25.1%, 1.2%)
Percentage of inappropriateness by site of infection, n(%)			
Respiratory	92/124 (74.2)	183/226 (81.0)	6.8% (-2.5%, 16.0%)
Bone and Joint	4/5 (80.0)	0 (0)	NA
Ear Nose Throat	11/15 (73.3)	112/120 (93.3)	20.0% (-2.8%, 42.8%)
Skin Soft tissue	27/30 (90.0)	66/87 (75.9)	**-14.1% (-28.1%, -0.1%)**
Gastrointestinal	16/24 (66.7)	21/36 (58.3)	-8.3% (-33.1%, 16.5%)
Intra-abdominal	15/21 (71.4)	34/52 (65.4)	-6.0% (-29.3%, 17.2%)
Oral and Dental	1/3 (33.3)	1/1 (100.0)	66.7% (13.3%, 120.0%)
Systemic	1/1 (100.0)	4/5 (80.0)	-20.0% (-55.1%, 15.1%)
Sepsis/Bacteraemia	0/2 (0)	4/9 (44.4)	**44.4% (12.0%, 76.9%)**
Urinary tract	9/15 (60.0)	15/30 (50.0)	-10.0 (-40.6%, 20.6%)

Bolded text indicates confidence limits do not cross the null

**Incorrect dosing includes both over- and under-dosing of antimicrobials. Incorrect route of administration means an antibiotic was not prescribed in the most appropriate route for its indication.*

***Others: Emergency medicine, Intensive/critical care, and Orthopaedic surgery.*

Definitions: 2nd CEP: Second-generation Cephalosporin, 3rd CEP: Third-generation Cephalosporin, Beta-Lactam/BLI: Beta-lactam with beta-lactam inhibitor.

AWaRe classification is a tool used to consider the impact of different antibiotic classes on antimicrobial resistance. "Access" category antibiotics display low resistance potential, are narrow spectrum and of low cost, "Watch" antibiotics are broader-spectrum, higher cost and required in severe presentations, whereas "Reserve" category antibiotics are the last choice to treat multi-drug-resistant infections.

Figure 3.1: Number of inpatients per month in each study site from Jan 2022 to Sept 2022 (Intervention period: March to August 2022)

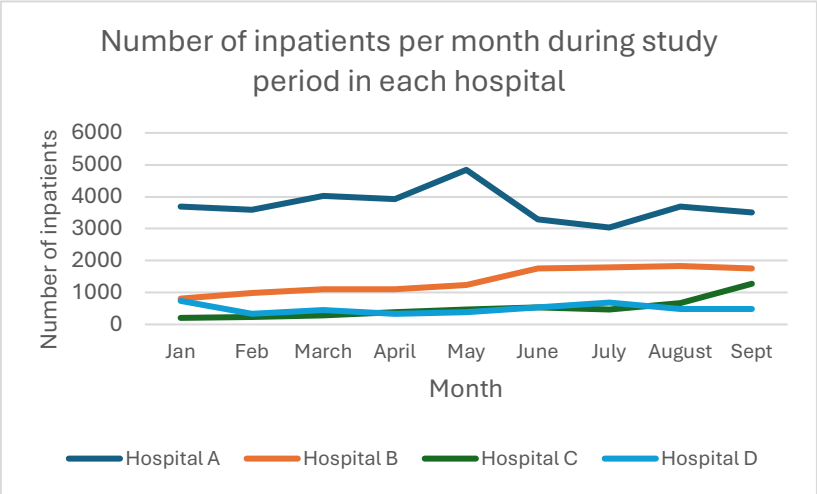
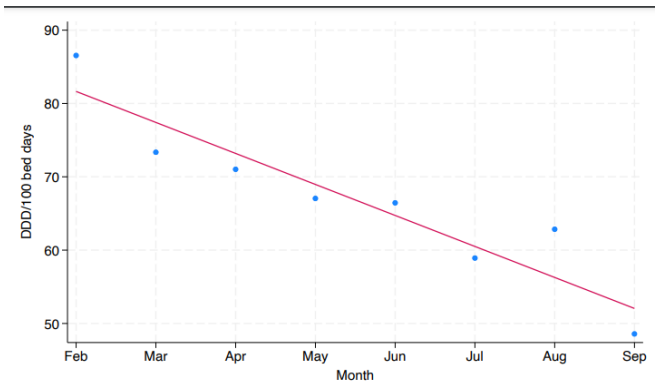


Figure 3.2: Average DDD/100 bed-days over the intervention period for all sites reflecting median antimicrobial consumption per month (Intervention period: March to August 2022)



DDD: Defined Daily Doses

Supplementary material for Chapter 3

Table S3.1: Number of inpatients per month in each study site from February 2022 to September 2022 (Intervention period: March to August 2022)

Number of inpatients	February	March	April	May	June	July	August	September
Hospital A	3590	4020	3928	4843	3295	3036	3688	3514
Hospital B	988	1099	1095	1243	1756	1784	1830	1757
Hospital C	227	286	391	467	526	471	660	1274
Hospital D	339	442	331	387	529	678	490	478

NB: There was inpatient data missing for a total of 3 weeks over June and July in Hospital A due to Information technology glitches

Table S3.2: Antimicrobial consumption in each hospital in Defined Daily Doses (DDD)/100 bed-days

Antimicrobial consumption in DDD/100 bed-days	February	March	April	May	June	July	August	September
Hospital A	49.18	58.37	62.04	54.88	63.98	66.72	67.57	58.94
Hospital B	48.78	42.60	84.57	75.34	70.78	67.47	74.49	57.92
Hospital C	166.00	136.05	76.73	70.20	64.31	59.68	52.87	25.73
Hospital D	82.18	56.41	60.79	67.75	66.67	41.83	56.39	51.80
Average DDD/100 bed-days	86.53	73.36	71.03	67.04	66.43	58.92	62.83	48.60

DDD: Defined Daily Dose

Table S3.3: Number of inpatients on antimicrobials on the days of audit before and after AMS intervention

Hospital	Number of inpatients on antibiotics on day of NAPS audit	Number of inpatients	Proportion	Number of inpatients on antibiotics on day of NAPS audit	Number of inpatients	Proportion	Risk Difference (95% CI) (After – Before)
	Before			After			
Hospital A	126	256	49.2	303	550	55.1	5.9% (-1.5, 13.3)
Hospital B	38	56	67.9	177	266	66.5	-1.3% (-14.8, 12.2)
Hospital C	48	114	42.1	43	125	34.4	-7.7% (-20.0, 4.6)
Hospital D	28	62	45.2	47	86	54.7	9.5% (-6.8, 25.8)
Total	240	488	49.2	570	1027	55.5	6.3% (0.9, 11.7)

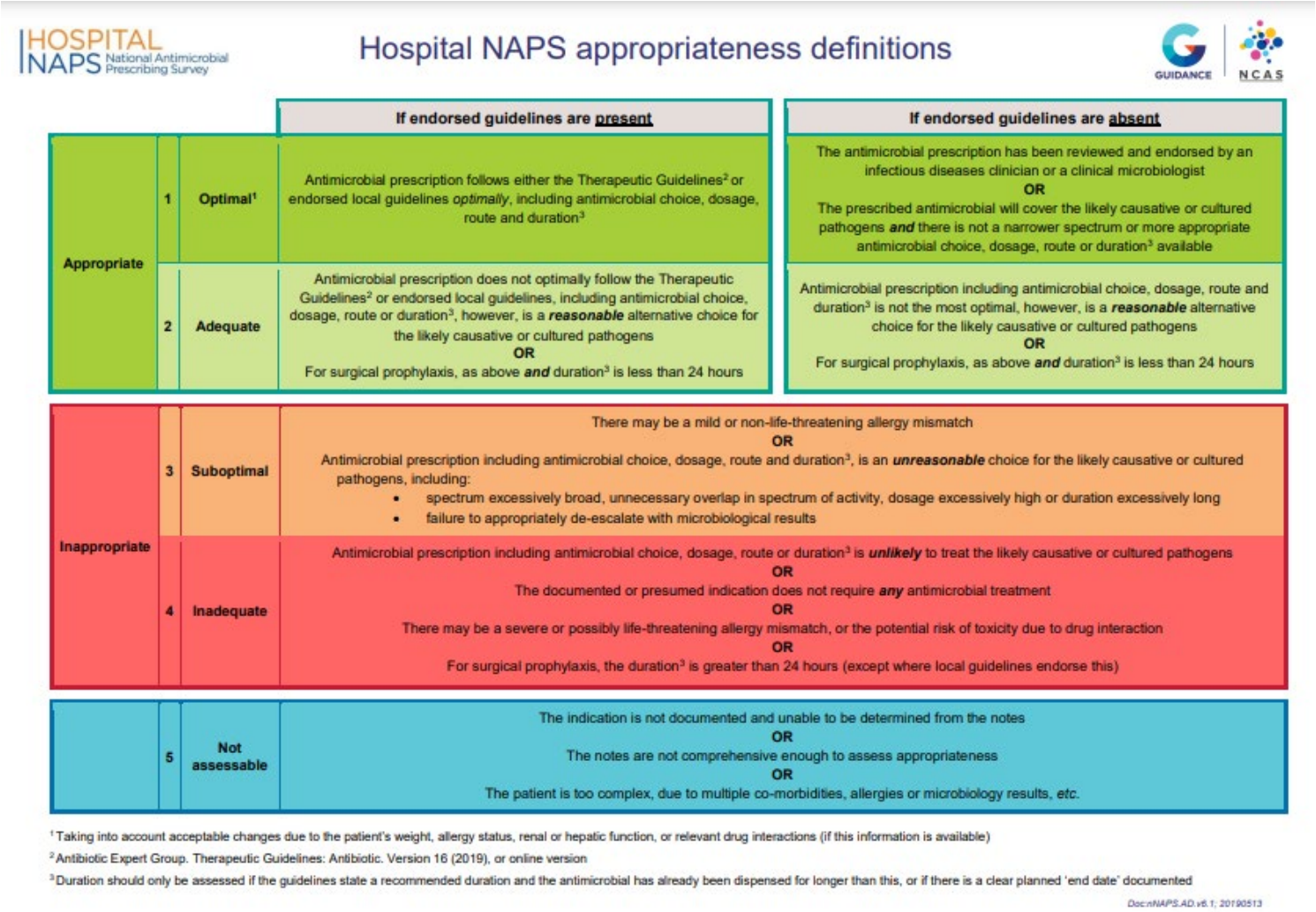
AMS: Antimicrobial Stewardship, NAPS: National Antimicrobial Prescribing Survey - audit tool adapted from Australia, CI: Confidence intervals

Table S3.4: Mortality rates in each hospital before and after the intervention period in each hospital

Hospital	Number of deaths in January 2022	Number of inpatients in January 2022	Mortality ratio	Mortality rate per 100,000 people	Number of deaths in Sept 2022	Number of inpatients in Sept 2022	Mortality ratio	Mortality rate per 100,000 people	Difference between mortality of January and September (RD, 95% Confidence Intervals)	2-sided Fisher's exact P value
Hospital A	14	3696	14/3696	379 per 100, 000	5	3513	5/3513	142 per 100, 000	0.37 (0.11, 1.10)	0.081
Hospital B	1	808	1/808	123 per 100, 000	0	1756	0/1756	0 per 100, 000	NA	NA
Hospital C	0	204	0/204	0 per 100, 000	0	1273	0/1273	0 per 100, 000	NA	NA
Hospital D	1	737	1/737	136 per 100, 000	0	477	0/477	0 per 100, 000	NA	NA
Overall	16	5445	16/5445	293 per 100, 000	5	7019	5/7019	71 per 100, 000	0.32 (0.09, 0.92)	0.031

RD: Risk difference, NA: Not applicable

Figure S3.1: National Antimicrobial Prescribing Survey (NAPS) Australia appropriateness definitions by which each antimicrobial prescription was assessed and categorised



			If endorsed guidelines are present	If endorsed guidelines are absent
Appropriate	1	Optimal[1]	Antimicrobial prescription follows either the Therapeutic Guidelines[2] or endorsed local guidelines *optimally*, including antimicrobial choice, dosage, route and duration[3]	The antimicrobial prescription has been reviewed and endorsed by an infectious diseases clinician or a clinical microbiologist **OR** The prescribed antimicrobial will cover the likely causative or cultured pathogens ***and*** there is not a narrower spectrum or more appropriate antimicrobial choice, dosage, route or duration[3] available
	2	Adequate	Antimicrobial prescription does not optimally follow the Therapeutic Guidelines[2] or endorsed local guidelines, including antimicrobial choice, dosage, route or duration[3], however, is a ***reasonable*** alternative choice for the likely causative or cultured pathogens **OR** For surgical prophylaxis, as above ***and*** duration[3] is less than 24 hours	Antimicrobial prescription including antimicrobial choice, dosage, route and duration[3] is not the most optimal, however, is a ***reasonable*** alternative choice for the likely causative or cultured pathogens **OR** For surgical prophylaxis, as above ***and*** duration[3] is less than 24 hours
Inappropriate	3	Suboptimal	There may be a mild or non-life-threatening allergy mismatch **OR** Antimicrobial prescription including antimicrobial choice, dosage, route and duration[3], is an ***unreasonable*** choice for the likely causative or cultured pathogens, including: • spectrum excessively broad, unnecessary overlap in spectrum of activity, dosage excessively high or duration excessively long • failure to appropriately de-escalate with microbiological results	
	4	Inadequate	Antimicrobial prescription including antimicrobial choice, dosage, route or duration[3] is ***unlikely*** to treat the likely causative or cultured pathogens **OR** The documented or presumed indication does not require ***any*** antimicrobial treatment **OR** There may be a severe or possibly life-threatening allergy mismatch, or the potential risk of toxicity due to drug interaction **OR** For surgical prophylaxis, the duration[3] is greater than 24 hours (except where local guidelines endorse this)	
	5	Not assessable	The indication is not documented and unable to be determined from the notes **OR** The notes are not comprehensive enough to assess appropriateness **OR** The patient is too complex, due to multiple co-morbidities, allergies or microbiology results, *etc.*	

[1] Taking into account acceptable changes due to the patient's weight, allergy status, renal or hepatic function, or relevant drug interactions (if this information is available)

[2] Antibiotic Expert Group. Therapeutic Guidelines: Antibiotic. Version 16 (2019), or online version

[3] Duration should only be assessed if the guidelines state a recommended duration and the antimicrobial has already been dispensed for longer than this, or if there is a clear planned 'end date' documented

Doc:nNAPS.AD.v6.1; 20190513

Link between Chapter 3 and 4

Chapter 3 described the implementation of AMS interventions in four district hospitals in Vietnam and assessed their impact on the antimicrobial consumption and appropriateness of antimicrobial prescribing. The study did not demonstrate significant improvements in either co-primary outcome. Chapter 4 presents the findings of the impact of these AMS interventions on the prevalence of multidrug-resistant organism (MRO) carriage in hospital inpatients.

While data for both chapters were collected from the same four hospital sites, it is important to note that the patient populations were distinct. The MRO carriage study used separate cross-sectional cohorts pre- and post- the AMS intervention period, comprising patients who met eligibility criteria and consented to swab collection, regardless of whether they were receiving antimicrobials. These were not the same patients audited for antimicrobial appropriateness in Chapter 3.

Chapter 4: The effect of an AMS intervention upon multidrug-resistant organisms in Vietnamese district hospitals

This chapter contains an article that has been submitted for publication.

Authors

Jaslyn Doshi[1], Thai Duy Pham[2], Yen Ngoc Pham[3], Thuy Thu Ma[3], Linh Thuy Duong[3], Qingbin Li[1], Thanh Ha Nguyen[2], Jon Iredell[4], Matthew Watts[4,5], Thu Anh Nguyen[1,3], Hoang Huy Tran[2], Greg J Fox[1*], Annaleise R Howard-Jones[6,7*]

Author contributions

GJF, AHJ,TAN and JI contributed to conceptualising of the study, study design, and provided scientific output into study protocol. AHJ, JD, TDP and HHT contributed toward development of laboratory protocol. YPN, TTM, LTD led trial implementation and participated in clinical sample collection. TDP,THN and HHT performed microbiological testing of clinical samples. JD and AHJ provided remote support to laboratory team. JD performed data analysis under the supervision of AHJ and GJF. QL performed statistical analysis of data. AHJ, GJF, JI and MW provided guidance in scientific output in manuscript. JD wrote all sections of the manuscript. All authors reviewed the manuscript and provided edits.

Abstract

Introduction: Antimicrobial resistance (AMR) is a critical global health challenge, with Southeast Asia identified as a hotspot of multidrug-resistant organism (MRO) carriage in hospitalised patients and the general population. This study aimed to evaluate the prevalence of gastrointestinal and nasal MRO carriage in district hospital inpatients in Vietnam and assess the effect of an antimicrobial stewardship (AMS) intervention upon MRO carriage.

Methods: A prevalence survey was undertaken among inpatients at four district hospitals in Vietnam. The prevalence, antimicrobial susceptibility profiles and genotypic analysis of extended spectrum β -lactamase (ESBL)-producing Enterobacterales and carbapenemase-producing Enterobacterales (CPE) from stool or rectal swabs, and methicillin-resistant *Staphylococcus aureus* (MRSA) from nasal swabs were assessed. Following a six-month audit and feedback program at all hospitals, the survey was repeated. A participant survey was conducted to determine risk factors associated with MRO carriage.

Results: A total of 402 inpatients had nasal swabs and rectal or stool samples collected. Enterobacterales isolates demonstrated high prevalence of antibiotic resistance. Over three quarters of participants carried organisms with $bla_{\text{CTX-M}}$ (ESBL) genes (76.1%), with low prevalence seen for CPE (2.7%), and MRSA carriage (3.0%). Risk factors for ESBL-producing Enterobacterales carriage included female sex, age over 65 years old, recent antibiotic use, smoking and being in an urban hospital. The prevalence of ESBL-producing Enterobacterales or CPE was unchanged after the AMS intervention. MRSA carriage reduced from 5% to 1% following the intervention period [-4.0%, 95% CI -7.2%, -0.7%)

Conclusion: The prevalence of ESBL-producing Enterobacterales carriage was high among inpatients in public district hospitals in Vietnam, while the prevalence of CPE and MRSA carriage was low. AMS interventions showed a modest reduction in prevalence of MRSA carriage.

Keywords: antimicrobial resistance; antimicrobial stewardship; Vietnam; multidrug-resistant organism; district hospitals; extended-spectrum beta-lactamase; carbapenemase-producing; Enterobacterales; methicillin-resistant *Staphylococcus aureus*

Introduction

Rising prevalence of antimicrobial resistance (AMR) represent a critical global health challenge, with resistance to existing antibiotics far outpacing the development of new agents, leading to a crisis of untreatable infections.[1,2] Escalating drug resistance threatens human health, with profound implications for public health, economies, and societies worldwide.[1] Antibiotic overuse and misuse in hospitals, the community, as well as in the agricultural and animal sectors all contribute to the increasing prevalence of extended-spectrum β-lactamase (ESBL)- and carbapenemase-producing Enterobacterales (CPE) and methicillin-resistant *Staphylococcus aureus* (MRSA). A meta-analysis reported global intestinal carriage of ESBL-producing *Escherichia coli* at 16.5% in the community, and up to 27% in with Southeast Asia.[3] The prevalence of carbapenem-resistant Enterobacterales (CRE) carriage is estimated to be between 4.5% to 10% globally among predominantly tertiary-hospitalised patients and the community, with a much higher prevalence reported in Asia.[4-6] MRSA carriage among nursing home residents globally has been estimated at 14.7%. Rising prevalence of multidrug-resistant organisms (MROs) colonisation drives amplified transmission and is the main risk factor for subsequent infection.[7] This can lead to treatment failure, with associated morbidity and mortality risk.[8]

Vietnam, a middle-income country in South-east Asia is a recognised AMR "hotspot".[9] Hospitalised patients and people in the community have demonstrated a higher prevalence of MRO carriage compared to overall global prevalence studies.[10-15] Most of the published data from hospitals are in tertiary settings, with gaps in the literature on prevalence of these MROs in lower levels of healthcare in LMICs including Vietnam.

The extent of AMR in Vietnam highlights the critical need for coordinated strategies.[16] Antimicrobial stewardship (AMS) plays a pivotal role in addressing this challenge by promoting the responsible use

of antibiotics to minimise resistance, improve patient outcomes, and preserve the effectiveness of existing treatments.[17,18]

This study aimed to assess the prevalence of MRO carriage—specifically ESBL-producing Enterobacterales, CPE, and MRSA—among inpatients at district hospitals in Vietnam, and to identify patient factors associated with MRO carriage. Additionally, it examined the antibiotic susceptibility patterns and genotypic profiles of the isolated organisms. Lastly, the study evaluated the impact of an AMS program on MRO prevalence among inpatients.

Methods

Study design, setting and population

A before-and-after study was undertaken at four public district hospitals in two provinces in northern and southern Vietnam (Supplementary Table S4.1, Figure S4.1). Data were collected at two timepoints in each hospital, before the implementation of AMS interventions, and from a different set of inpatients in the final two weeks of a six-month AMS intervention. Study participants were inpatients in any ward in the district hospital that had been admitted for over 48 hours at the time of sampling, over 18 years of age, and willing to provide both a stool sample or rectal swab and a nasal swab.

Antimicrobial stewardship interventions

A six-month antimicrobial stewardship program was implemented at all sites. The AMS interventions were based upon a World Health Organisation(WHO) toolkit for AMS in resource-limited settings and the Australian national AMS program, in alignment with the Vietnam Ministry of Health policy.[17,19,20] All hospitals received the same AMS interventions consisting of four components: (i) Establishing

AMS committees and teams; (ii) Development and distribution of antimicrobial guidelines; (iii) Healthcare worker education and training; and (iv) Periodic audit and feedback. Details of the AMS interventions are provided in supplementary material (Supplementary Table S4.2).

Each hospital had formal national infection control policies in place, including recommendations for hand hygiene, sterilisation regulations for procedures and medical devices, and the usage of isolation precautions for patients with multidrug-resistant bacteria, and environmental cleaning. These remained unchanged during the course of the study.

Enrolment and specimen collection

Participants were inpatients at four district hospitals that fitted inclusion criteria and had consented to provide stool samples or rectal swabs and nasal swabs. Participant data were collected by questionnaire. This included age, gender, ward admitted in, smoking status, antibiotic use during present admission, self-reported antibiotic use in the previous 12 months and hospitalisation within the previous 12 months. Self-reported past history of intensive care unit (ICU) admission, dialysis and exposure to invasive devices such as nasogastric tube insertion, indwelling urinary catheter insertion or central venous catheters were also documented.

Outcomes

The primary outcome was the proportion of inpatients with rectal carriage of Enterobacterales carrying $bla_{CTX\text{-}M}$ (as the indicator ESBL gene) in the district hospitals. Rectal carriage of Enterobacterales with $bla_{\text{NDM-1}}$, bla_{KPC} and $bla_{\text{OXA-48}}$-like (as representative carbapenemase genes), and nasal MRSA carriage was also analysed. Next, we analysed antibiotic susceptibilities per organism.

We compared the antibiotic susceptibility profiles before and after the AMS program and assessed patient risk factors associated with MRO carriage.

Laboratory methods

Rectal swabs were collected directly with eSwabs (Copan, Italy). Stool samples were collected in a sterile container, mixed thoroughly after collection and sampled in three separate locations using an eSwab, before being stored in Amies transport medium. An anterior nasal swab was collected on each participant using an eSwab liquid Amies collection system (Copan, Italy), moistened with sterile 0.9% normal saline. Samples were kept at 2 to 8°C and transported to the microbiology lab within 48 hours of collection.

Isolation and Characterisation of Enterobacterales Isolates

eSwab rectal and stool-derived specimens were inoculated onto MacConkey agar supplemented with cefotaxime (2 µg/mL) and onto ChromAgar Orientation plates (ThermoFisher, Paris, France) supplemented with meropenem (2 µg/ml), the latter following the procedure of Yen et al.[13] These media were incubated aerobically for 18 to 24 hours at 37°C and colonies were identified using Matrix-Assisted Laser Desorption/Ionization Time-of-Flight mass spectrometry (MALDI-TOF MS).[21] Stool and rectal swab-derived isolates were combined into a single Enterobacterales dataset for downstream analysis. Non-Enterobacterales isolates were excluded from further analysis.

Phenotypic and genotypic drug resistance testing

Phenotypic antimicrobial susceptibility testing (AST) was performed on all Enterobacterales isolates using standardised Clinical and Laboratory Standards Institute (CLSI) agar dilution methodology.[22] Organisms were determined as susceptible(S), intermediate(I) or resistant(R) to cefotaxime, cefoxitin, cefepime, ciprofloxacin, gentamicin, and meropenem according to CLSI breakpoints. Isolates were

classified as “non-susceptible” if testing in the I or R range. Isolates were also assessed phenotypically for production of ESBL using CLSI double disk method, with a cefotaxime (30 µg) disc with and without clavulanic acid (10 µg). Isolates were tested for presence of $bla_{CTX\text{-}M}$ gene using an end-point polymerase chain reaction (PCR) assay (Supplementary Table S4.3). Enterobacterales isolates with a meropenem minimum inhibitory concentration (MIC) exceeding 0.25mg/L was assessed by PCR for presence of $bla_{\text{NDM-1}}$, bla_{KPC} and $bla_{\text{OXA-48}}$ genes (Supplementary Table S4.3).

Isolation and characterisation of Methicillin-Resistant Staphylococcus aureus (MRSA)

Methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated from individual nasal swab samples using mannitol salt agar (MSA) containing Cefoxitin(8µg/ml). Media were incubated aerobically for 24hours at 37°C. Colonies were identified using MALDI-TOF MS analysis and phenotypic AST characterisation performed using standardised CLSI agar dilution techniques. Organisms were determined as susceptible, intermediate or resistant to oxacillin, cefoxitin, ciprofloxacin, clindamycin, sulfamethoxazole/trimethoprim and vancomycin according to CLSI breakpoints. The samples were then assessed by PCR for presence of the *nuc* and *mecA* genes (Supplementary Table S4.3).

Sample size

The sample size calculation for comparing the prevalence of CPE, ESBL and MRSA was based upon Vietnamese studies in which 45% of non-ICU patients were colonised with CRE[12], and 18% of a community population carried MRSA in the anterior nasal cavity (Howard-Jones *et al*, unpublished). An *a priori* estimation of a drop of 15% carriage following AMS intervention was assumed for CRE, and 10% carriage for MRSA, given published data on the impact of AMS interventions on MRO carriage were lacking at the time. An alpha of 0.05 and 80% power was assumed to assess changes in carriage prevalence with all MROs. A total of 196 participants needed to be recruited at each time point to ensure the study was adequately powered.

Statistical analyses

Descriptive statistics were used to analyse participant characteristics, as well as organism characteristics, including the number of identified isolates and their antibiotic susceptibility profiles. The prevalence of MRO carriage per participant and the proportion of non-susceptible organisms before and after the AMS intervention were compared using a two-proportion z-test with Fisher's exact method.

A mixed-effects binary regression to evaluate participant factors associated with carriage of each MRO, determined *a priori* was performed. The model employed a robust variance estimator, accounting for clustering at the hospital level. Both univariable and multivariable analyses were conducted. Results were presented as risk ratios (RRs) with 95% confidence intervals (CIs).

A Directed Acyclic Graph (DAG) developed using DAGitty,[23] guided the model specification by visualizing hypothesized relationships between variables (Supplementary Figure S4.2). All variables identified by the DAG were included in the multivariate model to estimate their independent associations with MRO carriage while controlling for other factors. This captured the unique contribution of each variable and accounted for shared variability between predictors. Multicollinearity was assessed using variance inflation factors (VIFs), and analysis was conducted if VIF was less than 10. In the event of small sample size, descriptive analysis was performed.

Ethical issues

Ethical approval for this study was provided by the Institutional Review Board of the National Institute of Hygiene and Epidemiology (NIHE) in Vietnam (IRB – VN01057/IORG 0008555), and the

Human Research Ethics Committee at the University of Sydney (Project no:2021/193). Participants received an information sheet about the study and the samples being collected and provided written informed consent. Data were de-identified to protect participant confidentiality.

Results

A total of 202 participants were recruited pre-intervention (March 2022) , and 200 participants following the AMS intervention period (August 2022) across four district hospitals. 202 enteric and nasal isolates each were collected before the AMS interventions, and 200 enteric and nasal isolates each were collected after the AMS interventions. Characteristics of participants are presented in Table 4.1. Overall, 365 Enterobacterales (from 402 enteric collections) and 12 MRSA isolates (from 402 nasal collections) were analysed. A batch containing five samples from Ca Mau was impacted by suboptimal transport conditions (8-10°C, rather than the pre-specified 2-8°C, for 6 hours) but were still included in the analysis and valid culture results obtained.

Prevalence of MROs

Enterobacterales isolates identified from stool or rectal swabs included 299 *Escherichia coli,* 54 *Klebsiella pneumoniae* complex, 8 *Enterobacter cloacae* complex, 3 *Klebsiella oxytoca* and 1 *Klebsiella aerogenes* isolates (Supplementary Table S4.4 and S4.5). All isolates showed a high percentage of non-susceptibility to cefotaxime (100%, 365/365 isolates), cefoxitin (59.2%, 216/365 isolates), cefepime (90%, 328/365 isolates), ciprofloxacin (77%, 281/365 isolates), and gentamicin (54.5%, 199/365 isolates). Only a small percentage were non-susceptible to meropenem(3%, 10/365 isolates) (Table 4.2). A high percentage of MRSA isolates were resistant to clindamycin (92%, 11/12 isolates), but none were resistant to vancomycin (0%, 0/12 isolates) (Supplementary Table S4.6). Within the

study population, 76.1% of participants were colonised with *bla*$_{CTX\text{-}M}$-carrying Enterobacterales, 2.7% with CPE and 3.0% with MRSA (Table 4.3).

Comparison before and after the antimicrobial stewardship intervention

No major difference was seen in the proportion of Enterobacterales isolates non-susceptible to antibiotics before and after the implementation of AMS interventions (Supplementary Table S4.7). Similarly, at the participant level, no difference was observed in the carriage of Enterobacterales with *bla*$_{CTX\text{-}M}$ and carbapenemase genes - *bla*$_{\text{NDM-1}}$, *bla*$_{\text{OXA-48}}$-like and *bla*$_{\text{KPC}}$ - before and after the intervention. The prevalence of *bla*$_{CTX\text{-}M}$ gene carriage was 77.7% before, and 74.5% after the AMS intervention period [-3.2% (95% CI: -11.5, 5.1, p = 0.45)], whereas CPE gene carriage was 2.5% before, and 3.0% after the intervention [0.5% (95% CI: -2.7, 3.7)]. The proportion of participants with MRSA carriage reduced significantly from 10 of 202 isolates (5%) to 2 of 200 isolates (1%), a reduction of 4.0% with the AMS intervention (95% CI: -7.2, -0.7, p=0.04).

Factors associated with MRO carriage

The univariable and multivariable risk factors for ESBL carriage in the overall cohort are presented in Table 4.5. Female sex, age over 65 years, antibiotic use (current or previous), being a smoker (current or previous), being in the obstetrics & gynaecology ward and urban hospital location were identified as significant risk factors for ESBL-producing Enterobacterales carriage. The number of isolates with CPE and MRSA carriage were too small to analyse statistically, so descriptive analysis of risk factors was performed, identifying female sex and age over 65 years as potential risk factors(Supplementary Table S4.8).

Discussion

This before-and-after study found high prevalence of antibiotic resistance in district hospital settings in Vietnam. It demonstrated a high prevalence of rectal carriage of ESBL-producing Enterobacterales with relatively low prevalence of CPE and MRSA. Implementation of AMS interventions reduced the nasal carriage of MRSA but had no significant effect on prevalence of multidrug-resistant Enterobacterales carriage.

The high overall prevalence of Enterobacterales carrying $bla_{CTX\text{-}M}$ at 76%, is comparable with the steady and concerning rise of ESBL-producing organism carriage reported in Vietnam. Studies from predominantly tertiary hospitals in Vietnam have documented prevalences of 25% in 2010-12,[10] 59% in 2016-17,[24] and 65% in 2020-21.[15] In the community, studies of healthy individuals have shown a prevalence ranging from 35% to 51% in 2013.[25] These findings indicate that ESBL-producing Enterobacterales are widespread in hospitals and in the community, although data from district hospitals are lacking.[26] Conversely, the prevalence of CPE and MRSA carriage observed in this study was lower than reported in previous research where 52% of tertiary hospital inpatients were CRE-colonised,[12] and 33.8% of the community had nasopharyngeal carriage of MRSA.[27] Persons colonised with MROs not only are at high risk of developing MRO infections over time but also serve as an important source of transmission to other people.[28] Our data thus demonstrate the value in conducting comprehensive cross-sector surveillance programs to monitor these important differences in MRO colonisation prevalences between tertiary inpatient, community and (in our study) district hospital inpatients.

A high proportion of Enterobacterales isolates were not susceptible to a wide range of commonly-used antimicrobials, including broad-spectrum antibiotics such as ciprofloxacin and cefepime, as demonstrated in previous studies.[29] It likely reflects the long-standing overuse of these broad-

spectrum antibiotics in the community and in hospitals.[30] These findings are particularly concerning as treatment decisions within district hospitals, with limited or absent access to microbiological services (Supplementary Table S4.1), typically rely on empiric Ministry of Health-endorsed regimens, encompassing many of these agents.

For instance, while oral ciprofloxacin is the recommended antibiotic for patients presenting with urinary tract infections (UTIs),[31] findings from this study indicate that 77% of Enterobacterales, a common pathogen in UTIs, were non-susceptible to ciprofloxacin. This raise concerns that patients are receiving empiric therapy that may be ineffective, while also driving AMR escalation as a result of alterations in the target enzymes (DNA gyrase and topoisomerase IV) entry and efflux, or plasmid-mediated resistance mechanisms,[32] induced by antibiotic selection pressure. When faced with clinical failures in such scenarios, clinicians may increasingly resort to using broader-spectrum empirical antibiotics, further complicating efforts to adhere to proper stewardship principles in daily practice. Carbapenems are one example of broader spectrum use that warrants caution. Although meropenem resistance was low in our study, increased use – driven by resistance to other antibiotics – could drive future resistance, as observed with ESBL-producing organisms.

To mitigate these risks, avoiding the use of antibiotics if not indicated, as well as optimising dose, duration, and choice of antibiotics, ideally supported by laboratory data, is paramount. Qualitative research would be beneficial in elucidating drivers of broad-spectrum antibiotic use within hospital settings in district hospitals in Vietnam.

The prevalence of MRSA carriage showed a significant reduction with AMS interventions. Some studies have shown a similar reduction in MRSA prevalence with AMS interventions.[33,34] However, this needs to be interpreted with caution in the context of a low overall prevalence and differences in

patient characteristics in the baseline and post-intervention groups (Table 4.1), which may have resulted in a biased effect estimate. In contrast, no significant changes were seen in the prevalence of ESBL-producing Enterobacterales and CPE carriage after the implementation of the AMS interventions in this study. Phenotypic susceptibility profiles were also largely unaffected by the intervention.

Literature on the impact of AMS on MRO prevalence is mixed, with some studies showing a reduction in antibiotic resistance and MRO prevalence, and others not.[35,36] The most recent Cochrane review on effectiveness of AMS[18] was unable to draw definitive conclusions about its impact on reducing AMR due to heterogenous study designs, as well as the presence or absence of concurrent infection control practices confounding findings. Individual studies, however, have shown mixed effects.[33,37,38]

We acknowledge the limitation that two cross-sectional snapshots, pre- and post-intervention, do not fully account for temporal variation, and thus causality cannot be definitively attributed to the intervention. The lack of effect observed with AMS intervention on participant-level carriage of ESBL-producing Enterobacterales and CPE in this study most likely derives from the modest reduction in antimicrobial consumption seen in the main before-and-after study (Doshi et al, unpublished data). It is also important to note that many of the drivers of MRO carriage are not likely to be affected by AMS interventions in healthcare facilities. This includes easy access to antibiotics in the community without a prescription, as well as agricultural and animal use of antibiotics with impact on environmental reservoirs,[39] which lead to the presence and persistence of MROs in the environment. Furthermore, our study did not analyse MRO colonisation of hospital environmental reservoirs such as sinks, drains and sluices, which may act as persistent point sources within the healthcare environment.

This illustrates the importance of using a One Health approach with AMS implementation across human, animal and environmental health, to determine its impact on MRO prevalence. Additionally, infection prevention and control (IPC) measures are essential complements to AMS, as they play a critical role in reducing the transmission and carriage of multi-resistant organisms within healthcare settings, as demonstrated in the literature.[40] Enhancing resources for MRO surveillance is also essential in reducing AMR.[41,42]

Risk factor analysis unsurprisingly showed an increase in ESBL-producing Enterobacterales carriage in patients who were currently or previously on antibiotics, consistent with findings in the literature.[43] Females, age over 65 years, and smoking were risk factors identified in this study, with literature on this showing mixed results.[44,45] Inpatients in Obstetrics and Gynaecology wards were more likely to have ESBL carriage. This may have been confounded by female preponderance and/or the small participant numbers on this ward. Nevertheless, this finding carries implications for IPC practices and empiric antibiotic guidelines for peripartum women and neonates.

This study had several strengths. It focuses on district hospitals, a setting that is under-represented in the literature from Vietnam and other LMICs.[18] Even though the before-and-after study design introduced bias without controlling for temporal factors, it was useful to analyse the effect of a bundle of AMS interventions on MRO carriage, an area which has had mixed results in the literature.[18]

This study also had several limitations. Our analysis focused on a representative subset of ESBL and carbapenemase genes – $bla_{\text{CTX-M}}$ for ESBLs, and $bla_{\text{NDM-1}}$, bla_{KPC} and $bla_{\text{OXA-48}}$-like genes for carbapenemase genes. However, the prevalence of other circulating AMR genes was not specifically examined, such as extended-spectrum bla_{SHV} and bla_{TEM}, or, $bla_{\text{IMP-4}}$-like, $bla_{\text{NDM-4}}$, $bla_{\text{NDM-5}}$ and $bla_{\text{NDM-7}}$

carbapenemases, leading to potential under-estimation of overall ESBL and CPE carriage prevalence. Additionally, non-beta-lactamase mechanisms causing resistance such as reduced permeability, efflux pumps or porin defects without the presence of carbapenemase genes were not interrogated.[46] Detailed genomic characterisation of MRO isolates would enable a more granular understanding of these factors to inform MRO carriage risk at the district hospital level. Additionally, the small sample size and lower-than-expected prevalence of CPE and MRSA limited the power of analysis of the effect of AMS interventions. The timing of this study, conducted during the COVID-19 pandemic, may have contributed to lower prevalence rates due to the concurrent public health infection control measures in place. The short duration of intervention also was potentially insufficient to show a difference in the prevalence of rectal carriage of Enterobacterales. Ad hoc sampling of inpatients as well as the nature of self-reporting in the participant questionnaire could also have introduced bias to the risk factor analysis.

Several important policy implications can be drawn from this study. It provides a framework for MRO surveillance and the design and implementation of AMS programs in this understudied population. The antibiotic susceptibility profiles of the MROs identified in this study, and in potential longitudinal surveillance programs, has value in informing guidelines on antibiotic use and AMS in district hospital settings. If clinical isolates had timely access to microbiological diagnostic services as described in this study, it would further enable targeted antimicrobial prescribing based on sensitivity patterns.

Future research should explore the effect of AMS program on MRO prevalence using a randomised controlled study design, with matched cohorts to reduce confounding bias. Evaluating the effect of incorporating IPC practices upon carriage of resistant isolates in this setting will also be of value. Additionally, applying AMS principles to address out-of-hospital antibiotic exposure and community-

level drivers of resistance from a One Health perspective could provide critical insights into developing a holistic framework for combating AMR.

In conclusion, this study in four Vietnamese district hospitals found a high prevalence of ESBL-producing Enterobacterales carriage, but relatively low prevalence of CPE and MRSA carriage. This presents an opportune window to strengthen AMS and IPC programs in district hospitals. These findings provide valuable guidance for AMR surveillance priorities in lower-level healthcare settings, not only in Vietnam but also in other LMICs facing similar challenges.

Tables

Table 4.1: Descriptive analysis of participant demographics before and after antimicrobial stewardship intervention

Demographics	At baseline N (%)	After the 6-month AMS intervention N (%)	Total, N (%)
Number of participants			
Total participants	202/202 (100%)	200/200(100%)	402/402(100%)
Nasal swabs collected	202/202(100%)	200/200(100%)	402/402(100%)
Rectal swabs collected	202/202(100%)	200/200(100%)	402/402(100%)
Age			
18-40	24/202 (11.9%)	28/200 (14.0%)	52/402 (12.9%)
41-64	76/202 (37.6%)	75/200 (37.5%)	151/402 (37.6%)
>65	102/202 (50.5%)	97/200 (48.5%)	199/402(49.5%)
Gender			
Male	99/202 (49.0%)	77/200 (38.5%)	176/402 (43.8%)
Female	103/202 (51.0%)	123/200 (61.5%)	226/402 (56.2%)
Clinical department			
Medicine*	159/202 (78.7%)	138/200 (69.0%)	297/402(73.9%)
Infectious Diseases	3/202 (1.5%)	30/200 (15.0%)	33/402 (8.2%)
Surgery**	21/202 (10.4%)	13/200 (6.5%)	34/402 (8.4%)
Obstetrics & Gynaecology	6/202 (3.0%)	10/200 (5.0%)	16/402 (4.0%)
Intensive care &Emergency	13/202 (6.4%)	9/200 (4.5%)	22/402 (5.5%)
Smoking status			
Current smoker	10/202 (5.0%)	25/200 (12.5%)	35/402 (8.7%)
Previous smoker	53/202 (26.2%)	41/200 (20.5%)	94/402 (23.4%)
Never smoked	139/202 (68.8%)	134/200 (67.0%)	273/402 (67.9%)
Current antibiotic use during present admission			
Yes	92/202 (45.5%)	95/200 (47.5%)	187/402 (46.5%)
No	103/202(51.0%)	100/200 (50.0%)	203/402 (50.5%)
Unsure	7/202 (3.5%)	5/200 (2.5%)	12/402 (3.0%)
Self-reported antibiotic use in the previous 12 months			
Yes	79/202 (39.1%)	51/200 (25.5%)	130/402 (32.3%)
No	100/202 (49.5%)	131/200 (65.5%)	231/402 (57.5%)
Unsure	23/202 (11.4%)	18/200 (9.0%)	41/402 (10.2%)
Other potential risk factors			
Hospital admission in the past 12 months	76/202 (37.6%)	53/200 (26.5%)	129/402 (32.1%)
Intensive care this admission	3/202 (1.5%)	2/200 (1.0%)	5/402 (1.2%)
Intensive care last hospital admission	4/202 (2.0%)	1/200 (0.5%)	5/402 (1.2%)
Dialysis	0/202(0)	0/200 (0)	0/402 (0)
Invasive devices#	2/202 (1.0%)	1/200 (0.5%)	3/402 (0.7%)

AMS: Antimicrobial stewardship

*Medicine: Includes General Medical, Oncology, Cardiology and Traditional Medicine

**Surgery: General Surgery and Orthopaedics

#Invasive devices included: nasogastric tubes, indwelling urinary catheters or central venous catheters

Table 4.2: Phenotypic antibiotic sensitivities of all Enterobacterales isolates from rectal swab/stool samples

Organisms	Total isolates, n	Cefotaxime		Cefoxitin		Cefepime		Ciprofloxacin		Gentamicin		Meropenem	
		S	N	S	N	S	N	S	N	S	N	S	N
Escherichia coli	299	0 (0%)	299 (100%)	124 (41.5%)	175 (58.5%)	22 (7.4%)	277 (92.3%)	73 (24.4%)	226 (75.6%)	136 (45.5%)	163 (54.5%)	291 (97.3%)	8 (2.7%)
Klebsiella pneumoniae complex	54	0 (0%)	54 (100%)	22 (40.7%)	32 (59.3%)	10 (18.5%)	44 (81.5%)	9 (16.7%)	45 (83.3%)	24 (44.4%)	30 (55.6%)	52 (96.3%)	2 (3.7%)
Enterobacter cloacae complex	8	0 (0%)	8 (100%)	0 (0)	8 (100%)	3 (37.5%)	5 (62.5%)	1 (12.5%)	7 (87.5%)	4 (50.0%)	4 (50.0%)	8 (100%)	0 (0)
Klebsiella oxytoca	3	0 (0%)	3 (100%)	3 (100%)	0 (0)	2 (66.7%)	1 (33.3%)	1 (33.3%)	2 (66.7%)	2 (66.7%)	1 (33.3%)	3 (100%)	0 (0)
Klebsiella aerogenes	1	0 (0%)	1 (100%)	0 (0)	1 (100%)	0 (0)	1 (100%)	0 (0)	1 (100%)	0 (0)	1 (100%)	1 (100%)	0 (0)
Total, N (%)	365	0 (0%)	365 (100%)	149/365 (40.8%)	216/365 (59.2%)	37/365 (10.1%)	328/365 (89.9%)	84/365 (23.0%)	281/365 (77.0%)	166/365 (45.5%)	199/365 (54.5%)	355/365 (97.3%)	10/365 (2.7%)

AMS: Antimicrobial stewardship

S: Susceptible N: Non-susceptible - either intermediate or resistant to that antibiotic

Table 4.3: Prevalence of bla_{CTX-M}-producing Enterobacterales, carbapenemase-producing Enterobacterales and Methicillin-resistant Staphylococcus aureus at the participant level

Hospitals	Hospital A, n(%) (Hanoi)		Hospital B, n(%) (Hanoi)		Hospital C, n(%) (Ca Mau)		Hospital D, n(%) (Ca Mau)		Total Before	Total After	Total	Difference in proportions statistical analysis (95%CI)
	Before	After	Before	After	Before	After	Before	After				
Total number of patients	100	100	50	50	27	25	25	25	202	200	402	NA
Extended spectrum β-lactamase (ESBL) isolation												
Prevalence of *bla_{CTX-M}–producing Enterobacterales carriage* (number of participants colonised with *bla_{CTX-M}* /total participants	82/100 (82.0%)	80/100 80.0%	39/50 78.0%	38/50 76.0%	18/27 66.7%	21/25 84.0%	18/25 72.0%	10/25 40.0%	157/202 77.7%	149/200 74.5%	306/402 76.1%	-3.2% (95% CI: -11.5, 5.1)
Carbapenemase-producing Enterobacterales(CPE) isolation												
bla_{NDM-1}	1	4*	2	-	-	-	1	0	4	4*	8*	NA
bla_{KPC}	1	1	-	-	-	-	-	-	1	1	2	NA
$bla_{OXA-+48}$		3*	-	-	-	-	-	-	-	3*	3*	NA
Total prevalence of CPE carriage (number of participants colonised with CPE /total participants)	2/100 2.0%	6/100 8.0%	2/50 4.0%	0.0%	0.0%	0.0%	1/25 8.0%	0.0%	5/202 2.5%	6/200 3.0%	11/402 2.7%	0.5% (95% CI: -2.7, 3.7)
Methicillin-resistant Staphylococcus aureus (MRSA) isolation												
Prevalence of MRSA carriage (number of participants colonised with MRSA /total participants)	2/100 = 2%	0	0	1/50= 2%	3/27= 11.1%	0	5/25= 20%	1/25 = 4%	10/202= 5.0%	2/200= 1.0%	12/402 = 3.0%	**-4.0% (95% CI: -7.2, -0.7)**

* Two participants in Hospital A after interventions were carrying two CPE genes each– bla_{NDM-1} and bla_{OXA-48} in the same organism. Hence, although total CPE genes isolated were 8, the prevalence per participant was 6/100. *Bolded text indicates confidence limits do not cross the null.*

Table 4.4: Prevalence of bla_{CTX-M}- and carbapenemase-producing Enterobacterales isolated in rectal carriage per isolate before and after AMS intervention

Isolates	Total isolates (Before Intervention)	Total isolates (After Intervention)	Number of isolates with bla_{CTX-M} gene/total isolates (%)		Difference in proportions in *bla_{CTX-M}* before vs after intervention %, (95%CI)	Number of isolates with carbapenemase genes/ total isolates (%)		Difference in proportions in carbapenemase before vs after intervention %, (95%CI)
			Before Intervention	After Intervention		Before Intervention	After Intervention	
Escherichia coli	152	147	135/151* (89.4%)	122/146* (83.6%)	-5.8% (95%CI: -13.6, 1.9)	3/152 (2.0%)	4/147 (2.7%)**	0.7% (95%CI: -2.7, 4.2)
Klebsiella pneumoniae complex	24	30	17/22* (77.3%)	23/30 (76.7%)	-0.6% (95% CI: -23.8, 22.5)	2/24(8.3%)	2/30(6.6%)**	-1.7% (95% CI: -15.9, 12.5)
Enterobacter cloacae complex	6	2	2/6 (33.3%)	2/2 (100%)	66.7% (95% CI: -28.9, 104.4)	0/6 (0)	0/0 (0)	N/A
Klebsiella oxytoca	3	0	3/3 (100%)	0/0(0)	N/A	0/3 (0)	0/0 (0)	N/A
Klebsiella aerogenes	0	1	0/0 (0)	1/1 (100%)	N/A	0/0 (0)	0/0 (0)	N/A
Total	185	180	157/182* (84.9%)	148/179* (82.7%)	-2.6% (95% CI: -10.2, 5.0)	5/185 (2.7%)	6/180 (3.3%)	0.6% (95%CI: -2.9, 4.1)

** Denominators indicate the number of isolates where Ceftriaxone minimum inhibitory concentration (MIC) and/or extended spectrum β-lactamase(ESBL) screen was used to rule-out ESBL, upon which bla_{CTX-M} was performed*

*** 1 Escherichia coli and 1 Klebsiella pneumoniae complex isolate carried both bla_{NDM-1} and bla_{OXA-48} genes each. Klebsiella oxytoca* and *Klebsiella aerogenes were* not analysed due to small numbers in *bla_{CTX-M}* carriage. No carbapenemase genes detected in *Klebsiella oxytoca, Klebsiella aerogenes* and *Enterobacter cloacae* complex.

Carbapenemase genes tested: *bla_{NDM-1}*, *bla_{KPC}* and *bla_{OXA-48}* genes

Table 4.5: Risk factors for bla_{CTX-M}-producing Enterobacterales carriage by univariable and multivariable analysis

Variable	*bla_{CTX-M}* producing Enterobacterales carriage (n)	Total participants (n)	Proportion (%)	Univariable model		Multivariable model	
				cRR (95% CI)	p	aRR (95% CI)	p
Total	306	402	76.1	--	--	--	--
Time period							
Before intervention	157	202	77.7	Ref.	Ref.	Ref.	Ref.
After intervention	149	200	74.5	0.96 (0.84, 1.10)	0.547	0.97 (0.88, 1.06)	0.475
Age							
18-40 yrs	36	52	69.2	Ref.	Ref.	Ref.	Ref.
41-64	115	151	76.2	1.10 (0.93, 1.31)	0.276	1.09 (0.92, 1.29)	0.312
>65 yrs	155	199	77.9	1.13 (0.99, 1.28)	0.074	**1.19 (1.03, 1.37)**	**0.017**
Gender							
Male	125	176	71.0	Ref.	Ref.	Ref.	Ref.
Female	181	226	80.1	**1.13 (1.03, 1.24)**	**0.010**	**1.26 (1.13, 1.41)**	**<0.001**
Department							
Medicine	228	297	76.8	Ref.	Ref.	Ref.	Ref.
Surgery	23	34	67.7	0.88 (0.69, 1.13)	0.318	0.95 (0.84, 1.08)	0.455
Emergency Department/Intensive Care	17	22	77.3	1.01 (0.88, 1.15)	0.923	0.98 (0.88, 1.08)	0.637
Infectious Diseases	23	33	69.7	0.91 (0.74, 1.11)	0.339	0.90 (0.73, 1.10)	0.294
Obstetrics and Gynaecology	15	16	93.8	**1.22 (1.00, 1.48)**	**0.045**	**1.19 (1.11, 1.28)**	**<0.001**
Smoking status							
Never smoked	206	273	75.5	Ref.	Ref.	Ref.	Ref.
Current or previous smoker	100	129	77.5	1.03 (0.99, 1.07)	0.168	**1.19 (1.14, 1.24)**	**<0.001**
Antibiotic use (current or in the previous 12 months)							
No	114	154	74.0	Ref.	Ref.	Ref.	Ref.
Yes	187	237	78.9	1.07 (0.95, 1.19)	0.274	**1.11 (1.01, 1.22)**	**0.024**
Recent hospital admission in 12 months							
No	201	256	78.5	Ref.	Ref.	Ref.	Ref.

Variable	*bla*$_{CTX-M}$ producing Enterobacterales carriage (n)	Total participants (n)	Proportion (%)	Univariable model		Multivariable model	
				cRR (95% CI)	p	aRR (95% CI)	p
Yes	101	129	78.3	1.00 (0.88, 1.13)	0.965	0.95 (0.86, 1.04)	0.257
Region							
Ca Mau(rural)	67	102	65.7	Ref.	Ref.	Ref.	Ref.
Hanoi (urban)	239	300	79.7	1.21 (0.96, 1.53)	0.106	**1.10 (1.05, 1.15)**	**<0.001**

cRR: Crude Risk Ratio aRR: Adjusted Risk Ratio

Analysis accounts for clustering at a hospital level

We used a complete-case approach for both univariable and multivariable analysis, where "don't know" responses were excluded for analysis.

Bolded text indicates confidence limits do not cross the null

Supplementary material for Chapter 4

Table S4.1: Characteristics of hospitals

Hospitals	Hospital A	Hospital B	Hospital C	Hospital D
Province	Hanoi	Hanoi	Ca Mau	Ca Mau
Urban/Rural	Urban	Urban	Rural	Rural
Distance from closest provincial (tertiary referral) hospital	3.3km	10.3km	2.7km	42.7km
Microbiology lab testing access	Access to basic microbiology tests available e.g. microscopy and bacterial culture, with drug susceptibility testing available if requested, but not utilised commonly in daily practice	Access to send-away microbiology tests to an external laboratory unit.	Only microscopy available	Only microscopy available

Table S4.2: AMS interventions

AMS interventions	Description
Establishing AMS committees and teams	An AMS committee was appointed at each facility, including a senior hospital leader, heads of clinical departments, and head of the pharmacy. Committees' roles were to endorse antimicrobial guidelines, adapt the AMS interventions to their hospital's needs, oversee its implementation, and supervise AMS teams. The AMS committee met every 1-2 months to discuss the progress of implementation of activities in their hospitals. AMS teams were also established at each facility to deliver the AMS interventions. Teams comprised at least one doctor (with specialist Infectious Diseases training where possible) and one pharmacist. Teams were responsible for distributing and promoting guidelines, conducting periodic audits of antimicrobial us, and providing clinical guidance to departments based upon the audit findings. Teams were trained using a standard manual, through both in-person and online sessions, delivered by experienced physicians and pharmacists.
Development and distribution of antimicrobial guidelines	Antimicrobial guidelines for common conditions in district hospitals were developed with input from Infectious Diseases physicians in Australia and Vietnam, based on MoH guidelines[31] and local antibiograms from Vietnamese tertiary healthcare settings. Guidelines covered respiratory, skin and soft tissue, urinary tract infections and surgical prophylaxis with separate recommendations for adults and children. These were translated and printed in Vietnamese; and then distributed in paper form to each participating ward at the study sites.
Healthcare worker education and training	Two workshops were held for all doctors and pharmacists at all facilities, delivered by experienced AMS clinicians. Workshops addressed the rationale for AMS, appropriate prescribing, diagnosis of common conditions, guideline use, antimicrobial dosing, de-escalation, and surgical prophylaxis. Example case scenarios of antimicrobial use were presented for staff to practise.
Audit and feedback	Periodic audits of patient medical records were conducted by AMS teams and study staff during the six-month intervention period using a template from the Australian Hospital National Antimicrobial Prescribing Survey (Hospital NAPS)[47] to assess appropriateness of antimicrobial use against guidelines. A baseline audit was conducted prior to the intervention, followed by a feedback session to the entire hospital staff upon commencement of the intervention. The feedback presented general prescribing trends, cases of suboptimal practice, and recommendations for improving prescribing habits. During the intervention period, this audit and feedback process was repeated in one to three major hospital departments, depending on the hospital's capacity over the six-month intervention period. In these sessions, feedback was performed immediately after each audit, allowing changes in prescribing to be incorporated in real-time. Feedback was delivered in a respectful and non-judgmental manner to foster staff engagement. It also encouraged constructive dialogue about how prescribing practices can be improved. Audit and feedback reports were shared with the relevant departments and presented at AMS committee meetings.

Table S4.3: Polymerase chain reaction primer targets

Primer	Sequence (5'-3')	Size (bp)	Antibiotic resistance encoding
bla$_{CTX-M-F}$	CGATGTGCAGTACCAGTAA	585	ESBL
bla$_{CTX-M-R}$	TTAGTGACCAGAATCAGCGG		
bla$_{OXA48-F}$	TTGGTGGCATCGATTATCGG	744	Carbapenemase
bla$_{OXA48-R}$	GAGCACTTCTTTTGTGATGGC		
bla$_{KPC-F}$	ATGTCACTGTATCGCCGTCT	881	Carbapenemase
bla$_{KPC-R}$	TTACTGCCCGTTGACGCCCA		
bla $_{Kp-NDM1-F}$	ATGCACCCGGTCGCGAAGCTGAG	492	Carbapenemase
bla $_{Kp-NDM1-R}$	TTCGACCCAGCCATTGGCGGCGA		
mecA-F	5'-CCTAGTAAAGCTCCGGAA-3'	314 bp	Methicillin resistance
mecA-R	5'-CTAGTCCATTCGGTCCA-3'		
nuc1	(5'-GCG ATT GAT GGT GAT ACG GTT-3')	270bp	N/A
nuc2	(5'-AGC CAA GCC TTG ACG AAC TAA AGC-3')		

Polymerase chain reaction (PCR) cycling conditions are as follows:

bla$_{CTX-M}$ *gene: denaturation step at 94℃ for 5 min; 30 cycles of 94℃ for 36 sec, 60℃ for 36 sec, and 72℃ for 1 min; and final extension at 72℃ for 5 min.*

bla$_{KPC}$ *and bla*$_{OXA-48}$ *genes: denaturation step at 94℃ for 5 min; 30 cycles of 94℃ for 1 min, 60℃ for 1 min, and 72℃ for 1 min; and final extension at 72℃ for 7 min.*

bla$_{NDM-1}$ *gene: denaturation step at 94℃ for 4 min; 30 cycles of 94℃ for 36 sec, 60℃ for 36 sec, and 72℃ for 50 sec; and final extension at 72℃ for 5 min.*

mecA gene: denaturation step at 95℃ for 5 min; 30 cycles of 95℃ for 2 min, 58℃ for 30 sec, and 72℃ for 30 sec; and final extension at 72℃ for 7 min.

Nuc gene: denaturation step at 94°C for 5 min; 30 cycles of 94 °C for 1 min, 50 °C for 1 min, and 72 °C for 2 min, and a final extension step at 72 °C for 10 min.

Applied Biosystems GeneAmp PCR System 9700 was used with Gotaq Green Master Mix 2X – Promega reagent.

Table S4.4: Phenotypic and genotypic (bla_{CTX-M}) extended-spectrum beta-lactamase producing Enterobacterales isolation

Organism	Number of isolates	Number of isolates undergoing *bla_{CTX-M}* gene testing	Phenotypic ESBL production	bla_{CTX-M} positive	bla_{CTX-M} positivity rate
Escherichia coli	299	297	230 /297 (77.4%)	257	257/297 (86.5%)
Klebsiella pneumoniae complex	54	52	37/52 (71.1%)	40	40/52 (76.9%)
Enterobacter cloacae complex	8	8	4/8 (50.0%)	4	4/8 (50%)
Klebsiella oxytoca	3	3	2/3 (66.7%)	3	3/3 (100%)
Klebsiella aerogenes	1	1	1/1 (100%)	1	1/1 (100%)

Table S4.5: Phenotypic and genotypic Carbapenemase-producing Enterobacterales (CPE) isolation

Organism	Number of isolates	Meropenem MIC>0.25mg/L, qualifying for CPE gene testing	Carbapenemase gene positive	CPE positivity rate
Escherichia coli	299	21	6	6/299 (2.0%)
Klebsiella pneumoniae complex	54	7	1	1/54 (1.9%)
Enterobacter cloacae complex	8	1	0	0 (0)
Klebsiella oxytoca	3	0	0	0(0)
Klebsiella aerogenes	1	0	0	0 (0)

Table S4.6: Antibiotic sensitivities and genotypic testing results of MRSA isolates

Organism	Oxacillin		Ciprofloxacin		Clindamycin		Sulfamethoxazole/Trimethoprim		Vancomycin		Presence of *mecA* gene
MRSA	S	N	S	N	S	N	S	N	S	N	
	0 (0)	12 (100%)	7 (58.3%)	5 (41.7%)	1 (8.3%)	11 (91.7%)	11 (91.7%)	1 (8.3%)	12 (100%)	0 (0)	12 (100%)

S: Susceptible N: Non-susceptible - either intermediate or resistant to that antibiotic

Table S4.7: Difference in proportions of Enterobacterales non-susceptible to antibiotics before and after intervention

Organisms non-susceptible	Cefotaxime		Cefoxitin		Cefepime		Ciprofloxacin		Gentamicin		Meropenem	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Escherichia coli	152/152 (100%)	147/147 (100%)	90/152 (59.2%)	85/147 (57.8%)	138/152 (90.8%)	139/147 (94.6%)	110/152 (72.4%)	116/147 (78.9%)	87/152 (57.2%)	76/147 (51.7%)	4/152 (2.6%)	4/147 (2.7%)
Difference in non-susceptibility in *Escherichia coli* before and after intervention (95% Confidence interval)	N/A		-1.4% (-12.6, 9.8)		3.8% (-2.1, 9.7)		6.5% (-3.2, 16.2)		-5.5% (-16.8, 5.8)		0.1 (-3.6, 3.7)	
Klebsiella pneumoniae complex	24/24 (100%)	30/30 (100%)	11/24 (45.8%)	21/30 (70.0%)	18/24 (75.0%)	26/30 (86.7%)	17/24 (70.8%)	28/30 (93.3%)	18/24 (75.0%)	12/30 (40.0%)	1/23 (4.3%)	1/30 (3.3%)
Difference in non-susceptibility in *Klebsiella pneumoniae* complex before and after intervention (95% Confidence interval)	N/A		24.2% (-1.6, 50.0)		11.7% (-9.5, 32.8)		22.5% (2.2, 42.8)		**-35.0% (-59.6, -10.4)**		-1.0% (-11.5, 9.5)	
Enterobacter cloacae complex	6/6 (100%)	2/2 (100%)	6/6 (100%)	2/2 (100%)	3/6 (50.0%)	2/2 (100%)	5/6 (83.3%)	1/2 (50.0%)	2/6 (33.3%)	2/2 (100%)	0/6 (0%)	0/2 (0%)
Klebsiella oxytoca	3/3 (100%)	0/0 (0%)	0/3 (0%)	0/0 (0%)	3/3 (100%)	0/0 (0%)	2/3 (66.7%)	0/0 (0%)	1/3 (33.3%)	0/0 (0%)	0/3 (0%)	0/0 (0%)
Klebsiella aerogenes	0/0 (0%)	1/1 (100%)	0/0 (0%)	1/1 (100%)	0/0 (0%)	1/1 (100%)	0/0 (0%)	1/1 (100%)	0/0 (0%)	1/1 (100%)	0/0 (0%)	0/1 (100%)
Total	185/185 (100%)	180/180 (100%)	107/185 (57.8%)	109/180 (60.6%)	162/185 (87.6%)	168/180 (93.3%)	134/185 (72.4%)	145/180 (80.6%)	108/185 (58.4%)	91/180 (50.6%)	5/185 (2.7%)	5/180 (2.8%)
Difference in non-susceptibility in all organisms before and after intervention (95% Confidence interval)	N/A		2.8% (-7.3, 12.9)		5.7% (-0.3, 11.7)		8.2% (-0.5, 16.9)		-7.8% (-18.0, 2.4)		0.1% (-3.3, 3.5)	

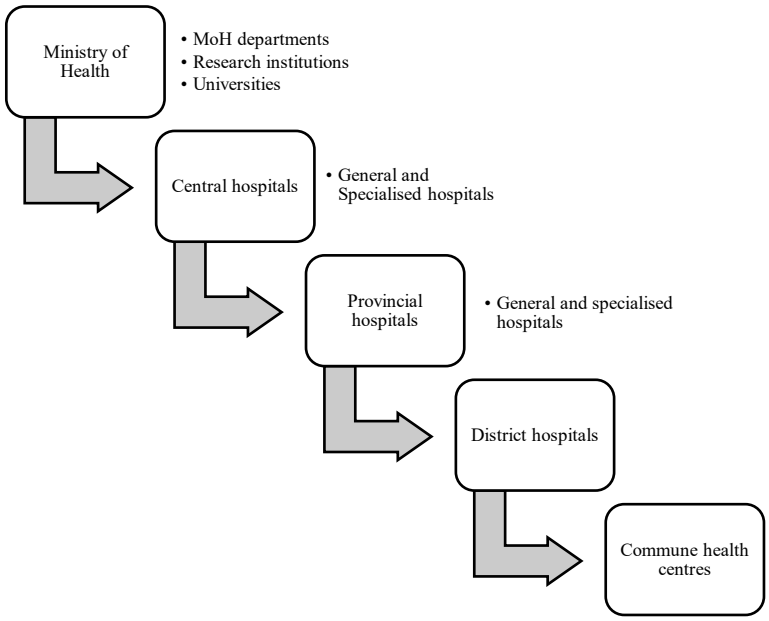
Table S4.8: Descriptive analysis of risk factors for prevalence of carbapenemase-producing Enterobacterales (CPE) and methicillin-resistant Staphylococcus aureus (MRSA) carriage

Risk Factors	**Presence of CPE - number of patients with positive isolates, all patients in the category, (%)**	**Presence of MRSA - number of patients with positive isolates, all patients in the category, (%)**
Number of patients with isolates	**11/402 (2.7%)**	**12/402 (3.0%)**
Age		
18-40	0/52 (0)	0/52 (0)
41-64	4/151 (2.6%)	4/151 (2.6%)
>65	7/199 (3.5%)	8/199 (4.0%)
Gender		
Male	4/176(2.3%)	2/176 (1.1%)
Female	7/226(3.1%)	10/226 (4.4%)
Department		
Medicine	9/297 (3.0%)	9/297 (3.0%)
Surgery	2/34 (5.9%)	0/34 (0)
Emergency /Intensive care unit	0/22 (0)	2/22 (9.1%)
Infectious Diseases	0/33 (0)	1/33 (3.0%)
Obstetrics and Gynaecology	0/16 (0)	0/16 (0)
Smoking status		
Current/previous smoker	2/129 (1.6%)	2/129 (1.6%)
Never smoked	9/273 (3.3%)	10/273 (3.7%)
Region		
Hanoi (urban)	10/300 (3.3%)	3/300 (1.0%)
Ca Mau (rural)	1/102 (1.0%)	9/102 (8.8%)
Antibiotic/hospital risk factors		
Current or past 12months antibiotics	7/187(3.7%)	5/187 (2.7%)
Recent hospital admission in 12 months	8/101 (7.9%)	2/101 (2.0%)

Medicine: General Medicine, Cardiovascular, Oncology and Traditional Medicine wards

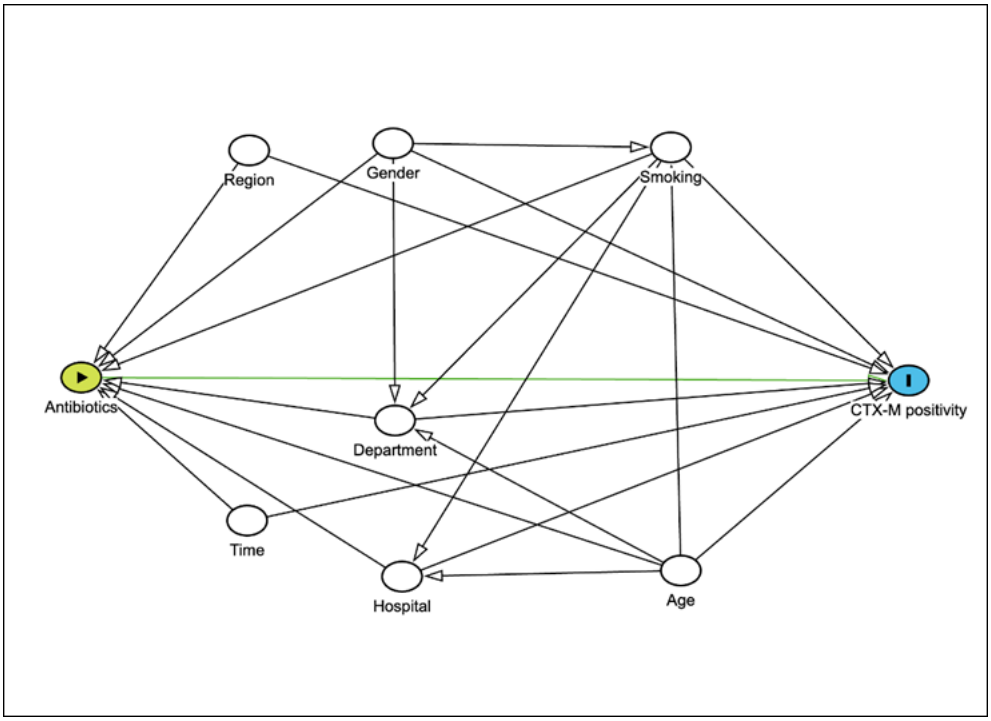
Surgery: General Surgery and Orthopaedics wards

Figure S4.1: Healthcare structure in Vietnam



(From Ha et al 2015)[48]

Figure S4.2: Direct Acyclic Graph (DAG) of risk factors for bla_{CTX-M}-producing Enterobacterales carriage[23]



Time: Time phase of the study, classified as before or after Antimicrobial stewardship (AMS) intervention; Age: age group of the patient (18-40 years, 41-64 years, 65 years and above); Gender: biological sex of the patient (Male/Female); Department: hospital department where the patient was admitted (e.g., Medicine, Surgery, ED/ICU, Infectious Diseases, Obstetrics and Gynaecology); Smoking: smoking status, categorized as never smoked vs. current or previous smoker; Antibiotics: current antibiotic use or previous antibiotic use in the last 12 months; Hospital: recent hospital admission in the past 12 months; Region: geographic location of the patient (e.g., Ca Mau, Hanoi)

References for Chapter 4

1. World Health Organisation. Antimicrobial resistance fact sheet. 2023. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance (accessed 15/7/2024).

2. World Health Organisation. 2021 Antibacterial agents in clinical and preclinical development: an overview and analysis, 2022. www.who.int/publications/i/item/9789240047655 (accessed 15/07/2024).

3. Bezabih YM, Sabiiti W, Alamneh E, et al. The global prevalence and trend of human intestinal carriage of ESBL-producing Escherichia coli in the community. *Journal of Antimicrobial Chemotherapy* 2021; **76**(1): 22-9.

4. Li Y, Ma L, Ding X, Zhang R. Fecal carriage and genetic characteristics of carbapenem-resistant enterobacterales among adults from four provinces of China. *Frontiers in Epidemiology* 2024; **3**.

5. Chowdhury F, Mah-E-Muneer S, Bollinger S, et al. Prevalence of Colonization With Antibiotic-Resistant Organisms in Hospitalized and Community Individuals in Bangladesh, a Phenotypic Analysis: Findings From the Antibiotic Resistance in Communities and Hospitals (ARCH) Study. *Clinical Infectious Diseases* 2023; **77**(Supplement_1): S118-S24.

6. Zaidah AR, Mohammad NI, Suraiya S, Harun A. High burden of Carbapenem-resistant Enterobacteriaceae (CRE) fecal carriage at a teaching hospital: cost-effectiveness of screening in low-resource setting. *Antimicrobial Resistance & Infection Control* 2017; **6**(1): 42.

7. Massart N, Camus C, Benezit F, Moriconi M, Fillatre P, Le Tulzo Y. Incidence and risk factors for acquired colonization and infection due to extended-spectrum beta-lactamase-producing Gram-negative bacilli: a retrospective analysis in three ICUs with low multidrug resistance rate. *Eur J Clin Microbiol Infect Dis* 2020; **39**(5): 889-95.

8. Burnham JP, Olsen MA, Kollef MH. Re-estimating annual deaths due to multidrug-resistant organism infections. *Infection control and hospital epidemiology* 2019; **40**(1): 112-3.

9. World Health Organization. Antimicrobial resistance - Western Pacific -Viet Nam. 2024. https://www.who.int/vietnam/health-topics/antimicrobial-resistance (accessed 16/08/2022).

10. Dat VQ, Vu HN, Nguyen The H, et al. Bacterial bloodstream infections in a tertiary infectious diseases hospital in Northern Vietnam: aetiology, drug resistance, and treatment outcome. *BMC infectious diseases* 2017; **17**(1): 493.

11. Ngoc-Nga P-T, Nhut-Thang N, Hong-Ha N, Trung-Son L, To HTN, Bich-Van T-T. Drug Susceptibility and Prevalence of ESBL in Escherichia coli Isolates from Infection Patients in Can Tho General Hospital.

12. Tran DM, Larsson M, Olson L, et al. High prevalence of colonisation with carbapenem-resistant Enterobacteriaceae among patients admitted to Vietnamese hospitals: Risk factors and burden of disease. *J Infect* 2019; **79**(2): 115-22.

13. Yen NTP, Nhung NT, Phu DH, et al. Prevalence of carbapenem resistance and its potential association with antimicrobial use in humans and animals in rural communities in Vietnam. *JAC-antimicrobial resistance* 2022; **4**(2): dlac038.

14. Thai SN, Vu HTT, Vu LTK, et al. First Report on Multidrug-Resistant Methicillin-Resistant Staphylococcus aureus Isolates in Children Admitted to Tertiary Hospitals in Vietnam. *J Microbiol Biotechnol* 2019; **29**(9): 1460-9.

15. Tran H, Nguyen B, Tran H, Tran H. A cross-sectional study of the antibiotic resistant prevalence of ESBL-producing Enterobacteriaceae in Vietnam. *Journal of Health Sciences* 2022.

16. World Health Organization. Global Action Plan on Antimicrobial Resistance. 2015. https://www.who.int/publications/i/item/9789241509763 (accessed 15/07/2024).

17. World Health Organisation. Antimicrobial Stewardship programmes in health-care facilties in Low- and Middle-income countries - a WHO practical toolkit. 2019. https://www.who.int/publications/i/item/9789241515481 (accessed 10/01/2023).

18. Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017; **2**(2): Cd003543.

19. Son NT. Decision No. 5631/QD-BYT 2020 Guidance on management of the antibiotic use in hospitals. 2020. https://english.luatvietnam.vn/decision-no-5631-qd-byt-of-the-ministry-of-health-on-promulgating-the-guidance-on-management-of-the-antibiotic-use-in-hospit-196563-doc1.html (accessed 15/03/2022).

20. Australian Commission on Safety and Quality in Health Care. Antimicrobial Stewardship in Australian Health Care. Sydney, Australia: ACSQHC, 202322/11/2024).

21. Patel R. MALDI-TOF MS for the Diagnosis of Infectious Diseases. *Clinical Chemistry* 2015; **61**(1): 100-11.

22. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing: CLSI supplement M100. . CLSI M100. 34 ed; 2024.

23. Textor J, van der Zander B, Gilthorpe M, Liśkiewicz M, Ellison G. "Robust causal inference using directed acyclic graphs: the R package 'dagitty'.". *International Journal of Epidemiology* 2016; **45**: 1887-94.

24. Vu TVD, Choisy M, Do TTN, et al. Antimicrobial susceptibility testing results from 13 hospitals in Viet Nam: VINARES 2016–2017. *Antimicrobial Resistance & Infection Control* 2021; **10**(1): 78.

25. Nguyen VT, Jamrozy D, Matamoros S, et al. Limited contribution of non-intensive chicken farming to ESBL-producing Escherichia coli colonization in humans in Vietnam: an epidemiological and genomic analysis. *Journal of Antimicrobial Chemotherapy* 2019; **74**(3): 561-70.

26. Singh SR, Teo AKJ, Prem K, et al. Epidemiology of Extended-Spectrum Beta-Lactamase and Carbapenemase-Producing Enterobacterales in the Greater Mekong Subregion: A Systematic-Review and Meta-Analysis of Risk Factors Associated With Extended-Spectrum Beta-Lactamase and Carbapenemase Isolation. *Frontiers in Microbiology* 2021; **12**.

27. Van Nguyen K, Zhang T, Thi Vu BN, et al. Staphylococcus aureus nasopharyngeal carriage in rural and urban northern Vietnam. *Transactions of The Royal Society of Tropical Medicine and Hygiene* 2014; **108**(12): 783-90.

28. Smith RM, Lautenbach E, Omulo S, et al. Human Colonization With Multidrug-Resistant Organisms: Getting to the Bottom of Antibiotic Resistance. *Open forum infectious diseases* 2021; **8**(11): ofab531.

29. Phu DH, Wongtawan T, Truong DB, Van Cuong N, Carrique-Mas J, Thomrongsuwannakij T. A systematic review and meta-analysis of integrated studies on antimicrobial resistance in Vietnam, with a focus on Enterobacteriaceae, from a One Health perspective. *One Health* 2022; **15**: 100465.

30. Castanheira M, Simner PJ, Bradford PA. Extended-spectrum β-lactamases: an update on their characteristics, epidemiology and detection. *JAC-antimicrobial resistance* 2021; **3**(3).

31. Ministry of Health Vietnam. Instructions for Use of Antibiotics - Decision No. 708/QD-BYT. Hanoi, Vietnam, 2015. https://kcb.vn/thu-vien-tai-lieu/tai-lieu-huong-dan-su-dung-khang-sinh.html (accessed 31/03/2022).

32. Jacoby GA. Mechanisms of Resistance to Quinolones. *Clinical Infectious Diseases* 2005; **41**: S120-S6.

33. Wang H, Wang H, Yu X, et al. Impact of antimicrobial stewardship managed by clinical pharmacists on antibiotic use and drug resistance in a Chinese hospital, 2010-2016: a retrospective observational study. *BMJ open* 2019; **9**(8): e026072.

34. Kalaba M, Kosutic J, Godman B, et al. Experience with developing antibiotic stewardship programs in Serbia: potential model for other Balkan countries? *Journal of comparative effectiveness research* 2018; **7**(3): 247-58.

35. Bertollo LG, Lutkemeyer DS, Levin AS. Are antimicrobial stewardship programs effective strategies for preventing antibiotic resistance? A systematic review. *American journal of infection control* 2018; **46**(7): 824-36.

36. Abo YN, Freyne B, Kululanga D, Bryant PA. The Impact of Antimicrobial Stewardship in Children in Low- and Middle-income Countries: A Systematic Review. *Pediatr Infect Dis J* 2022; **41**(3s): S10-s7.

37. O'Riordan F, Shiely F, Byrne S, O'Brien D, Ronayne A, Fleming A. Antimicrobial use and antimicrobial resistance in Enterobacterales and Enterococcus faecium: a time series analysis. *Journal of Hospital Infection* 2022; **120**: 57-64.

38. Xu YL, Hu LM, Xie ZZ, Dong YW, Dong L. [Impact of antimicrobial stewardship program on antimicrobial usage and detection rate of multidrug-resistant gram-negative bacteria]. *Zhonghua Er Ke Za Zhi* 2019; **57**(7): 553-8.

39. Styczynski A, Herzig C, Luvsansharav U-O, McDonald LC, Smith RM. Using Colonization to Understand the Burden of Antimicrobial Resistance Across Low- and Middle-Income Countries. *Clinical Infectious Diseases* 2023; **77**(Supplement_1): S70-S4.

40. Moehring RW, Anderson DJ. Antimicrobial Stewardship as Part of the Infection Prevention Effort. *Current Infectious Disease Reports* 2012; **14**(6): 592-600.

41. Tacconelli E, Sifakis F, Harbarth S, et al. Surveillance for control of antimicrobial resistance. *The Lancet Infectious Diseases* 2018; **18**(3): e99-e106.

42. Food and Agriculture Organization of the United Nations. Antimicrobial resistance. 2024. https://www.fao.org/antimicrobial-resistance/en/ (accessed 10/11/2024).

43. Karanika S, Karantanos T, Arvanitis M, Grigoras C, Mylonakis E. Fecal Colonization With Extended-spectrum Beta-lactamase–Producing Enterobacteriaceae and Risk Factors Among Healthy Individuals: A Systematic Review and Metaanalysis. *Clinical Infectious Diseases* 2016; **63**(3): 310-8.

44. Raffelsberger N, Buczek DJ, Svendsen K, et al. Community carriage of ESBL-producing Escherichia coli and Klebsiella pneumoniae: a cross-sectional study of risk factors and comparative genomics of carriage and clinical isolates. *mSphere* 2023; **8**(4): e0002523.

45. Xiao T, Wu Z, Shi Q, et al. A retrospective analysis of risk factors and outcomes in patients with extended-spectrum beta-lactamase-producing Escherichia coli bloodstream infections. *Journal of global antimicrobial resistance* 2019; **17**: 147-56.

46. Pierce VM, Simner PJ, Lonsway DR, et al. Modified Carbapenem Inactivation Method for Phenotypic Detection of Carbapenemase Production among Enterobacteriaceae. *Journal of Clinical Microbiology* 2017; **55**(8): 2321-33.

47. National Centre for Antimicrobial Stewardship. The National Antimicrobial Prescribing Survey. 2024. https://www.ncas-australia.org/National_Antimicrobial_Prescribing_Survey (accessed 08/04/2022).

48. Ha B, Mirzoev T, Morgan R. Patient Complaints in healthcare services in Vietnam's Health system. *SAGE Open Medicine* 2015; **3**.

Chapter 5: The effect of Antimicrobial Stewardship interventions upon antimicrobial consumption and appropriateness in Vietnamese district hospitals: a cluster randomised trial

This chapter contains an article that has been accepted for publication.

Authors:

Jaslyn Doshi[1], Yen Pham Ngoc[2], Thu Thuy Ma[2], Linh Thuy Duong[2], Van Thi Thuy Pham[3], Van Giap Vu[4]Rodney James[5,6], Qingbin Li[1], Quy Trinh Van[2], Tu Son Nguyen[3], Thi Thu Trang Tran[3], Pham Minh Thu Vo[7], Van An Ngo[4], Huu Phuc Phan[8], Ngoc Canh Hoang[8], Justin Beardsley[9,10], Thu Anh Nguyen[1,2], Greg J. Fox[1,11]

Author contributions

GJF and TAN contributed to funding acquisition and conceptualisation of the trial. GJF, TAN, and YPN contributed to the trial design and provided scientific input. GJF, TAN, YPN, JD and TTM led the trial implementation. LTD, VTTP, VGV, RJ, TSN, TTTT, PMTV, VAN, HPP and NCH implemented the study, providing scientific input. JD, JB, YPN and GJF contributed to the data checking and analysis. QL and JD conducted the data and statistical analysis. JD drafted the manuscript. All authors contributed to manuscript review and editing.

Abstract

Background: Inappropriate antimicrobial use is a key driver of antimicrobial resistance. Antimicrobial stewardship (AMS) promotes the judicious use of antimicrobials to address this problem. This study evaluated the effect of an AMS program on antimicrobial prescribing practices in district hospitals in Vietnam.

Methods: A cluster randomised controlled trial was conducted in 16 district hospitals in northern and southern Vietnam over four months. Hospitals were randomly assigned to intervention or control groups. Interventions included establishing AMS committees and teams, distributing antimicrobial guidelines, training healthcare workers, providing patient educational material, and conducting periodic audits with feedback on antimicrobial prescribing. Co-primary outcomes were the "difference in differences" in (i) total antimicrobial consumption and (ii) inappropriate prescribing according to standardised guidelines, before and after the intervention, between intervention and control groups. Secondary outcomes included antimicrobial costs and all-cause mortality. After the intervention period, control sites also received the AMS program.

Findings: The AMS intervention was implemented in eight hospitals between April 2022 and July 2022, while eight other hospitals received standard care. At baseline and post-intervention, 877 and 1220 antimicrobial prescriptions were reviewed in intervention hospitals, and 1277 and 1454 prescriptions in control hospitals respectively. Inappropriate antimicrobial prescribing exceeded 60% in each hospital at baseline. After the intervention period, inappropriate prescribing in the intervention group reduced by 6·3% (95%CI: -10·9%, -1·7%) relative to the control group. Total antimicrobial consumption did not vary between groups, but antimicrobial costs reduced in the intervention group. No difference in all-cause mortality was observed.

Interpretation: AMS interventions effectively reduced inappropriate antimicrobial prescribing in district hospitals in Vietnam, underscoring the importance of AMS in resource-limited settings.

Funding: Centre for Health Security, Australian Department of Foreign Affairs and Trade.

Trial registry: Australia and New Zealand Clinical Trials Registry (ANZCTR) number 12622000715774

Background

Antimicrobial resistance (AMR) is a major public health challenge, rendering life-saving antimicrobials increasingly ineffective.[1] AMR is primarily driven by the overuse and misuse of antimicrobials in healthcare, agriculture, aquaculture, and industry.[1] Low- and middle-income countries (LMICs) are disproportionately impacted due to a high incidence of infectious diseases, inadequate water sanitation, and underdeveloped healthcare infrastructure.[2]

Vietnam, a middle-income country in the World Health Organisation (WHO) Western Pacific region has one of Asia's highest rates of AMR.[3] Surveillance studies report rising resistance among common pathogens,[3-6] with 14,300 deaths attributable to AMR in 2019, making it the country's third leading cause of death.[7] Between 2000 and 2015, Vietnam ranked eleventh globally in total antimicrobial consumption.[8] More recently, Vietnam was reported to have the highest antimicrobial consumption globally among 67 countries at 54.0 defined daily doses (DDD) per 1,000 inhabitants per day in 2023, as well as the highest relative increase in consumption of 111.2% from 2016 to 2023.[9] Overuse is driven by easy access to antibiotics without prescriptions in the community, inappropriate antimicrobial prescribing in hospital settings, unnecessary hospitalisations and patient demands.[3,10] Limited access to microbiology services to guide therapy also contribute to inappropriate prescribing.[3]

In response, Vietnam's Ministry of Health (MoH) instituted a National Action Plan against AMR extending to 2030.[11,12] Central to this plan was the implementation of antimicrobial stewardship (AMS) in healthcare settings.[13] AMS promotes judicious use antimicrobials[14] through education for prescribers, audit and feedback of antimicrobial appropriateness, development of local guidelines for antimicrobial use, and regular surveillance of antimicrobial consumption and AMR.[14] Proven benefits

include reduced antimicrobial use, improved appropriateness in prescribing, shorter hospital stays, lower mortality, and cost-effectiveness.[15-17] Several international and national resources are available to support the implementation of AMS programs in hospitals, including guidance from WHO and health departments in several countries.[14,18,19]

Evidence from high-income and some LMIC settings have shown that AMS can reduce antimicrobial use and healthcare costs, improve prescribing appropriateness, and lower mortality.[15-17,20] However, most AMS research in LMICs and the Asia-Pacific region are observational or using before-and-after designs prone to bias. They are also primarily focused on tertiary hospitals,[21-23] leaving a gap in evaluating AMS in community-level facilities, which provide most hospital-level care in LMICs.

The Vietnamese healthcare system is divided into four levels: national, provincial, district and commune(Supplementary Figure S5.1). In 2020, the Vietnamese government operated 952 district hospitals and 11,100 commune health facilities, which serve as the primary point of contact for medical care in rural and urban areas. District hospitals offer basic medical, surgical and intensive care, but often lack subspecialty services and access to microbiological laboratories capable of drug susceptibility testing. Despite high antimicrobial use,[10,24] these facilities face resource constraints in implementing the national AMS action plan.

This study evaluated the effectiveness of an AMS program in district-level hospitals across rural and urban Vietnam.

Methods

Study design and setting

We conducted a parallel-group, partially blinded, cluster randomised controlled trial (RCT), with a post-intervention cross-over design, in 16 district hospitals in Vietnam. Hospitals were randomly selected from two provinces in northern and southern Vietnam. The cluster and unit of randomisation was the district hospital. Intervention group hospitals received a package of AMS interventions, while control group hospitals received the standard of care. A clustered design enabled a single approach to be delivered in each hospital and minimised a contamination effect between groups.

Randomisation and blinding

District hospitals were selected by simple random sampling within two participating provinces, among hospitals located less than two hours' drive from a provincial centre (Supplementary Table S5.1). Restricted randomisation, stratified by province, was employed by excluding combinations that led to substantial imbalances in inpatient bed numbers between groups. Randomisation and generation of allocation sequence was performed by a person blinded to the identity of the districts. Owing to the nature of the intervention, healthcare workers at facilities could not be blinded to group allocation. To minimise contamination between groups, research staff limited interactions with control sites until after outcome data had been collected (Supplementary Figure S5.2). Prior to the intervention period, a survey of pre-existing AMS activities was performed (Supplementary Table S5.1).

Intervention group activities

The package of AMS interventions was developed by the research team, following WHO guidance for implementation of AMS in LMICs and national AMS guidelines in Australia and Vietnam.[13,14,18] Hospital staff were informed about the study through dissemination of booklets outlining planned activities. The intervention was designed to influence prescribing behaviour while also strengthening system-level capacity. Its adoption and effectiveness were expected to be shaped by contextual factors including staffing resources, availability of diagnostics, institutional culture, and existing prescribing hierarchies.

AMS interventions comprised four components:

(i) AMS committees and teams

An AMS committee was established to oversee the governance of the AMS program in each hospital, comprising of a senior hospital leader, heads of clinical departments and the head of the pharmacy. Committees' roles were to endorse antimicrobial guidelines, determine the specific timing of AMS interventions, oversee their implementation, and supervise the AMS teams. Meetings to review progress of implementation in the hospitals occurred every one to two months during the study (Table 5.1).

AMS teams were established at each hospital to deliver the interventions. Teams comprised at least one doctor (with Infectious Diseases training where available) and one pharmacist. Teams were responsible for distributing and promoting guidelines and conducting periodic audits of antimicrobial use followed by feedback sessions (described below). Teams were trained using a standard manual by experienced physicians and pharmacists both in-person and online. A second training session was

held in Hanoi for all intervention group AMS teams to encourage its continued application beyond the intervention period (Table 5.1).

(ii) Development and distribution of antimicrobial treatment guidelines

Antimicrobial guidelines for common presentations in district hospitals were developed with input from Infectious Diseases physicians in Vietnam and Australia, based on Vietnam MoH guidelines and local antibiograms from Vietnamese tertiary hospitals. Guidelines covered respiratory, skin and soft tissue, urinary tract infections and surgical prophylaxis for adults and children. These were translated and printed in Vietnamese; and distributed in paper form to all participating wards. For conditions not listed, doctors were advised to follow the MoH national treatment guidelines.

(iii) Education and training regarding appropriate antimicrobial use

Two workshops were held for all doctors and pharmacists at all intervention sites, delivered by experienced AMS clinicians and pharmacists (Table 5.1). Workshops covered AMS rationale, diagnosis of common conditions, guideline use, appropriate prescribing, antimicrobial dosing, de-escalation, surgical prophylaxis, and included practice case scenarios.

Printed educational booklets were provided to patients in inpatient and outpatient departments. These materials explained AMR and key AMS concepts in simplified Vietnamese language. Health promotional posters focusing upon the benefits of AMS in promoting appropriate antimicrobial use were also displayed. Surveys on knowledge, attitudes and practices of healthcare workers and patients on AMS and antimicrobial use were collected pre- and post-intervention.

(iv) Audit and feedback

Periodic audits of inpatient medical records were performed during the four-month intervention period (Table 5.1) using the Australian Hospital National Antimicrobial Prescribing Survey (NAPS)[25] template. Reviewers, consisting of each hospital's AMS teams and clinicians and pharmacists from the study team, assessed the appropriateness of antimicrobial use against standard guidelines (described above) or Ministry of Health (MoH) guidelines. A baseline audit preceded the intervention, followed by a feedback session presenting prescribing trends, suboptimal practices and improvement recommendations to the entire hospital staff upon commencement of the intervention. This audit and feedback process was repeated in one to three major hospital departments, depending on the hospital's capacity over the four-month intervention period (Table 5.1).

Audits were performed on all inpatients in that ward on the day, followed by immediate deidentified feedback to ward doctors as a group, allowing real-time changes to be incorporated. Audit and feedback reports were shared with the respective departments and AMS committees. Departments demonstrating the greatest commitment to improving prescribing practices were recognised as "AMS champions" at the conclusion of the intervention.

Control group activities

The hospitals in the control group received the usual standard of care, which did not include any stewardship interventions (Supplementary Figure S5.2).

At the end of the intervention period, and after study outcomes were collected, the control sites were also offered the package of AMS interventions (Supplementary Figure S5.2). Both intervention and control sites were encouraged to continue the package of AMS interventions beyond the study.

Outcomes

The co-primary outcomes were: (i) the "difference in differences (DiD)" in total antimicrobial consumption (the difference before and after in the intervention group, versus before and after in the control group); and (ii) the "DiD" in the proportion of inappropriate antimicrobial prescription between groups.

Antimicrobial consumption

Antimicrobial consumption was measured in Defined Daily Dose (DDD) per 100 occupied bed-days, a standardised approach endorsed by WHO. [26] DDD was derived from the total antimicrobial usage across an entire hospital over one month, where doses were based upon the average maintenance dose used for the drug's main indication in an adult.[26] Quantification of antimicrobials was based upon inventory records of antimicrobials that were dispensed by Pharmacy departments to the wards each month, as data about individual antimicrobial administration were not routinely collected. The number of bed-days each month was defined as the number of days a patient occupied a bed overnight in hospital, collected from hospital information systems. This approach included all inpatients in the denominator, irrespective of whether they received antimicrobials, to provide a standardised measure of hospital-wide antimicrobial consumption. Dosing for children, which is often reported as Days of Therapy (DOT), could not be derived from facility records. For this reason, the adult DDD metric was applied to all comparison calculations.[27]

Antimicrobial appropriateness

The appropriateness of antimicrobial prescriptions was assessed using the Australian Hospital NAPS audit tool before and after the intervention. Assessments were performed by study staff independent of the hospital staff, in both intervention and control groups.[25]

Medical records of all inpatients were collected and reviewed at 8am on the designated day. A form was completed by trained research staff, capturing information on name and class of antimicrobial, dose, route, documented clinical indication, start and end date, as well as patients' age, weight, serum creatinine, allergies, and surgical procedures, if any. The clinical indication for each prescribed antimicrobial was determined based on documented symptoms and vital signs, examination and clinical investigations in the medical record. If the documented clinical information did not support the recorded diagnosis, the study team physicians used clinical judgment to establish the diagnosis. Each prescription was assessed against either the study or MoH guidelines. For conditions where guidelines were unavailable, physicians again used clinical judgement. The appropriateness of each prescription was categorised based on pre-defined definitions, (1) Optimal (2) Adequate (3) Suboptimal (4) Inadequate (5) Not assessable (Supplementary Figure S5.3). Discrepancies were resolved by discussion amongst the AMS team and study staff or referred to an independent assessor blinded to the hospital if no consensus was reached. The audit process was repeated in all inpatients on another designated day at the end of the four-month intervention period across all sites (Table 5.1). All assessments were recorded on paper forms, transcribed into an online database, and independently reviewed by a blinded assessor, who verified the data and scored appropriateness according to guidelines to ensure consistency across sites.

Secondary outcomes

Secondary outcomes included (i) all-cause mortality and (ii) the total cost of antimicrobial drugs dispensed during the month before and after the intervention, between intervention and control groups. Mortality was defined as the number of deaths reported including both in-hospital deaths and critically ill patients discharged home with a documented disposition of “expected death”. This was measured over a one-month period pre-intervention and post-intervention in both intervention and control sites. The mortality rate per inpatient was then calculated for the month before the intervention and the final month of the intervention, with the denominator being the total number of inpatients admitted that month. Antimicrobial formulary cost information was derived from amounts dispensed, available from hospital pharmacy records.

Sample size calculation

For the outcome of antimicrobial appropriateness, the sample size was based upon the assumption that the intervention would result in 14% less inappropriateness in the intervention group (before versus after) compared to the control group (before versus after).[28] A power of 80% and two-sided significance level of 5% was applied. An intra-cluster correlation coefficient (ICC) of 0.0048 was assumed, based upon comparable assessment of antimicrobial use in primary health care settings[29], with a design effect of 5.7. The sample size for appropriateness required a total of 1900 patient records be evaluated across all the hospitals, both before and after the intervention period. For the outcome of antimicrobial consumption, without accounting for ICC, and an expected 25% reduction in DDD[8], the sample size for patient audits required was 672. Therefore, the total sample size for the audits was 1900 people in total before and after the intervention period.

Data collection & statistical analysis

Data were collected using paper records and entered in an online database provided by the Australian NAPS.[25] The comparative measure for the co-primary outcomes was the difference of differences (DiD) estimated using an interaction term between time and group allocation. The analysis populations for both outcomes included all participants with available outcome data at each time point. Monthly trends in average antimicrobial consumption were assessed using a linear mixed-effects model with robust variance estimation, accounting for clustering at both the province and hospital levels. The model evaluated changes in DDD/100 bed-days per month from March to August, comparing intervention and control groups.

For antimicrobial appropriateness, binary outcomes were used, categorising "Optimal" and "Adequate" as appropriate, and "Suboptimal" and "Inadequate" as inappropriate, excluding "Not assessable" cases. A binary regression model with an identity link (linear probability model) was used with a robust variance estimator, clustered at province and hospital levels, to compare the inappropriate prescriptions as a proportion of all prescriptions. Results are presented as absolute risk differences with 95% confidence intervals. Prespecified subgroup analyses assessed DiD for reasons for inappropriateness in antimicrobial prescribing, the proportion of oral antimicrobial prescriptions, prolonged surgical prophylaxis, compliance to guidelines, WHO AWaRe categories,[30] use of broad-spectrum antimicrobials, and site of infection, respectively

DiD for antimicrobial cost comparing the intervention and control groups was also evaluated using a linear mixed effects model. The DiD in all-cause mortality rates was assessed using binary regression with an identity link, consistent with the model used for antimicrobial appropriateness. Statistical analyses were conducted using STATA-18.[31]

Ethical issues

Ethics approval for this study was obtained from the National Institute of Hygiene and Epidemiology in Vietnam (IRB – VN01057/IORG 0008555) and University of Sydney in Australia (2022/034). A leader in each site provided consent to conduct the study.

Results

The study was implemented between April and July 2022 in sixteen urban and rural hospitals in two provinces in northern and southern Vietnam, Hanoi and Ca Mau (Supplementary Figure S5.2). Characteristics of each hospital are shown in Supplementary Table S5.1. The numbers of participants in each AMS intervention are recorded in Supplementary Table S5.2. The number of inpatients recorded on the audit days and proportion taking antimicrobials before and after intervention are displayed in Supplementary Table S5.5.

Antimicrobial consumption

The consumption of antimicrobials in each group, expressed in DDD/100 bed-days per month, is shown in Supplementary Table S5.3. Between March and August, the average monthly decrease in antimicrobial use was estimated at -1·4 (95%CI -3·8, 1·1) DDD/100 bed-days for the intervention group, and at -0·6 (95%CI -3·0, 1·9) DDD/100 bed-days for the control group. There was no significant difference before and after the intervention period in the two groups, with a monthly DiD of -0·8 (95%CI -2·7, 4·3) DDD/100 bed-days (Figure 5.1).

Appropriateness of antibiotic prescribing

Baseline demographic data of inpatients included in the appropriateness audits are presented in Supplementary Table S5.4. There was an imbalance in age between the two groups, which was adjusted for in the model to account for potential confounding. Before the intervention, 877 and 1220 prescriptions (646 and 954 inpatients respectively) in the intervention and control arms respectively were analysed for appropriateness. After the intervention, 1277and 1454 prescriptions (1008 and 1159 inpatients respectively) in the intervention and control arms respectively, were analysed. There was no difference in the proportion of inpatients on antimicrobials on the day of the audit (Supplementary Table S5.5).

Inappropriate prescribing ranged between 60% to 90% of all antimicrobial prescriptions across all 16 hospitals (Supplementary Table S5.6). Inappropriate use was more common among paediatric patients at 78.5% (95% CI: 78.4%, 78.7%), compared to adult patients at 73.7% (95% CI: 70.8%, 76.7%) with a 4.8% (95% CI: 2.0%, 7.6%) difference.

Inappropriate prescriptions increased from 77.9% to 81.6% in the intervention group, and from 72.4% to 80.8% in the control group, before and after the intervention. Although inappropriate prescriptions increased in both groups, the increase was smaller in the intervention group compared to the control, with an age-adjusted DiD of -6·3% (95%CI -10·9%, -1·7%), suggesting a relative reduction in inappropriateness following the AMS program. The proportion of inappropriate prescriptions in each hospital is recorded in Supplementary Table S5.6. The most commonly provided feedback during audit and feedback sessions are included in Supplementary Table S5.7.

Subgroup analyses of inappropriate prescribing according to ward, reasons for which prescriptions were categorised as inappropriate, site of infection and other clinical factors captured in the audit are displayed in Tables 5.2, 5.3, and 5.4 respectively, as well as Supplementary Table S5.8, Supplementary Table S5.9 and Supplementary Figure S5.4.

Secondary outcomes

Total monthly antimicrobial formulary costs increased in both groups over the intervention period (Supplementary Table S5.10). Comparing post-intervention to pre-intervention period, the intervention group costs demonstrated a monthly reduction estimated at USD -$1300 (95%CI -$2314, -$284) relative to the control group (Figure 5.2).

No difference was observed in all-cause inpatient mortality between groups (RD=0·24%, 95% CI -0·01%, 0·49%). The monthly all-cause mortality rate in the intervention group was 0.29% pre-intervention and 0.24% after, with an estimated risk difference -0.05%, (95% CI -0.20%, 0.09%)]. The mortality rate in the control group was 0.74% pre-intervention, and 0.45% post-intervention, with a risk difference of -0.29% (95% CI -0·50%, -0.09%) (Supplementary Table S5.11).

Discussion

This cluster RCT revealed alarmingly high rates of inappropriate antimicrobial use at district public hospitals in Vietnam. Although officially required to deliver AMS programs, none of the participating hospitals were routinely doing so at the time of the study. Our four-month AMS intervention reduced inappropriate antimicrobial prescribing, compared to the standard of care. While overall antimicrobial consumption did not change, individual hospital consumption trends showed a modest reduction in the intervention sites, which did not reach statistical significance. A decrease in

antimicrobial cost was also observed, highlighting potential benefits of the AMS programme. No change in mortality rates between groups showed that AMS interventions are safe in this setting. While the absence of change in mortality is somewhat reassuring, this should be interpreted cautiously given the modest reduction in inappropriate prescribing and the study's limited power to detect small differences. Importantly, this cluster RCT demonstrated that implementing an AMS program in urban and rural district hospitals is feasible with hands-on guidance, aligning with Vietnamese MoH directives.

This multi-centre trial fills a gap in the literature for AMS in district hospital settings, as previous AMS studies in Vietnam were mainly uncontrolled studies, and focused on tertiary hospitals, showing mixed benefits.[21,22,32] A tertiary hospital saw reduced DOT and Length of therapy (LOT) after 5 years of AMS implementation without negative clinical impact, while another improved compliance to guidelines and reduced costs over a year.[21,32] In a tertiary paediatric setting, antibiotic consumption did not reduce, but there was an improvement in WHO AWaRe "Access" category antibiotics.[22]

In contrast, a few studies in lower levels of healthcare have been published from other LMICs. In Kenya, a cluster RCT conducted in eight district hospitals demonstrated a decrease in inappropriate antibiotic prescriptions from 74% to 42% (p=0·04) through education and guideline dissemination.[33] In China, a cluster RCT in 25 township hospitals using antimicrobial guidelines, training and feedback sessions showed an absolute risk reduction of 29% (95% CI −42%,−16%; p=0·0002) in antibiotic prescriptions in children with upper respiratory tract infections [34] In Thailand, a before-and-after study in district hospitals called the "Antibiotic Smart Use" initiative reported reductions of 18% to 46% in antibiotic use for common conditions.[35] Our study adds to the literature of AMS in community healthcare setting in LMICs by achieving a reduction in inappropriate antimicrobial prescribing.

The high proportion of antimicrobial consumption observed in this study aligns with previous research showing Vietnam among the top global users.[8] Key drivers in hospitals include perceived patient and family demands, professional hierarchy influencing junior doctors to follow senior prescribing habits, and limited microbiology services leading to excessive broad-spectrum empiric use.[36] A recent qualitative study in commune level health centres identified patient expectations and concerns over health insurance companies scrutiny, prompting doctors to favour antibiotics, deemed as the "strongest" and "cheapest" option,[37] likely relevant to our findings.

Another important finding in this study was exceptionally high inappropriate antimicrobial use in district hospitals, assessed using the validated Hospital NAPS tool.[25] In other settings where this tool was used, inappropriateness was 23% in Australia (300 hospitals – all levels), 30% in Canada (38 tertiary and community hospitals), 40% in Malaysia (two university hospitals) and 50% in Bhutan(one tertiary hospital). [38,39] In contrast, Vietnamese district hospitals had much higher rates (70–80%) at baseline, likely due to unrestricted antibiotic access and limited AMS education and training.[40,41]

When analysed based on wards, General Surgical and Obstetrics & Gynaecology had the highest proportions of inappropriate prescribing, primarily due to prolonged prophylaxis beyond the recommended 24 hours, which did not improve post- intervention. This likely stems from beliefs that extended antimicrobial use compensates for deficient operating theatre facilities and poor infection control.[42] Extensive studies globally have culminated into the “WHO Global Guidelines for the Prevention of Surgical Site Infection”, which indicate that prolonged surgical prophylaxis provide little benefit; and may cause harm.[43] We also noted more broad-spectrum antibiotics use than guideline recommendations. For example, third-generation cephalosporins were frequently used for surgical prophylaxis instead of first-generation cephalosporins, which better target Gram-positive organisms,

the more likely pathogen. Similarly, antibiotics were frequently administered for spontaneous vaginal deliveries, contrary to guidelines.

Consistent with prior observational studies in Vietnam,[24,36] inappropriate use of antibiotics for viral infections was a key finding in this study, which did not improve with intervention. Underdosing of antibiotics was also particularly common, contributing to AMR by promoting selection pressure of resistant strains.[44] For example, intravenous ampicillin/sulbactam was given twice daily instead of four times. A possible explanation was insufficient nursing staff to administer medications as prescribed. AMS intervention successfully improved dosing practices in our study, but other issues such as overuse of broad-spectrum antibiotics, inappropriate narrow-spectrum choices, prolonged treatment durations, and inappropriate administration routes persisted.

Compliance with study and national MoH guidelines was low, with prescribers habitually using unpublished guidelines, such as those established locally within the hospital or adapted from a tertiary hospital. Substantial discrepancies in drug choice, duration, and dosing between these guidelines led to significant variation in prescribing practices.[45] Furthermore, the recommended 2015 MoH guideline[46] had not been updated to reflect evolving local resistance patterns. Vietnam also lacks resources to develop local antibiograms, making it challenging to follow WHO recommendations for tailoring guidelines based on local resistance data and applying stewardship principles of using the most effective, narrowest-spectrum antibiotics.[14]

The intervention was feasible to deliver and generally well-received by healthcare workers. This included the application of national guidelines, integration of audit and feedback into routine care, and the strengthening of the role of clinical pharmacists in stewardship activities. Periodic education sessions served to reinforce awareness and embed stewardship practices into clinical routines. We

acknowledge that in AMS interventions more broadly, successful implementation is often influenced by local circumstances such as availability of human resources, staff capabilities, and leadership support.[16] While these broader influences are highly relevant, a detailed exploration of these elements lies outside the scope of the present paper. These findings are likely generalisable to other district hospitals in Vietnam and similar LMIC settings with constrained resources, provided contextual adaptations are made.

This cluster RCT had several notable strengths. The randomised design minimised bias by balancing confounders between intervention and control groups, while the parallel group design avoided temporal biases. This was especially important during the COVID-19 pandemic, which likely affected antibiotic prescribing, drug availability, and staffing. The inclusion of a large number of urban and rural sites across both northern and southern Vietnam enhances its representativeness.

Furthermore, the AMS interventions were implemented in a standardised manner across multiple hospitals. Additionally, using the Hospital NAPS audit tool - a standardised validated tool used in several countries - allowed us to benchmark the appropriateness of antimicrobial prescribing in our study compared to other countries. Auditing all hospital admissions on antibiotics in a day further ensured population representativeness. Lastly, measuring antimicrobial consumption and costs highlighted potential financial benefits, while monitoring mortality outcomes ensured that patient safety was not compromised.

This study also has several limitations. An important limitation of this study was the short four-month intervention period, which was constrained by delays related to the COVID-19 pandemic. This timeframe may have been insufficient to observe meaningful changes in prescribing behaviour. These include seasonal variation in respiratory infections, pandemic-related disruptions to hospital

admissions and antimicrobial supply chain limitations. Nevertheless, the randomised trial design likely ensured these factors were balanced between groups. . Poor documentation in medical records may have led to misclassification, affecting data accuracy. The inevitable lack of blinding of healthcare workers in facilities may have introduced bias in outcome ascertainment, although standardised procedures were followed to classify outcomes. This was partially mitigated by a blinded second assessor who only had access to written notes in the audit form.

A major limitation was the use of DDD as the sole metric for antimicrobial consumption, which may have overestimated actual use. DOT however, could not be measured due to the absence of necessary infrastructure across study sites. From our baseline NAPS data collection however, we estimate that the paediatric populations across intervention and control hospitals are roughly similar(Table S4). Although some hospitals reported prior AMS activities, these were limited, lacked dedicated resources, and were not sustained or monitored. Thus, while potential bias cannot be excluded, baseline stewardship implementation was considered minimal. Furthermore, as only two point-prevalence audits using the NAPS tool were conducted to assess appropriateness, findings may be influenced by temporal variation; however, the standardised approach across sites mitigates this limitation. Finally, the audit feedback interventions were only implemented in one to three major departments in each hospital as expansion to other wards was beyond capability of the local hospital staff. Greater investment in human resources will be required to ensure scale-up of AMS activities in this setting is sustainable.

Future research in district health settings should focus on extending the evaluation period and a larger-scale implementation, which will provide valuable insights into long-term efficacy, adaptability and sustainability. An evaluation of the impact of other AMS interventions, such as restrictive prescribing of antimicrobials, and changes in prescribing habits with access to microbiological

services, will also be important in a district hospital setting to inform alternative options for AMS in Vietnam.[15,20]

This study has important policy implications. Our findings have already contributed to Vietnam's MoH handbook on implementing AMS interventions in district hospitals.[47] Similar initiatives in other LMICs, such as Thailand's "Antibiotic Smart Use" programme in district hospitals expanded to include more hospitals and ultimately, was ultimately, integrated into Thailand's National Strategic Plan against AMR.[35,48] This study has the potential to drive similar change. Collaborating with policymakers, healthcare providers, insurance companies and the general population is crucial to scaling AMS interventions across all levels of healthcare and the community, aligning with WHO's Global Action Plan on AMR in human health.[49]

In conclusion, inappropriate antimicrobial prescribing remains a major challenge in Vietnam's district hospitals. This study demonstrates that while multifaceted AMS interventions are feasible and did not compromise patient outcomes, only modest reductions in inappropriate prescribing and costs were observed. Embedding stewardship practices into routine healthcare and scaling them up through coordinated, policy-driven efforts is crucial to advancing AMS in Vietnam and other similar resource-limited settings.

Tables and Figures

Table 5.1: Schedule of antimicrobial stewardship interventions at intervention and control sites

Activity	**Intervention sites** (8 hospitals)						**Control sites** (8 hospitals)	
	Pre-intervention	Intervention Month 1	Intervention Month 2	Intervention Month 3	Intervention Month 4	Post-intervention	Months 0 to 4	Month 4 (cross-over)
Facility-wide antimicrobial consumption data collection from pharmacies	X	X	X	X	X	X	NA	X
AMS Committee and team formation	X						NA	X
AMS Committee meetings		X	X	X	X	X	NA	X
Dissemination of antimicrobial guidelines	X						NA	X
Usage of antimicrobial guidelines for daily prescribing		X	X	X	X		NA	X
Dissemination of patient booklets on AMR and AMS		X	X	X	X		NA	X
Education to HCWs on appropriate antimicrobial prescribing			X		X		NA	X
Audit of antimicrobial appropriateness*	X		X*	X*		X	NA	X
Feedback session to prescribers regarding audit findings		X	X*	X*			NA	X

AMS – Antimicrobial stewardship; HCWs – Healthcare workers. NA = Not applicable. X = Activity conducted at the time point indicated by an 'X'

*Audits were conducted by AMS team in one to three wards per hospital selected by convenience.

Table 5.2: The proportion of inappropriate prescriptions identified during hospital audits, stratified by category of ward

Department	**Control group** (8 hospitals)			**Intervention group** (8 hospitals)			**Difference in inappropriate prescriptions between Intervention and Control groups**	
	Inappropriate prescriptions			Inappropriate prescriptions			"Difference of differences" [Intervention – Control]	Adjusted "Differences of Differences" (95% CI) ***
	Before (number inappropriate /total, %) ** Total=1220	After (number inappropriate /total, %) ** Total=1454	Difference (%)	Before (number inappropriate /total, %) ** Total=877	After (number inappropriate /total, %) ** Total=1277	Difference (%)		
Overall	883/1220 (72·4%)	1175/1454 (80·8%)	8·4%	683/877 (77·9%)	1042/1277 (81·6%)	3·7%	-4·7%	-6·3% (-10·9, -1·7)
Adult internal medicine wards*	218/313 (69·7%)	335/432 (77·6%)	7·9%	175/222 (78·8%)	220/282 (78·0%)	-0·8%	-8·7%	-8·8% (-19·7, 2·1)
Surgical wards†	213/259 (82·2%)	233/301 (77·4%)	-4·8%	195/242 (80·6%)	230/277 (83·0%)	2·4%	7·2%	7·2% (-7·1, 21·5)
Paediatric wards	233/306 (76·1%)	321/352 (91·2%)	15·1%	102/118 (86·4%)	331/359 (92·2%)	5·8%	-9·3%	-9·0% (-9·9, -8·1)
Obstetric wards	82/91 (90·1%)	94/111 (84·7%)	-5·4%	106/118 (89·8%)	102/119 (85·7%)	-4·1%	1·3%	1·5% (-10·2, 13·1)
Infectious Diseases wards	58/92 (63·0%)	99/124 (79·8%)	16·8%	28/37 (75·7%)	82/105 (78·1%)	2·4%	-14·4%	-13·5% (-35·9, 9·0)
Emergency Departments / Intensive Care Units	57/130 (43·9%)	67/102 (65·7%)	21·8%	65/125 (52·0%)	53/101 (52·5%)	0·5%	-21·3%	-23·1% (-45·2, -0·9)
Other wards§	22/29 (75·9%)	26/32 (81·3%)	5·4%	12/15 (80·0%)	24/34 (70·6%)	-9·4%	-14·8%	-18·8% (-22·5, -15·0)

*Adult internal Medicine wards included General Medicine (Adult), Interdisciplinary, Respiratory, Cardiology

† Surgical wards included General surgery, Anaesthesia, Trauma surgery

§Other wards included: Ophthalmology, Dental, Maxillofacial, Otorhinolaryngology

¶ For Infectious Diseases wards, the clustering effect at the hospital level was removed due to model instability, as it introduced unexpected variability

**Number of inappropriate antimicrobial prescriptions in a ward as a proportion of all prescriptions on the included wards

*** Adjusted for age and clustering effect at province and hospital level. Estimates were not adjusted for multiple testing

Table 5.3: The proportion of inappropriate prescriptions identified during hospital audits before and after the intervention period, stratified by reasons for inappropriateness

Reason for inappropriateness	**Control group** (8 hospitals)			**Intervention group** (8 hospitals)			**Difference in inappropriate prescriptions between Intervention and Control groups**	
	Inappropriate prescriptions			Inappropriate prescriptions			"Difference of differences" [Intervention – Control]	Adjusted "Differences of Differences" (95% CI) ***
	Before (number inappropriate /total, %) ** Total=1220	After (number inappropriate /total, %) ** Total=1454	Difference (%)	Before (number inappropriate /total, %) ** Total=877	After (number inappropriate /total, %) ** Total=1277	Difference (%)		
Overall	883/1220 (72·4%)	1175/1454 (80·8%)	8·4%	683/877 (77.9%)	1042/1277 (81·6%)	3·7%	-4·7%	**-6·3% (-10·9, -1·7)**
Spectrum too narrow	74/1220 (6·1%)	69/1454 (4·7%)	-1·4%	72/877 (8·2%)	53/1277 (4·2%)	-4·0%	-2·6%	-1·2% (-5·4, 2·9)
Spectrum too broad	400/1220 (32·8%)	445/1454 (30·6%)	-2·2%	330/877 (37·6%)	455/1277 (35·6%)	-2·0%	-0.2%	0·7% (-14·5, 15·8)
No antibiotics needed	230/1220 (18·9%)	403/1454 (27·7%)	8·8%	166/877 (18·9%)	392/1277 (30·7%)	11·8%	3·0%	0·7% (0·7, 0·8)
Incorrect route	259/1220 (21·2%)	347/1454 (23·9%)	2·7%	140/877 (16·0%)	244/1277 (19·1%)	3·1%	0·4%	0·1% (-3·0, 3·1)
Incorrect duration	167/1220 (13·7%)	209/1454 (14·4%)	0·7%	164/877 (18·7%)	175/1277 (13·7%)	-5·0%	-5·7%	-4·9% (-17·3, 7·6)
Incorrect dosing*	350/1220 (28·7%)	467/1454 (32·1%)	3·4%	234/877 (26·7%)	308/1277 (24·1%)	-2·6%	-6·0%	**-7·7% (-8·8, -6·6)**

*Incorrect dosing includes both over- and under-dosing of antimicrobials. Incorrect route of administration = antibiotic was not prescribed in the most appropriate route for its indication.

**Number of inappropriate antimicrobial prescriptions stratified by reasons for inappropriateness as a proportion of all prescriptions on the day of audit.

*** Adjusted for age and clustering effect at province and hospital level. Estimates were not adjusted for multiple testing

Bolded text indicates confidence limits do not cross the null.

Table 5.4: Appropriateness of dispensing in 16 hospitals, stratified by clinical factors

Clinical factor	**Control group** (8 hospitals)			**Intervention group** (8 hospitals)			**Difference in inappropriate dispensing between groups**	
	Inappropriate prescriptions			**Inappropriate prescriptions**			"Difference of differences" [Intervention – Control]	Adjusted "Differences of Differences" (95% CI) **
	Before (number/total, %) * Total=1220	After (number /total, %) * Total=1454	Difference (%)	Before (number/total, %) * Total=877	After (number /total, %) * Total=1277	Difference (%)		
Route of administration of antimicrobials								
Intravenous	889/1220 (72·9%)	1058/1454 (72·8%)	-0·1%	670/887 (76·4%)	944/1277 (73·9%)	-2·5%	-2·4%	-2·2% (-2·5, -1·9)
Oral	281/1220 (23·0%)	329/1454 (22·6%)	-0·4%	180/887 (20·5%)	278/1277 (21·8%)	1·3%	1·7%	1·4% (-1·8, 4·7)
Compliance with guidelines								
Compliant with guidelines	236/1220 (19·3%)	189/1454 (13·0%)	-6·3%	180/887 (20·5%)	148/1277 (11·6%)	-8·9%	-2·6%	-1·4% (-4·9, 2·1)
Non-compliant with guidelines	933/1220 (76·5%)	1223/1454 (84·1%)	7·6%	645/887 (73·6%)	1044/1277 (81·8%)	8·2%	0·6%	-1·3% (-8·4, 5·8)
No guidelines available at the facility†	50/1220 (4·1%)	39/1454 (2·7%)	-1·4%	49/887 (5·6%)	81/1277 (6·3%)	0·7%	2·1%	2·9% (-0·4, 6·3)

Clinical factor	**Control group** (8 hospitals)			**Intervention group** (8 hospitals)			**Difference in inappropriate dispensing between groups**	
	Inappropriate prescriptions			**Inappropriate prescriptions**			"Difference of differences" [Intervention – Control]	Adjusted "Differences of Differences" (95% CI) **
	Before (number/total, %) * Total=1220	After (number /total, %) * Total=1454	Difference (%)	Before (number/total, %) * Total=877	After (number /total, %) * Total=1277	Difference (%)		
WHO AWaRe category#								
"Access"	577/1220 (47·3%)	615/1454 (42·3%)	-5·0%	257/877 (29·3%)	508/1277 (39·8%)	10·5%	15·5%	15·2% (-4·8, 35·1)
"Watch"	628/1220 (51·5%)	825/1454 (56·7%)	5·2%	616/877 (70·2%)	756/1277 (59·2%)	-11·0%	-16·2%	-16·1% (-35·5, 3·2)
"Reserve"	0 (0)	2 (0·1%)	0·1%	0 (0)	2 (0·2)	0·2%	0·1%	N/A
"Uncategorised"	15(1·2%)	12(0·8%)	-0·4%	4 (0·5%)	11 (0·9%)	0·4%	0·8%	N/A
Prolonged duration of surgical antimicrobial prophylaxis among patients having surgery								
Proportion of prolonged surgical prophylaxis/all surgical prophylaxis	139/165 (84·2%)	128/167 (76·6%)	-7·6%	91/112 (81·3%)	115/138 (83·3%)	2·0%	9·6%	6·1% (95% CI: -7·8, 20·1)
According to age group								
Adult	596/837 (71·2%)	740/963 (76·8%)	5·6%	539/711 (75·8%)	605/803 (75·3%)	-0·5%	-6·1%	-5·7% (-10·6, -0·8)
Paediatric	287/383 (74·9%)	435/491 (88·6%)	13·7%	144/166 (86·8%)	437/474 (92·2%)	5·4%	-8·3%	-7·5% (-10·4, -4·6)

N/A : Not applicable

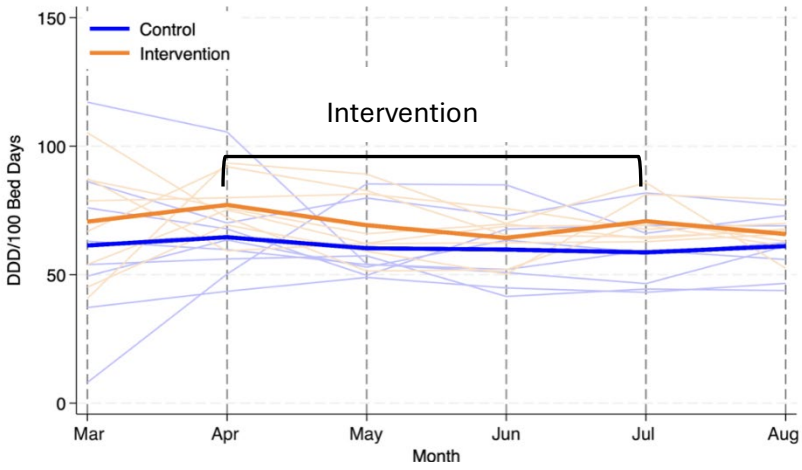
*Number of antimicrobial prescriptions with the specified clinical factor as a proportion of all prescriptions on the day of audit.

** Adjusted for age and clustering effect at province and hospital level. Estimates were not adjusted for multiple testing. Subgroup analyses are exploratory and subject to increased variability, especially in small sample sizes. Large effect sizes observed in these subsets may result from statistical noise, regression to the mean, or multiple comparisons. Wide confidence intervals indicate reduced precision.

† Where guidelines weren't available for certain conditions in either study or Ministry of Health guidelines, clinical judgement was applied by doctor in AMS team or independent blind assessor with experience in AMS

WHO AWaRe classification is a tool used to consider the impact of different antibiotic classes on antimicrobial resistance. "Access" category antibiotics display low resistance potential, are narrow spectrum and of low cost, "Watch" antibiotics are broader-spectrum, higher cost and required in severe presentations, whereas "Reserve" category antibiotics are the last choice to treat multi-drug resistant infections.[30]

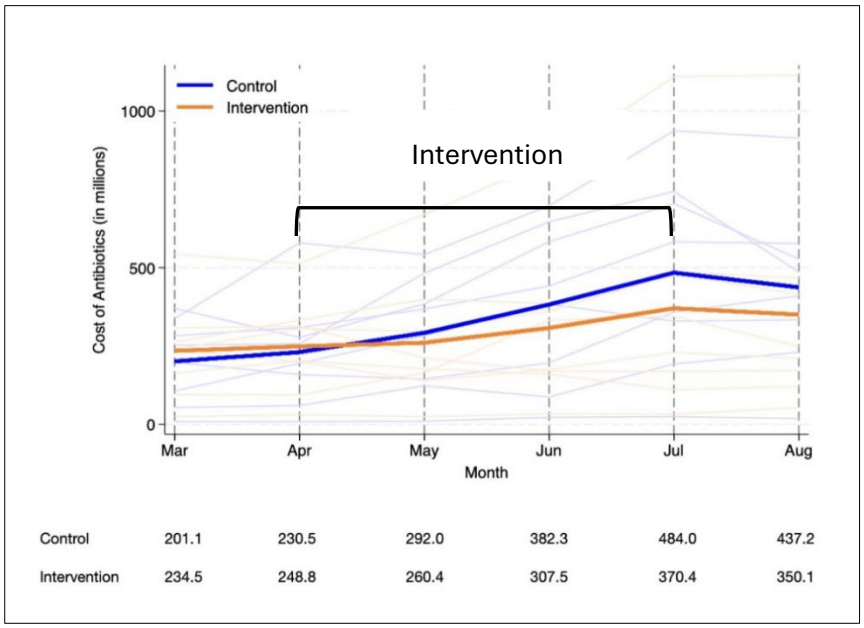
Figure 5.1: DDD/100 bed-days for hospitals in the control and intervention arms per month from March to August 2022(Intervention period: April – July 2022)



Control	61.4	64.6	60.2	59.8	58.6	61.1
Intervention	70.6	77.1	69.2	64.3	70.8	65.8

DDD – Defined Daily Dose

Figure 5.2: Total formulary costs for antimicrobials each month in hospitals in the intervention and control arm from March to August 2022, in Vietnamese Dong (VND)



Control	201.1	230.5	292.0	382.3	484.0	437.2
Intervention	234.5	248.8	260.4	307.5	370.4	350.1

Supplementary material for Chapter 5

Table S5.1: Characteristics of hospitals in control and intervention groups

Hospital	Inpatient bed capacity	Province	Distance to closest provincial hospital	Available imaging	Presence of electronic health information system	Pre-existing record of antimicrobial consumption	Microbiology testing	Recommended antibiotic guidelines	Established AMS activities
Control 1	320	Hanoi	15·0km	Xray and abdominal ultrasound	Yes	No	Microscopic testing* and bacterial culture Drug susceptibility testing	Hospital and MoH guidelines	No pre-existing activities, but plans in place
Control 2	367	Hanoi	14·0km	Xray, CT scan and abdominal ultrasound	Yes	No	Microscopic testing*	Only MoH guidelines	Restricted antibiotic list requiring prior approval for use available - compliance unclear
Control 3	355	Hanoi	14·8km	Xray, CT scan and abdominal ultrasound	Yes	Only costs recorded	Microscopy and bacterial culture PCR, immunoassay Drug susceptibility testing	MoH guidelines	No
Control 4	320	Hanoi	21·2km	Xray and abdominal ultrasound	Yes	Only costs recorded	Rapid tests Microscopic testing*	Hospital and MoH guidelines	Local guidelines + Restricted antibiotic list requiring prior approval for use available - compliance unclear
Control 5	200	Hanoi	7·2km	Xray and abdominal ultrasound	Yes	No	PCR, immunoassay Microscopic testing*	MoH guidelines	No
Control 6	450	Ca Mau	34·1km	Xray and abdominal ultrasound	Yes	Only costs recorded	Microscopic testing*and bacterial culture	Hospital and MoH guidelines	Local guidelines + Restricted antibiotic list requiring prior approval

Hospital	Inpatient bed capacity	Province	Distance to closest provincial hospital	Available imaging	Presence of electronic health information system	Pre-existing record of antimicrobial consumption	Microbiology testing	Recommended antibiotic guidelines	Established AMS activities
							Immunoassay Drug susceptibility testing		for use available - compliance unclear
Control 7	330	Ca Mau	26·0km	Xray and abdominal ultrasound	Yes	No	Microscopic testing*	Hospital, Provincial DoH and MoH guidelines	Local guidelines + Restricted antibiotic list requiring prior approval for use available - compliance unclear
Control 8	100	Ca Mau	77·0km	Xray and abdominal ultrasound	Yes	Only costs recorded	Microscopic testing*	Hospital, Provincial DoH and MoH guidelines	No pre-existing activities, but plans in place
Intervention1	300	Hanoi	9·0km	Xray, CT scan and abdominal ultrasound	Yes	Only costs recorded	Immunoassay; Microscopic testing*	Hospital and MoH guidelines	Having plans for AMS. Local guidelines + Restricted antibiotic list requiring prior approval for use available
Intervention 2	350	Hanoi	5·1km	Xray, CT scan and abdominal ultrasound	Yes	Only costs recorded	Microscopy and bacterial culture PCR, immunoassay Drug susceptibility testing (after doctors' consultation)	Hospital and MoH guidelines	Having plans for AMS. Local guidelines + Restricted antibiotic list requiring prior approval for use available
Intervention 3	200	Hanoi	3·6km	Xray and abdominal ultrasound	Yes	DDD, DOT and costs recorded	Microscopic testing*	MoH guidelines	Restricted antibiotic list requiring prior approval for use available (Imipenem+ cilastatin; Meropenem)
Intervention 4	230	Hanoi	8·8km	Xray and abdominal ultrasound	Yes	No	Microscopic testing*	Hospital, Provincial DoH	No, but plans in place

Hospital	Inpatient bed capacity	Province	Distance to closest provincial hospital	Available imaging	Presence of electronic health information system	Pre-existing record of antimicrobial consumption	Microbiology testing	Recommended antibiotic guidelines	Established AMS activities
								and MoH guidelines	
Intervention 5	343	Hanoi	11·0km	Xray and abdominal ultrasound	Yes	No	Immunoassay; Microscopic testing* Rapid tests	Hospital, Provincial DoH and MoH guidelines	AMS program started from 2020 AMS committee Local guidelines + Restricted antibiotic list requiring prior approval for use
Intervention 6	220	Ca Mau	28·5km	Xray and abdominal ultrasound	Yes	No	Microscopic testing*	MoH guidelines	No pre-existing activities, plans in place
Intervention 7	220	Ca Mau	30·4km	Yes - Xray and Ultrasound	Yes	Only costs recorded	Microscopic testing*	MoH guidelines	No
Intervention 8	300	Ca Mau	54·1km	Xray and abdominal ultrasound	Yes	No	Microscopic testing*	Hospital, Provincial DoH and MoH guidelines	Local guidelines + Restricted antibiotic list requiring prior approval for use available

**Microscopic testing included sputum AFB, fungal and parasitic testing*
MoH: Ministry of Health, Provincial DoH: Provincial Department of Health, CT : Computerised tomography
Each hospital code represents one hospital, that includes multiple hospital wards.

Table S5.2: Training and stakeholder engagement for healthcare workers in the eight intervention hospitals

AMS activities at intervention sites	Number of healthcare workers participating in all intervention sites
Training for research staff on AMS and the use of Hospital NAPS audit tool	23
Training of AMS team staff on AMS interventions and the use of Hospital NAPS audit tool	82
Stakeholder meeting with AMS committee and research staff	122
Internal AMS committee meetings	
• Meeting 1	57
• Meeting 2	72
• Meeting 3	72
• Meeting 4	72
Healthcare worker training and education session attendance	
• Workshop 1	608
• Workshop 2	291
Audit and feedback sessions	
• Feedback session 1	408
• Feedback session 2	52
Refresher training for AMS teams	33

AMS: Antimicrobial stewardship

NAPS: National Antimicrobial Prescribing Survey – Audit tool to determine appropriateness of antimicrobial prescription

Table S5.3: Monthly antimicrobial consumption in the eight intervention and eight control group hospitals

Hospital	Defined daily doses (DDD) per 100 bed-days					
	March	**April**	**May**	**June**	**July**	**August**
Control group hospitals						
Control 1	86·2	70·1	79·8	72·9	81·8	76·9
Control 2	53·9	56·1	57·3	41·5	44·4	43·8
Control 3	49·4	63·5	52·9	63·4	58·6	62·4
Control 4	76·0	67·8	49·7	67·7	69·2	69·0
Control 5	117·1	105·5	54·1	50·8	46·5	61·1
Control 6	63·0	59·7	53·9	52·0	59·4	55·9
Control 7	37·2	43·5	48·9	44·8	43·1	46·6
Control 8	8·0	50·2	85·3	84·9	66·1	73
Average monthly consumption	**61·4**	**64·6**	**60·2**	**59·8**	**58·6**	**61·1**
Intervention group hospitals						
Intervention 1	87·4	59·2	62·2	68·9	69·2	61·1
Intervention 2	86·9	75·8	65·9	69·7	64·0	67·7
Intervention 3	105·2	72·2	51·4	51·9	70·9	62·9
Intervention 4	78·7	79·9	81·4	75·7	67·6	69·9
Intervention 5	45·1	69·3	59·1	50·2	81·2	79·2
Intervention 6	53·9	75·2	62·0	62·4	62·8	65·8
Intervention 7	66·8	92·0	82·7	65·3	64·7	67·0
Intervention 8	40·7	93·4	89·1	69·9	85·8	52·5
Average monthly consumption	**70·6**	**77·1**	**69·2**	**64·3**	**70·8**	**65·8**

Each hospital code represents one hospital, that includes multiple hospital wards.

Table S5.4: Comparison of the standard mean difference in the characteristics of healthcare facilities and patients audited, before and after the intervention period in the control and intervention group hospitals

Demographics	Control			Intervention		
	Before intervention	After intervention	Standardised mean differences(SMD)[#]	Before intervention	After intervention	Standardised mean differences(SMD)[#]
	n=951	n=1158		n=645	n=1005	
Hospital factors						
Location						
Hanoi	808 (85·0)	884 (76·3)	0.22	501 (77·7)	811 (80·7)	0.07
Ca Mau	143 (15·0)	274 (23·7)		144 (22·3)	194 (19·3)	
Setting						
Urban	394 (41·4)	558 (48·2)	0.14	187 (29·0)	305 (30·4)	0.03
Rural	557 (58·6)	600 (51·8)		458 (71·0)	700 (69·7)	
Ward						
Adult internal medicine	249 (26·2)	346 (29·9)	0.01	166 (25·7)	222 (22·1)	0.32
Surgical	162 (17·0)	202 (17·4)		157 (24·3)	185 (18·4)	
Paediatric	275 (28·9)	322 (27·8)		107 (16·6)	324 (32·2)	
Obstetrics and Gynaecology	84 (8·8)	104 (9·0)		92 (14·3)	91 (9·1)	
Infectious Diseases	69 (7·3)	87 (7·5)		30 (4·7)	91 (9·1)	
Emergency Departments / Intensive Care Units	87 (9·2)	71 (6·1)		80 (12·4)	69 (6·9)	
Other wards*	25 (2·6)	26 (2·3)		13 (2·0)	23 (2·3)	
Patient factors						
Age group						
Paediatric (<16)	338 (35·5)	434 (37·5)	0.04	142 (22·0)	428 (42·6)	0.45
Adult (>16)	613 (64·5)	724 (62·5)		503 (78·0)	577 (57·4)	
Gender						
Male	483 (50·8)	589 (50·9)	0.002	331 (51·3)	527 (52·4)	0.02
Female	468 (49·2)	569 (49·1)		314 (48·7)	478 (47·6)	

**Other wards included: Ophthalmology, Dental, Maxillofacial, Otorhinolaryngology*

[#]Standardised differences (|SMD|) are reported as absolute values. An SMD < 0.1 indicates negligible imbalance; 0.1–0.2, small imbalance; 0.2–0.5, moderate imbalance; and > 0.5, large imbalance.

Table S5.5: Number of inpatients and proportion on antimicrobials in intervention and control group hospitals on the day of NAPS audit

Inpatients across all 16 hospital sites	Control (8 healthcare facilities)			Intervention (8 healthcare facilities)			"Difference of differences" [Intervention – Control]	Adjusted "Differences of Differences" (95% CI) **
	Before (number on antimicrobials/total inpatients, %) * Total=1623	After (number on antimicrobials/total inpatients, %) * Total=2112	Difference (%)	Before (number on antimicrobials/total inpatients, %) * Total=1132	After (number on antimicrobials/total inpatients, %) * Total=1825	Difference (%)		
Inpatients on antimicrobials	954/1623 (58·8%)	1159/2112 (54·9%)	-3·9%	646/1132 (57·1%)	1008/1825 (55·2%)	-1·9%	2·0%	2·1% (-2·8, 6·9)

NAPS: National Antimicrobial Prescribing Survey – Audit tool to determine appropriateness of antimicrobial prescription
*Number of patients prescribed antimicrobials as a proportion of all inpatients on the day of audit
** Adjusted for age and clustering effect at province and hospital level. Estimates were not adjusted for multiple testing

Table S5.6: Proportions of inappropriate prescriptions using Hospital NAPS audits before and after implementation of AMS interventions in the intervention and control group hospitals

Hospital	Proportion of inappropriate prescribing			Inferential analysis of difference in inappropriateness in prescribing (95%CI)**
	Before (number inappropriate /total antimicrobial prescriptions, %)*	After (number inappropriate /total antimicrobial prescriptions, %) *	Difference (After – Before) (%)	
Control group				
Control 1	179/251 71·3%	192/261 73·6%	2·3%	2·2% (-5·5, 10·0)
Control 2	133/158 84·2%	212/234 90·6%	6·4%	6·4% (-0·4, 13·2)
Control 3	158/213 74·2%	151/179 84·4%	10·2%	10·2% (2·2, 18·1)
Control 4	143/208 68·8%	167/195 85·6%	16·8%	16·9% (8·9, 24·9)
Control 5	140/192 72·9%	172/223 77·1%	4·2%	4·2% (-4·2, 12·6)
Control 6	74/117 63·2%	161/219 73·5%	10·3%	10·3% (-0·3, 20·8)
Control 7	26/34 76·5%	79/92 85·9%	9·4%	9·4% (-6·6, 25·4)
Control 8	30/47 63·8%	41/51 80·4%	16·6%	16·6% (-1·1, 34·2)

Intervention group				
Intervention 1	58/83 69·9%	116/168 69·0%	-0·9%	-0·8% (-13·0, 11·3)
Intervention 2	32/181 72·9%	208/258 80·6%	7·7%	7·7% (-0·4, 15·8)
Intervention 3	49/54 90·7%	93/106 87·7%	-3·0%	-3·0% (-13·0, 7·0)
Intervention 4	158/196 80·6%	265/292 90·8%	10·2%	10·1% (3·7, 16·6)
Intervention 5	138/174 79·3%	183/223 82·1%	2·8%	2·8% (-5·1, 10·6)
Intervention 6	47/57 82·5%	60/79 75·9%	-6·6%	-6·5% (-20·2, 7·2)
Intervention 7	78/96 81·3%	54/71 76·1%	-5·2%	-5·2% (-17·9, 7·5)
Intervention 8	23/36 63·9%	63/80 78·8%	14·9%	14·9% (-3·3, 33·0)

NAPS: National Antimicrobial Prescribing Survey – Audit tool to determine appropriateness of antimicrobial prescription
**Number of inappropriate antimicrobial prescriptions in inpatients in each hospital as a proportion of all prescriptions on the day of NAPS audit*
*** Adjusted for age. Estimates were not adjusted for multiple testing*

Table S5.7: List of most commonly provided feedback during audit and feedback sessions

General feedback provided in audit and feedback sessions
- Reduce the use of overly broad-spectrum antimicrobials - Ensure dosages of antimicrobials are adequate – a large number of antimicrobials were underdosed in either volume or frequency, taking into consideration weight, age and renal function. - Remember to use combination antibiotics for community-acquired pneumonia that are hospitalised which result in antimicrobial choice being too narrow - Avoid using antibiotics for viral infections such as viral upper respiratory tract infections and gastroenteritis. - Ensure accurate diagnosis is made of patient – e.g. Diagnosis of severity of community-acquired pneumonia - Use antimicrobial guidelines while prescribing antimicrobials - Reminders on de-escalation of antimicrobials from intravenous to oral route - Reminders about consulting hospital pharmacists for guidance on antimicrobials in general, especially in the event of drug supply shortages - Reminders on tools to calculate creatinine clearance - Responding to questions from ward doctors about their day-to-day patient cases

Table S5.8: The proportion of inappropriate prescriptions identified during hospital audits before and after the intervention period, stratified by site of infection

Site of infection	**Control group** (8 hospitals)			**Intervention group** (8 hospitals)			**Difference in inappropriate prescriptions between Intervention and Control groups**	
	Inappropriate prescriptions			Inappropriate prescriptions			"Difference of differences" [Intervention – Control]	Adjusted "Differences of Differences" (95% CI) **
	Before (number inappropriate /total, %) * Total=1220	After (number inappropriate /total, %) * Total=1454	Difference (%)	Before (number inappropriate /total, %) * Total=877	After (number inappropriate /total, %) * Total=1277	Difference (%)		
Respiratory ¶	349/512 (68·2%)	493/583 (84·6%)	16·4%	231/316 (73·1%)	386/472 (81·8%)	8·7%	-7·7%	-7·2% (-12·7, -1·6)
Gastrointestinal ¶	31/63 (49·2%)	50/73 (68·5%)	19·3%	54/68 (79·4%)	59/72 (81·9%)	2·5%	-16·8%	-16·7% (-19·0, -14·4)
Urinary tract	6/15 (40·0%)	34/53 (64·2%)	24·2%	22/38 (57·9%)	16/39 (41·0%)	-16·9%	-41·1%	-40·9% (-68·3, -13·5)
Skin Soft tissue	112/163 (68·7%)	119/161 (73·9%)	5·2%	131/147 (89·1%)	112/147 (76·2%)	-12·9%	-18·1%	-18·1% (-36·6, 0·4)
Intra-abdominal	36/53 (67·9%)	47/70 (67·1%)	-0·8%	33/57 (57·9%)	28/46 (60·9%)	3·0%	3·8%	1·2% (-7·1, 9·4)
Eye& Ear nose throat	95/107 (88·8%)	161/181 (89·0%)	0·2%	50/51 (98·0%)	152/159 (95·6%)	-2·4%	-2·6%	-2·5% (-5·9, 0·9)
Medical prophylaxis	10/14 (71·4%)	1/8 (12·5%)	-58·9%	12/22 (54·6%)	3/12 (25·0%)	-29·6%	29·3%	22·8% (10·0, 35·5)
Surgical prophylaxis	163/165 (98·8%)	155/167 (92·8%)	-6·0%	109/112 (97·3%)	138/138 (100%)	2·7%	8·7%	7·7% (7·4, 8·0)

*Number of inappropriate antimicrobial prescriptions stratified by reasons for inappropriateness as a proportion of all prescriptions on the day of audit.

** Adjusted for age and clustering effect at province and hospital level. Estimates were not adjusted for multiple testing. Subgroup analyses are exploratory and subject to increased variability, especially in small sample sizes. Large effect sizes observed in these subsets may result from statistical noise, regression to the mean, or multiple comparisons. Wide confidence intervals indicate reduced precision.

¶ For respiratory and gastrointestinal site of infection subgroups, a quadratic (age^2) term was included where model diagnostics indicated a non-linear relationship between age and the outcome. Including age^2 improves model fit where linear assumptions did not hold, ensuring more accurate estimations.

§ "Other" included Bone and Joint, Cardiovascular, Central nervous system, Genital, Oral and dental, Sepsis, Systemic infections and other conditions that weren't infections. For the 'Other' subgroup, the clustering effect at the health facility level was removed due to model instability, where unexpected variability was seen without improvement in model fit.

Table S5.9: The proportion of antimicrobials according to class prescribed in National Antimicrobial Prescribing Survey (NAPS) hospital audits before and after the intervention period

Broad-spectrum antimicrobial use	**Control group** (8 hospitals)			**Intervention group** (8 hospitals)			**Difference in antimicrobial class prescribed between Intervention and Control group**	
	Before (number of antimicrobials prescribed /total, %) * Total=1220	After (number of antimicrobials prescribed/total, %) * Total=1454	Difference (%)	Before (number of antimicrobials prescribed /total, %) * Total=877	After (number of antimicrobials prescribed /total, %) * Total=1277	Difference (%)	"Difference of differences" [Intervention – Control]	Adjusted "Differences of Differences" (95% CI) **
Second generation Cephalosporin	81/1220 (6·9%)	248/1454 (17·1%)	10·2%	83/877 (9·5%)	72/1277 (5·6%)	-3·9%	-14·1%	-15·7% (-20·6, -10·8)
Third generation Cephalosporin	334/1220 (27·4%)	327/1454 (22·5%)	-4·9%	356/877 (40·6%)	480/1277 (37·6%)	-3·0%	1·9%	3·2% (-9·9, 16·3)
Fluoroquinolones	123/1220 (10·1%)	128/1454 (8·8%)	1·3%	120/877 (13·7%)	128/1277 (10·0%)	-3·7%	2·4%	-0·8% (-4·0, 2·4)
Aminoglycosides	43/1220 (3·5%)	61/1454 (4·2%)	0·7%	57/887 (6·5%)	53/1277 (4·2%)	-2·3%	-3·0%	-2·8% (-5·9, 0·2)
Beta-lactam/Beta-lactam inhibitors	366/1220 (30·0%)	368/1454 (25·3%)	-4·7%	125/887 (14·3%)	338/1277 (26·5%)	12·2%	16·9%	15·7% (4·8, 26·6)
Carbapenems	7/1220 (0·6%)	20/1454 (1·4%)	0·8%	4/887 (0·5%)	1/1277 (0·1%)	-0·4%	-1·2%	-1·0% (-1·7, -0·3)

Table S5.10: Antimicrobial formulary costs in each hospital from March to August 2022 in VND (Intervention period: April to July 2022)

Hospital	Monthly expenditure (VND, millions)					
	March	April	May	June	July	August
Monthly expenditure upon antibiotics in the control group in VND						
Control 1	253	257	482	646	743	487
Control 2	370	277	384	583	705	528
Control 3	283	309	368	442	582	577
Control 4	106	195	283	384	329	334
Control 5	198	159	145	196	358	410
Control 6	337	579	542	698	937	913
Control 7	53	60	123	87	192	230
Control 8	8	8	9	22	25	18
Average	201	230	292	382	484	437
Monthly expenditure upon antibiotics in the Intervention group in VND						
Intervention 1	95	93	165	332	345	248
Intervention 2	543	513	670	843	1109	1114
Intervention 3	239	199	140	175	229	211
Intervention 4	240	305	297	361	480	415
Intervention 5	262	333	399	386	488	466
Intervention 6	25	30	24	33	32	54
Intervention 7	307	314	212	169	169	171
Intervention 8	164	203	177	159	110	120
Average	234	249	260	307	370	350

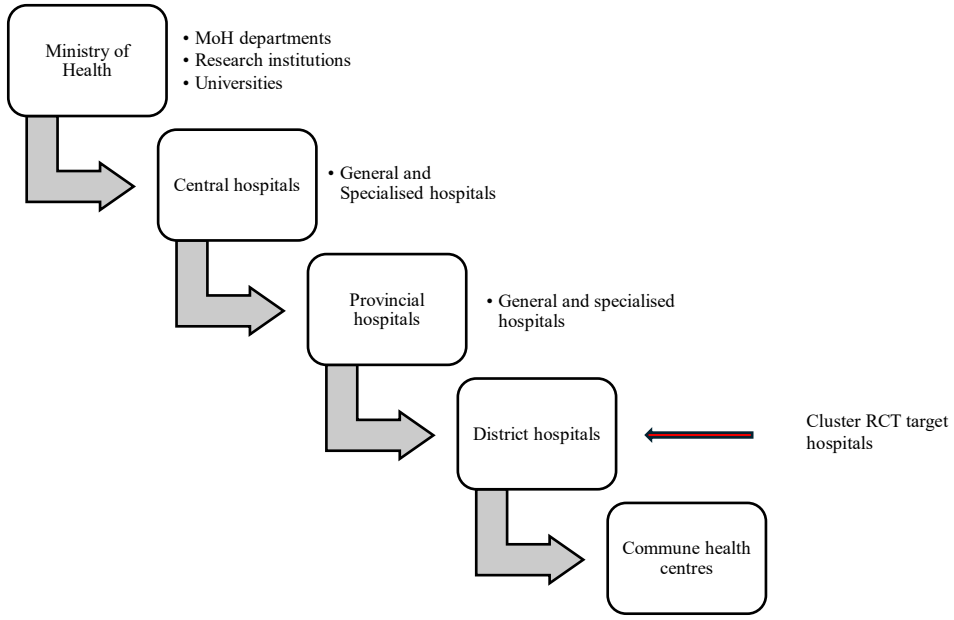
Each hospital code represents one hospital, that includes multiple hospital wards.
VND :Vietnamese Dong

Table S5.11: Monthly mortality rate at control and intervention group hospitals

Groups	Pre-intervention (March 2022)			Post intervention (August 2022)			Difference in mortality rate, RD (95%Confidence interval)
	Number of deaths, n	Number of inpatients, n	Mortality rate (%)	Number of deaths, n	Number of inpatients, n	Mortality rate (%)	
Control Sites	74	9935	74/9935= 0·74%	59	13020	59/13020= 0·45%	-0·29% (95%CI: -0·4, -0·08)
Intervention sites	26	8897	26/8897= 0·29%	27	11217	27/11217= 0·24%	-0·05% (95%CI: -0·2, 0·09)

Mortality defined as all-cause mortality that occur as while inpatient, and those discharged home with the disposition of death as determined by a physician. The heterogeneity chi-squared statistic is 0·86 with p-value of 0·353, showing no significant difference in the mortality rate changes between the two groups.

Figure S5.1: Health system structure in Vietnam



(From Ha et al. 2015[50])

Figure S5.2: Schedule of the pre-intervention and intervention period

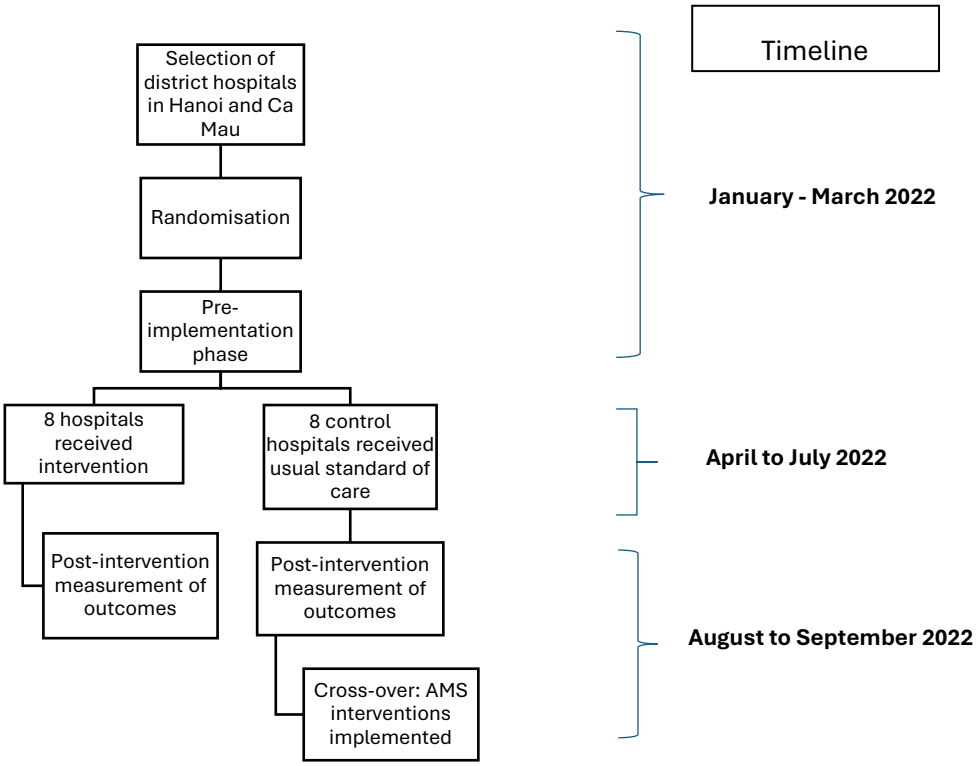
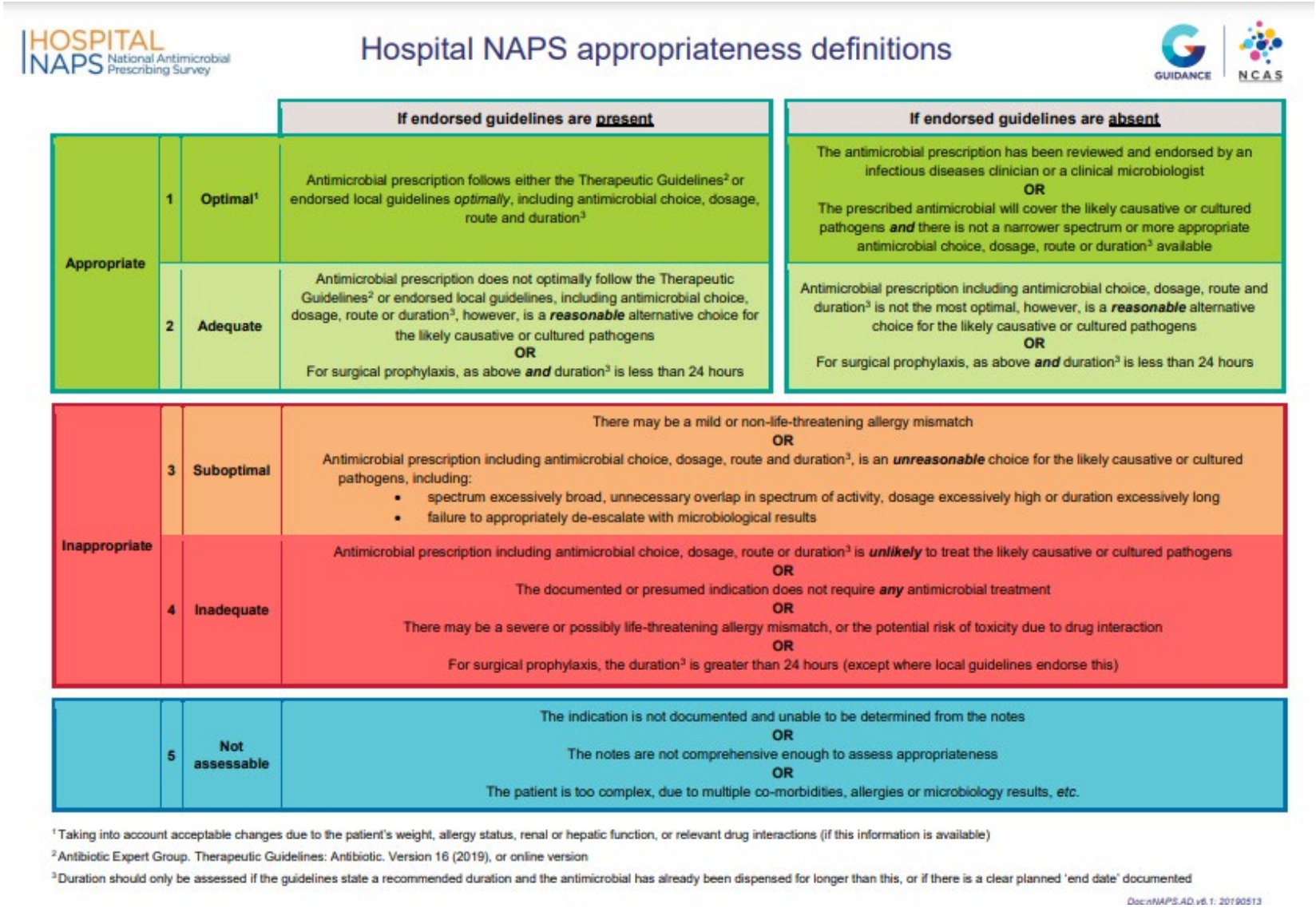


Figure S5.3: Hospital National Antimicrobial Prescribing Survey (Hospital NAPS)[23] Australia appropriateness definitions by which each antimicrobial prescription was assessed and categorised



HOSPITAL NAPS National Antimicrobial Prescribing Survey

Hospital NAPS appropriateness definitions

GUIDANCE | NCAS

			If endorsed guidelines are present	If endorsed guidelines are absent
Appropriate	1	Optimal[1]	Antimicrobial prescription follows either the Therapeutic Guidelines[2] or endorsed local guidelines *optimally*, including antimicrobial choice, dosage, route and duration[3]	The antimicrobial prescription has been reviewed and endorsed by an infectious diseases clinician or a clinical microbiologist **OR** The prescribed antimicrobial will cover the likely causative or cultured pathogens ***and*** there is not a narrower spectrum or more appropriate antimicrobial choice, dosage, route or duration[3] available
	2	Adequate	Antimicrobial prescription does not optimally follow the Therapeutic Guidelines[2] or endorsed local guidelines, including antimicrobial choice, dosage, route or duration[3], however, is a ***reasonable*** alternative choice for the likely causative or cultured pathogens **OR** For surgical prophylaxis, as above ***and*** duration[3] is less than 24 hours	Antimicrobial prescription including antimicrobial choice, dosage, route and duration[3] is not the most optimal, however, is a ***reasonable*** alternative choice for the likely causative or cultured pathogens **OR** For surgical prophylaxis, as above ***and*** duration[3] is less than 24 hours
Inappropriate	3	Suboptimal	There may be a mild or non-life-threatening allergy mismatch **OR** Antimicrobial prescription including antimicrobial choice, dosage, route and duration[3], is an ***unreasonable*** choice for the likely causative or cultured pathogens, including: • spectrum excessively broad, unnecessary overlap in spectrum of activity, dosage excessively high or duration excessively long • failure to appropriately de-escalate with microbiological results	
	4	Inadequate	Antimicrobial prescription including antimicrobial choice, dosage, route or duration[3] is ***unlikely*** to treat the likely causative or cultured pathogens **OR** The documented or presumed indication does not require ***any*** antimicrobial treatment **OR** There may be a severe or possibly life-threatening allergy mismatch, or the potential risk of toxicity due to drug interaction **OR** For surgical prophylaxis, the duration[3] is greater than 24 hours (except where local guidelines endorse this)	
	5	Not assessable	The indication is not documented and unable to be determined from the notes **OR** The notes are not comprehensive enough to assess appropriateness **OR** The patient is too complex, due to multiple co-morbidities, allergies or microbiology results, *etc.*	

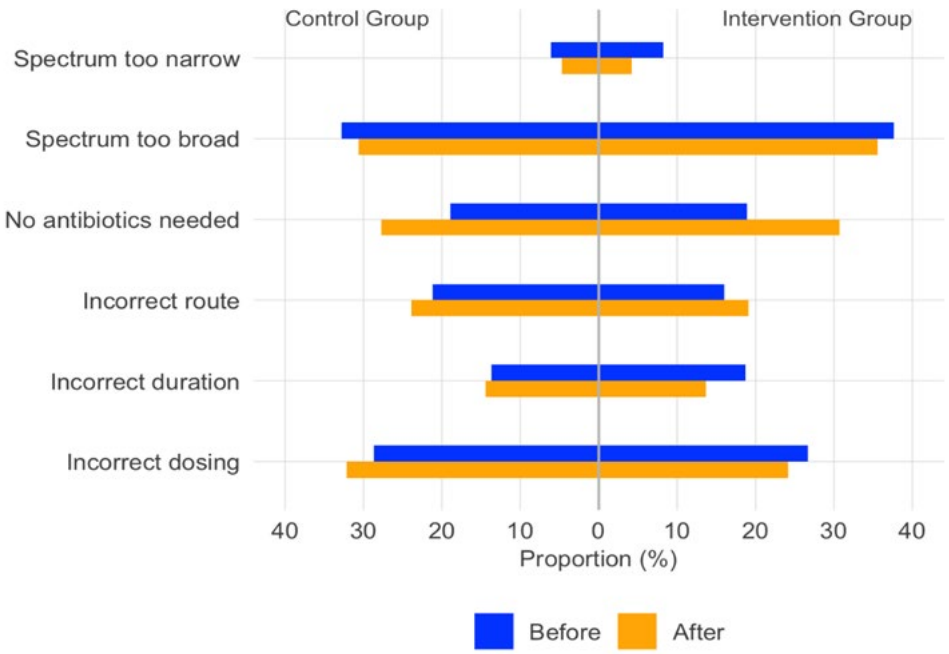
[1] Taking into account acceptable changes due to the patient's weight, allergy status, renal or hepatic function, or relevant drug interactions (if this information is available)

[2] Antibiotic Expert Group. Therapeutic Guidelines: Antibiotic. Version 16 (2019), or online version

[3] Duration should only be assessed if the guidelines state a recommended duration and the antimicrobial has already been dispensed for longer than this, or if there is a clear planned 'end date' documented

DescNAPS.AD.v8.1: 20190513

Figure S5.4: Tornado chart showing the proportion of inappropriate prescriptions according to their reasons in control and intervention group hospitals



References for Chapter 5

1. World Health Organisation. Antimicrobial resistance fact sheet. 2023. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance (accessed 15/7/2024).

2. Sulis G, Sayood S, Gandra S. Antimicrobial resistance in low- and middle-income countries: current status and future directions. *Expert review of anti-infective therapy* 2022; **20**(2): 147-60.

3. Torumkuney D, Kundu S, Vu GV, et al. Country data on AMR in Vietnam in the context of community-acquired respiratory tract infections: links between antibiotic susceptibility, local and international antibiotic prescribing guidelines, access to medicines and clinical outcome. *Journal of Antimicrobial Chemotherapy* 2022; **77**(Supplement_1): i26-i34.

4. Vu TVD, Do TTN, Rydell U, et al. Antimicrobial susceptibility testing and antibiotic consumption results from 16 hospitals in Viet Nam: The VINARES project 2012-2013. *Journal of global antimicrobial resistance* 2019; **18**: 269-78.

5. Larsson M, Nguyen HQ, Olson L, Tran TK, Nguyen TV, Nguyen CTK. Multi-drug resistance in Streptococcus pneumoniae among children in rural Vietnam more than doubled from 1999 to 2014. *Acta Paediatr* 2021; **110**(6): 1916-23.

6. Duong TN, Le TV, Tran KH, et al. Azole-resistant Aspergillus fumigatus is highly prevalent in the environment of Vietnam, with marked variability by land use type. *Environ Microbiol* 2021; **23**(12): 7632-42.

7. Global Research on Antimicrobial Resistance (GRAM) IfHMaEI, University of Oxford,. The burden of antimicrobial resistance (AMR) in Viet Nam: University of Oxford-IHME Strategic Partnership, 2022. https://www.healthdata.org/sites/default/files/2023-09/Viet_Nam.pdf (accessed 12/07/2024).

8. Klein EY, Van Boeckel TP, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proceedings of the National Academy of Sciences* 2018; **115**(15): E3463-E70.

9. Klein EY, Impalli I, Poleon S, et al. Global trends in antibiotic consumption during 2016–2023 and future projections through 2030. *Proceedings of the National Academy of Sciences* 2024; **121**(49): e2411919121.

10. McKinn S, Trinh DH, Drabarek D, et al. Drivers of antibiotic use in Vietnam: implications for designing community interventions. *BMJ global health* 2021; **6**(7).

11. Viet Nam Ministry of Health. National Action Plan on combatting drug resistance in period from 2013-2020 (Approved with Decision No.2174/QD-BYT). 2013. https://thuvienphapluat.vn/van-ban/The-thao-Y-te/Decision-2174-QD-BYT-2013-ratification-of-the-National-Action-Plan-to-Combat-Antimicrobial-Resistance-382068.aspx (accessed 16/08/2022).

12. Ministry of Health Vietnam. Decision No. 1121/QD-TTg dated September 25, 2023 on approval of The national strategy for prevention and control of drug resistance in Vietnam for the period of 2023 - 2030 with a vision towards 2045. 2023. https://lawnet.vn/en/vb/Decision-1121-QD-TTg-2023-The-national-strategy-for-prevention-and-control-of-drug-resistance-8DDD4.html (accessed 10/01/2025).

13. Vietnam Ministry of Health. Decision No. 5631/QD-BYT 2020: Guidance on management of the antibiotic use in hospitals. 2020. https://english.luatvietnam.vn/decision-no-5631-qd-byt-

of-the-ministry-of-health-on-promulgating-the-guidance-on-management-of-the-antibiotic-use-in-hospit-196563-doc1.html (accessed 15/03/2022).

14. World Health Organisation. Antimicrobial Stewardship programmes in health-care facilties in Low- and Middle-income countries - a WHO practical toolkit. 2019. https://www.who.int/publications/i/item/9789241515481 (accessed 10/01/2023).

15. Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017; **2**(2): Cd003543.

16. Schuts EC, Hulscher MEJL, Mouton JW, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. *The Lancet Infectious Diseases* 2016; **16**(7): 847-56.

17. Zay Ya K, Win PTN, Bielicki J, Lambiris M, Fink G. Association Between Antimicrobial Stewardship Programs and Antibiotic Use Globally: A Systematic Review and Meta-Analysis. *JAMA Network Open* 2023; **6**(2): e2253806-e.

18. Australian Commission on Safety and Quality in Health Care. Antimicrobial Stewardship in Australian Health Care. Sydney, Australia: ACSQHC, 202322/11/2024).

19. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clinical Infectious Diseases* 2016; **62**(10): e51-e77.

20. Pierce J, Apisarnthanarak A, Schellack N, et al. Global Antimicrobial Stewardship with a Focus on Low- and Middle-Income Countries. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2020; **96**: 621-9.

21. Nguyen-Thi H-Y, Bui TV, Tran-Thi H-N, et al. Evaluation of the impact before and after the application of an antimicrobial stewardship program at Dong Thap General Hospital, Vietnam, from 2017 to 2021. *Infection Prevention in Practice* 2023; **5**(4): 100311.

22. Nguyen HQ, Nguyen-Thi H, Huynh P, Le N, Nguyen N-Q, Hsia Y. Effectiveness of an enhanced antibiotic stewardship programme among paediatric patients in a tertiary hospital in Vietnam. *Journal of Hospital Infection* 2022; **127**: 121-8.

23. Son NT, Tra TT, Thao PTN. Antimicrobial stewardship program at a tertiary teaching hospital in Vietnam: a longitudinal observational study. *Clin Microbiol Infect Dis* 2017; **2**(1): 1-5.

24. Nguyen NV, Do NTT, Vu DTV, et al. Outpatient antibiotic prescribing for acute respiratory infections in Vietnamese primary care settings by the WHO AWaRe (Access, Watch and Reserve) classification: An analysis using routinely collected electronic prescription data. *The Lancet Regional Health–Western Pacific* 2023; **30**.

25. National Centre for Antimicrobial Stewardship. The National Antimicrobial Prescribing Survey. 2024. https://www.ncas-australia.org/National_Antimicrobial_Prescribing_Survey (accessed 08/04/2022).

26. World Health Organisation. ATC/DDD Toolkit. 2024. https://www.who.int/tools/atc-ddd-toolkit (accessed 23/02/2022).

27. Nguyen NP-t, Truong QT, Huynh TP, et al. Measurement of DDD and DOT metrics for optimizing antimicrobial surveillance in two tertiary hospitals in Viet Nam: A four-year retrospective study. *Pharmaceutical Sciences Asia* 2024; **51**: 301-13.

28. Cross EL, Tolfree R, Kipping R. Systematic review of public-targeted communication interventions to improve antibiotic use. *The Journal of antimicrobial chemotherapy* 2017; **72**(4): 975-87.

29. Vellinga A, Galvin S, Duane S, et al. Intervention to improve the quality of antimicrobial prescribing for urinary tract infection: a cluster randomized trial. *Cmaj* 2016; **188**(2): 108-15.

30. World Health Organization. The WHO AWaRe (access, watch, reserve) antibiotic book. 2022. https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.04 (accessed 02/07/2024).

31. StataCorp. Stata Statistical Software: Release 18. College Station, TX:StataCorp LLC; 2023.

32. Nguyen TS, Ton TT, Pham TNT. Antimicrobial stewardship program at a tertiary teaching hospital in Vietnam: a longitudinal observational study. *Clin Microbiol Infect Dis* 2017; **2**(1): 1-5.

33. Opondo C, Ayieko P, Ntoburi S, et al. Effect of a multi-faceted quality improvement intervention on inappropriate antibiotic use in children with non-bloody diarrhoea admitted to district hospitals in Kenya. *BMC pediatrics* 2011; **11**: 1-10.

34. Wei X, Zhang Z, Walley JD, et al. Effect of a training and educational intervention for physicians and caregivers on antibiotic prescribing for upper respiratory tract infections in children at primary care facilities in rural China: a cluster-randomised controlled trial. *The Lancet Global Health* 2017; **5**(12): e1258-e67.

35. Sumpradit N, Chongtrakul P, Anuwong K, et al. Antibiotics Smart Use: a workable model for promoting the rational use of medicines in Thailand. *Bulletin of the World Health Organization* 2012; **90**(12): 905-13.

36. Phuong NT, Hoang TT, Van PH, Tu L, Graham SM, Marais BJ. Encouraging rational antibiotic use in childhood pneumonia: a focus on Vietnam and the Western Pacific Region. *Pneumonia* 2017; **9**(1): 1-9.

37. Vu Minh D, Nguyen Thi Hong Y, Nagraj S, et al. Determinants of antibiotic prescribing in primary care in Vietnam: a qualitative study using the Theoretical Domains Framework. *Antimicrobial Resistance & Infection Control* 2024; **13**(1): 115.

38. James R, Nakamachi Y, Morris A, et al. The feasibility and generalizability of assessing the appropriateness of antimicrobial prescribing in hospitals: a review of the Australian National Antimicrobial Prescribing Survey. *JAC-antimicrobial resistance* 2022; **4**(1).

39. Royal Melbourne Hospital and the National Centre for Antimicrobial Stewardship. Antimicrobial prescribing practice in Australian hospitals - Results of the 2022 Hospital National Antimicrobial Prescribing Survey. Canberra: Department of Health and Aged Care, 202411/01/2025).

40. Thu TA, Rahman M, Coffin S, Harun-Or-Rashid M, Sakamoto J, Hung NV. Antibiotic use in Vietnamese hospitals: a multicenter point-prevalence study. *American journal of infection control* 2012; **40**(9): 840-4.

41. Nga DTT, Chuc NTK, Hoa NP, et al. Antibiotic sales in rural and urban pharmacies in northern Vietnam: an observational study. *BMC Pharmacology and Toxicology* 2014; **15**(1): 1-10.

42. Nguyen D, MacLeod WB, Phung DC, et al. Incidence and predictors of surgical-site infections in Vietnam. *Infection control and hospital epidemiology* 2001; **22**(8): 485-92.

43. World Health Organization. Global Guidelines for the Prevention of Surgical Site Infection, Second Edition. Geneva; 2018. (accessed.

44. Roberts JA, Kruger P, Paterson DL, Lipman J. Antibiotic resistance--what's dosing got to do with it? *Crit Care Med* 2008; **36**(8): 2433-40.

45. Pham GN, Dang TTH, Nguyen T-A, et al. Health system barriers to the implementation of the national action plan to combat antimicrobial resistance in Vietnam: a scoping review. *Antimicrobial Resistance & Infection Control* 2024; **13**(1): 12.

46. Ministry of Health Vietnam. Instructions for Use of Antibiotics - Decision No. 708/QD-BYT. Hanoi, Vietnam, 2015. https://kcb.vn/thu-vien-tai-lieu/tai-lieu-huong-dan-su-dung-khang-sinh.html (accessed 31/03/2022).

47. Ministry of Health Vietnam. Handbook for Guidance on Implementation of Antibiotic Use Management Program for District Hospitals - No. 2115/QD-BYT. In: Management DoMEaT, editor. Hanoi, Vietnam; 2023.

48. Sumpradit N, Wongkongkathep S, Malathum K, et al. Thailand's national strategic plan on antimicrobial resistance: progress and challenges. *Bulletin of the World Health Organization* 2021; **99**(9): 661-73.

49. World Health Organization. Global Action Plan on Antimicrobial Resistance. 2015. https://www.who.int/publications/i/item/9789241509763 (accessed 15/07/2024).

50. Ha B, Mirzoev T, Morgan R. Patient Complaints in healthcare services in Vietnam's Health system. *SAGE Open Medicine* 2015; **3**.

Chapter 6: Discussion

Antimicrobial resistance (AMR) remains a critical global health challenge, leading to increased morbidity, mortality, and healthcare costs, particularly in low- and middle-income countries (LMICs) like Vietnam.[1] Antimicrobial stewardship (AMS) programs comprise a pivotal solution to the problem of excessive and inappropriate antimicrobial use that drives the emergence of drug-resistant pathogens.[1] Vietnam presents a particularly relevant context for evaluating AMS interventions due to its high burden of AMR, widespread antimicrobial overuse, and the limited availability of stewardship programs, especially in district hospitals where resources and expertise are constrained.[2,3]

This thesis has evaluated antimicrobial consumption and the appropriateness of its use within Vietnamese district hospitals, while also quantifying the carriage of multidrug-resistant organisms (MROs) among inpatients. Furthermore, it has demonstrated the feasibility of implementing an AMS program in these hospitals and assessed its effect on antimicrobial consumption, appropriate prescribing, and prevalence of MRO carriage in hospital inpatients.

In Chapter 1, the global and Vietnam-specific context of AMR was examined. AMS was introduced as a key strategy to combat AMR through structured approaches at global, national, and local levels. Common AMS approaches were outlined, along with potential barriers to implementation within the Vietnamese healthcare system.

Chapter 2 presented a systematic review and meta-analysis of antimicrobial use and AMS interventions in Vietnam; summarising studies published in both English and Vietnamese journals since 2010. The review addressed three key domains: antimicrobial consumption (31 studies), appropriateness of prescribing (eight studies), and AMS interventions (34 studies). It highlighted the

current evidence on antimicrobial use and prescribing practices, while revealing a significant gap in data from Vietnamese district hospitals.

Chapter 3 reported the findings of VRESIST B before-and-after study, which evaluated antimicrobial consumption and appropriateness in prescribing in four district hospitals. This pilot study demonstrated the feasibility of implementing an AMS program incorporating antimicrobial guidelines, audit and feedback, and healthcare worker engagement.

Chapter 4 explored the prevalence of MRO carriage among inpatients in the four district hospitals in VRESIST B and evaluated the effects of AMS interventions on MRO prevalence.

Chapter 5 reported the findings from the VRESIST C cluster randomised controlled trial (RCT), evaluating the effectiveness of an AMS program upon antimicrobial consumption, prescribing appropriateness, antimicrobial costs and mortality among 8 intervention and 8 control group district hospitals.

Collectively, this body of research characterises four domains: (i)antimicrobial consumption (ii)appropriateness of antimicrobial prescribing (iii)prevalence of MRO carriage in hospital inpatients, and (iv)the effect of AMS interventions on outcomes related to (i), (ii) and (iii) across all chapters. Each domain is detailed below, with results from the systematic review and meta-analyses compared to findings from VRESIST B and C, providing a comprehensive analysis within each domain.

Antimicrobial consumption

Measurement of antimicrobial consumption is vital to understand and address AMR, as higher antimicrobial use exerts selective pressure on bacteria, promoting resistance. Standardised metrics like Defined Daily Dose (DDD)/100 bed-days for hospitals and DDD/1000 inhabitants per day for community settings provide a consistent framework for benchmarking antimicrobial use across healthcare settings and between countries.[4,5] These metrics are widely recognised as the gold standard for monitoring and comparing antimicrobial consumption. They are relatively straightforward for hospital systems to report, even in resource-limited settings, provided bed utilisation data is accessible.

Antimicrobial consumption was addressed in Chapters 2, 3 and 5. In the systematic review and meta-analyses (Chapter 2), the pooled estimate of antimicrobial consumption in Vietnam was 90.8 DDD/100 bed-days (95% CI:42, 139 DDD/100 bed-days), with most studies conducted in tertiary-level facilities. This estimate was comparable to other Southeast Asian countries.[6,7] In contrast, antimicrobial consumption in district level hospitals, as measured in VRESIST B and C studies (Chapter 3 and 5), was lower. Our studies found median antimicrobial consumption among the four district hospitals pre-intervention at 65.7 DDD/100 bed-days (VRESIST B). Mean consumption among the eight hospitals in the VRESIST C intervention group was 70.6 (95%CI 51.5, 89.7) DDD/100 bed-days and 61.4 (95%CI 33.9, 88.8) DDD/100 bed-days in the control group. These findings indicate similar levels of antimicrobial consumption across the district hospitals included in the VRESIST studies.

The differences in DDD/100 bed-days observed between our studies (VRESIST B and C) and the estimates from the systematic review are likely attributable to variations in study settings. While the systematic review predominantly included provincial and central referral hospitals, our studies

focused on district-level hospitals, where prescribing patterns and healthcare resources may differ. Tertiary hospitals often manage more complex and critically ill patients, who may require combination antibiotic therapy or prolonged treatment durations, leading to higher consumption.[8,9]

Another potential contributor to lower antimicrobial DDDs in district hospitals in VRESIST studies could be under-dosing of antimicrobials, which was observed in our audits. Comparatively, DDD/1000 inhabitants/day in Vietnam is among the highest both regionally and globally,[10] indicating that a substantial proportion of antimicrobial use remain in the community. Collectively, these findings demonstrate the importance of comprehensive surveillance of antimicrobial consumption across healthcare settings and the community to measure and monitor these important trends.

These observed differences also highlight the limitations of DDD metrics as a measure for antimicrobial consumption. The DDD for a given antimicrobial does not always align with doses recommended in clinical practice, and does not account for variations in dosing based on clinical indications, such as acute treatment, maintenance therapy, or prophylaxis.[11] Moreover, DDDs also do not consider individual patient factors that can influence treatment response, such as age, weight, ethnicity, disease type, and severity.[12] DDDs also cannot be directly inferred as the final administered dose in hospital inpatients as it is usually based on pharmacy dispensing data (including VRESIST studies). As a result, DDD-based drug utilisation data provide only an overall estimate of consumption and may not fully reflect actual prescribing patterns or usage trends.[11]

These limitations highlight the need to supplement DDD data with other metrics, such as Days of therapy (DOT), which measures the number of days patients receive antimicrobials.[13] DOT is the preferred metric for paediatric antimicrobial consumption, as it is not impacted by dosage adjustments related to body weight variations, making it more accurate for paediatric settings.[13] The

VRESIST studies were unable to calculate DOT, given the information systems in participating hospitals. Consequently, all antimicrobial consumption were reported as DDD. This factor may have introduced some bias in comparisons between time periods or groups. However, the proportion of paediatric presentations were similar before and after intervention across hospitals in both VRESIST B and C hospitals. Finally, the DDD metric also does not completely reflect good stewardship practices, as it does not account for antimicrobial spectrum. For example, Cefazolin and Metronidazole in an intra-abdominal infection would double the DDDs of using Meropenem.

Despite the limitations of the DDD metric, the findings from the review as well as VRESIST studies provided important insights into antimicrobial consumption in Vietnamese hospitals. These data are vital for benchmarking antimicrobial consumption against other hospitals, both nationally and internationally, to identify areas of concern. Additionally, it helped in tracking trends over time, allowing for an evaluation of the impact of intervention.

Other complementary approaches for assessing consumption include measuring the proportion of antimicrobials relative to total drug use. Studies included in the systematic review reported that 67% to 77% of hospital inpatients received antibiotics. Similarly, a high proportion of inpatients in district hospitals in VRESIST B and C were on antimicrobials, ranging from 55% to 60%. Although lower than the proportions observed in the systematic review, proportions of inpatients in district hospitals receiving antimicrobials remain significantly higher than in other countries, where antimicrobial use was reported at 37% across all levels of Australian hospitals[14] and 49.5% in the USA[15]

Another key framework relevant to antimicrobial consumption and AMS is the WHO “AWaRe” (Access, Watch, and Reserve) classification system.[16] “Access” antibiotics are first-line treatments for common infections with lower resistance potential, “Watch” antibiotics, broader-spectrum agents

recommended for limited use, and “Reserve” antibiotics, last-resort options reserved for treating multidrug-resistant infections.[16] To encourage rational antibiotic use, WHO has set a target for at least 60% of antibiotic use in healthcare settings to come from the "Access" category.[17] Some studies included in the systematic review (Chapter 2) reported antibiotic use by “AWaRe” categories. Among those, "Access" antibiotics were the most commonly used in both hospital inpatient and outpatient settings. However, our studies found a higher proportion of "Watch" antibiotics being used in district hospitals, compared to “Access” antibiotics. In the before-and-after study (Chapter 3), an improvement was observed with a reduction in the proportion of "Watch" antibiotics, and an increase in the proportion of "Access" antibiotics. No difference in the proportion of AWaRe categories was observed in the RCT (Chapter 5). Third-generation cephalosporins were the most common antibiotics prescribed across all diagnoses, followed by combination beta-lactam/beta-lactam inhibitors. Carbapenem use was reassuringly still low.

Total antimicrobial cost was also a commonly reported outcome in the literature and often used as an indirect marker of total consumption. However, in many healthcare settings, particularly in district hospitals with limited data systems, cost data was typically based on procurement records rather than actual usage. This means that reported antimicrobial costs reflected the amount purchased rather that what was actually administered to patients, making it a less precise measure of consumption. Other health economic outcomes, such as cost-effectiveness, cost-utility, and cost-benefit analyses consider the benefits gained relative to antimicrobial expenditure. However, these measures have yet to be reported for studies of AMS in Vietnam.[18] The systematic review demonstrated that antibiotics accounted for 31% (95%CI 26, 36%, I^2=99.8%) of total drug costs in a hospital, which is similar to the literature.[19] In the VRESIST studies, we compared the differences in formulary costs of antimicrobials that were dispensed by pharmacy before and after AMS interventions in both VRESIST studies (described below).

Other indicators of antimicrobial consumption, such as antimicrobial mass (e.g., in milligrams or grams), average hospital length of stay, and prescribed daily doses (PDD) were not undertaken as a part of this body of research, due to the lack of access to such data in district hospital settings. These measures have however been successfully collected in other contexts.[20-22] Collectively, understanding current usage levels enable the design of targeted, practical, and resource-appropriate AMS interventions for district hospitals to be incorporated into policy.

Appropriateness in antimicrobial prescribing

The appropriateness of antimicrobial prescribing was addressed in Chapters 2, 3 and 5. Antimicrobial prescribing appropriateness is widely regarded as a more meaningful measure of antimicrobial use and the effectiveness of an AMS program.[12] A comprehensive assessment of antimicrobial prescribing – considering choice, dose, route, duration and compliance to guidelines – should be conducted using validated, standardised audit tools. Additionally, reference guidelines should be up-to-date, evidence-based and tailored to local resistance patterns. However, in LMICs, resource constraints often make such comprehensive evaluations challenging. Antimicrobial guidelines are often developed without a particular eye on AMS principles, leading to inconsistencies in ensuring appropriate prescribing.[12] As a result, they often lack the quality and rigor needed to serve as reliable benchmarks for antimicrobial appropriateness.

This challenge became evident during the pre-implementation phase of our studies, where considerable variation was observed between the antimicrobial recommendations included in local guidelines used in different hospitals. To address this variability, we developed and implemented standardised antimicrobial guidelines for indications common to district hospitals. These were based on the Vietnamese Ministry of Health (MoH) guidelines[23] and informed by local antibiograms that had been derived from tertiary hospital data. This introduced a limitation, as these guidelines that

were last updated in 2015, and offered a wide range of antimicrobial choices for some conditions. Some of these were inconsistent with best practice in other settings, from an AMS perspective. This finding underscores the need for national antimicrobial guidelines to be evidence-based, appropriate to the local setting and integrates AMS principles.[24]

The audit tool used to assess appropriateness in antimicrobial prescribing in Chapters 3 and 5 was the validated Hospital National Antimicrobial Prescribing Survey (Hospital NAPS) tool from Australia.[25] This tool has been widely implemented in various healthcare settings across Australia, Canada, Bhutan, Malaysia, and Fiji and has been shown to improve appropriate antimicrobial prescribing across different healthcare levels.[25-27] Hospital NAPS provides a structured framework for evaluating antimicrobial prescribing based on indication, choice, dose, route of administration, duration, spectrum of activity, compliance with guidelines, allergies, surgical procedures, and antimicrobial stop date to enable systematic assessment.

The systematic review revealed a wide variation in inappropriate prescribing rates in Vietnam, ranging from 30% to 90%, with a pooled estimate of 63% (95% CI 47-79%). These rates differed across healthcare and community settings, with each study comparing prescribing practices against a different antimicrobial guideline or local antibiogram. Audit tools used to evaluate appropriateness, were mostly developed specifically for each study. In the VRESIST studies, the proportion of inappropriate prescribing in district hospitals using the Hospital NAPS audit tool was 78-80% in VRESIST B (Chapter 3) and 60-90% in VRESIST C (Chapter 5).

High levels of inappropriate antimicrobial prescribing can be attributed to several factors. These include patient expectations for antibiotics,[28] clinician approach to risk amidst diagnostic uncertainties stemming from limited access to microbiological testing[29] (which often result in

broader-spectrum and prolonged treatments), a lack of sufficient knowledge and awareness about AMS principles among healthcare providers,[29] and incentives to increase antimicrobial use from pharmaceutical and insurance companies.[28,30]

The detailed data collection using the Hospital NAPS audit tool (Chapter 3 and 5) also allowed us to analyse reasons for inappropriate antimicrobial prescribing, including incorrect route of administration, overly broad- or narrow-spectrum antimicrobial choice, incorrect dosing, and mismatches with allergies or microbiology results. This information was crucial in guiding the direction of AMS interventions. For instance, underdosing of antibiotics was commonly observed in the NAPS audits. Underdosing can contribute to AMR by applying selective pressure and promoting the emergence of antibiotic-resistant strains.[31] To address this, education on appropriate dosing was incorporated into training workshops.

Another key finding was the preference for intravenous (IV) antibiotics, despite guideline recommendations favouring oral administration for most common infections in district hospitals. While IV administration does not inherently cause AMR, it tends to involve broader-spectrum antibiotics, is often used in combination with other antibiotics, and achieves higher drug concentrations – all of which increase selective pressure leading to resistance.[32] AMS strategies such as de-escalation and IV-to-oral switch programs are essential in optimising antimicrobial use in district hospitals in Vietnam.

Additionally, the Hospital NAPS audit tool enabled ward-level analyses, identifying trends in inappropriate antimicrobial prescribing. A particularly high proportion of inappropriate prescriptions was observed in paediatric wards, ranging from 76% to 95% across both studies. The most common issue we identified was the use of antibiotics in viral infections, where antibiotics provide no benefit.

This pattern of inappropriate prescribing for viral illnesses has also been reported in other paediatric inpatient settings in Vietnam as well. For example, a study in a tertiary hospital in Ho Chi Minh city found that 90.1% of paediatric patients were prescribed antibiotics inappropriately,[33] while another study reported 68.2% of intravenous antibiotics were inappropriately administered to children with "non-severe" pneumonia in Central Vietnam.[34] These findings highlight the widespread issue of inappropriate antimicrobial use within paediatric populations.

Another area of concern was the inappropriate use of antibiotics seen in the surgical and obstetrics and gynaecology wards. This was primarily driven by the routine use of prolonged surgical and procedural prophylaxis. In both VRESIST studies, antibiotics initiated as prophylaxis for a surgery were almost always continued post-operatively beyond 24 hours, despite medical records indicating no signs of post-operative infection. This unnecessary empirical use contributed to the high rates of inappropriate prescribing in these wards. Similarly high rates of inappropriate surgical prophylaxis have been reported in previous studies, although definitions of appropriateness vary between studies.[35,36] Mothers undergoing spontaneous vaginal deliveries were also frequently prescribed antibiotics orally or intravenously despite the absence of a clinical infection. According to Vietnamese Ministry of Health (MoH) guidelines, prophylactic antibiotics should be limited to specific situations, such as third- or fourth-degree perineal tears, pre-operative prophylaxis for Caesarean sections, or selective use in instrumental deliveries.[23] However, our findings across both studies indicate that routine practice diverged significantly from these recommendations, with nearly all patients undergoing normal vaginal deliveries receiving antibiotics unnecessarily.

A key contributing factor to this misuse of antibiotics in surgery may be surgeons' lack of trust in infection control practices. A qualitative study performed following our studies found that doctors reported "poor hygienic environment" of health facilities, inducing fear of infection, which led to

prescription of antibiotics as a preventive measure (McKinn et al, unpublished). Published literature have also reported surgeons admitting to using antibiotics as a "substitute for infection control" due to concerns over operating theatre hygiene and fear of infection transmission amongst the overwhelming patient numbers.[37] The WHO strongly recommends against the use of antibiotics as a replacement for proper infection prevention and control (IPC) measures,[38] however, this practice remains widespread in LMICs.

The findings cumulatively provide a comprehensive assessment of inappropriate antibiotic prescribing across various clinical settings, as well as specific problem areas in antimicrobial prescribing through the VRESIST audit findings.

Multidrug-resistant organism carriage in district hospital inpatients

Another important aspect to the AMR discussion is the prevalence of multidrug-resistant organism (MRO) carriage, which was addressed in Chapter 4. A high prevalence of MROs has been reported in several studies involving hospitalised patients and the community in Vietnam,[39-43] however, data on district hospitals are lacking. Our study addressed this critical gap by evaluating the prevalence of common MROs, including Extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales, Carbapenemase-producing Enterobacterales (CPE) and Methicillin-resistant *Staphylococcus aureus* (MRSA) carriage in inpatients in four district hospitals. Additionally, we examined their antimicrobial susceptibility profiles and performed genotypic analysis.

Colonisation with ESBL-producing Enterobacterales or CPE is the main risk factor for subsequent infection, particularly in hospitalized and immunocompromised patients.[44,45] Not only that, persons colonised with MRO also serve as an important source of transmission to other people. These

infections were associated with higher morbidity and mortality, prolonged hospital stays, and increased healthcare costs due to limited treatment options. The failure to respond to first-line antimicrobial therapy in patients with undetected MRO as a causative pathogen can result in delayed effective treatment, leading to worse clinical outcomes.[46]

Colonisation with ESBL-producing Enterobacterales(bla_{CTX-M}) in the VRESIST study was high at 76%, exceeding previously reported rates both in tertiary hospital settings (64%) [43] and the community (51%).[47] This finding is consistent with evidence suggesting that MRO prevalence has been increasing over time.[48] In contrast, the prevalence of CPE (2.7%) and MRSA (3.0%) carriage found in district hospital inpatients in our study was much lower compared to previous reports, where 52% of inpatients in a Vietnamese tertiary hospital were colonised with carbapenem-resistant Enterobacterales (CRE)[41] and 34% of the community had nasopharyngeal MRSA carriage.[49] These findings highlight the importance of continuing comprehensive cross-sector surveillance nationwide to monitor differences in colonisation prevalence and track trends more effectively.

A few possible reasons for the lower prevalence of CPE and MRSA colonisation include lower antimicrobial consumption, as observed in the earlier findings of the VRESIST studies, compared to tertiary hospitals. Antibiotic use is a well-established risk factor for both CPE and MRSA carriage,[50,51] which may explain this difference. Additionally, this study was conducted just after a period of prolonged community isolation due to the COVID-19 pandemic, which resulted in lower hospital occupancy. Reduced social interaction and fewer hospital admissions may have unintentionally served as infection control measures, contributing to the observed lower prevalence.

High levels of antibiotic resistance were observed across all MROs to broad-spectrum antibiotics such as ciprofloxacin and cefepime. This was particularly concerning in the district hospital setting.

Ciprofloxacin is a common empiric treatment in urinary tract infections and infective exacerbations of chronic obstructive pulmonary disease. However, with 77% of MROs isolates exhibiting resistance to ciprofloxacin, empiric treatment for infections caused by these organisms may be ineffective. This challenge is further exacerbated by the lack of microbiological diagnostic capabilities in district hospitals, preventing clinicians from confirming MRO involvement in infections.

Having established the patterns of antimicrobial use, prescribing appropriateness, and MRO prevalence in district hospital settings, the next section examines the impact of antimicrobial stewardship (AMS) interventions in addressing these challenges.

The effect of antimicrobial stewardship (AMS) interventions

AMS interventions were addressed across all chapters in this thesis. The systematic review and meta-analyses (Chapter 2) evaluated the available evidence for AMS interventions in Vietnam. Published studies of AMS interventions implemented in human healthcare settings and the community were presented, as well as the impact of AMS interventions upon various outcomes. Outcomes of these studies predominantly included antimicrobial consumption and appropriateness of therapy. Other measures reported in these studies included the proportion of patients taking antibiotics, healthcare worker knowledge, prescribing practices of prescribers, mortality, cost, length of therapy, prevalence of surgical site infection, and compliance with guidelines.

Due to the heterogeneity of the outcome measures and AMS interventions themselves, pooled estimates of effect were not possible. Most studies examined the impact of bundled AMS interventions on prescribing appropriateness, with findings generally showing improvement post-implementation. Only four studies investigated the impact of AMS on standardised antimicrobial

consumption metrics (DDD and DOT) – where two studies reported a reduction,[52,53] while the other two showed no significant change.[54,55]

The AMS interventions studied were primarily before-and-after designs. Three RCTs evaluated laboratory diagnostic strategies, such as C-reactive protein testing and early microbiological organism identification from clinical samples, to improve prescribing appropriateness. Additionally, one RCT assessed the impact of an educational intervention on doctors' knowledge, attitudes, and prescribing practices.[56] Most studies were conducted in tertiary hospital settings, including national and provincial-level hospitals in Vietnam. Only one study evaluated the impact of AMS interventions in a district hospital,[56] another in the community,[57] and none in commune health centres or in the private sector.

Both intervention studies (VRESIST B and C) addressed gaps in the existing literature by implementing AMS interventions in district hospitals in north and south Vietnam (Chapters 3,4 and 5). These studies evaluated the effect of AMS interventions upon outcomes including antimicrobial consumption, appropriateness of prescribing, costs and prevalence of antimicrobial-resistant organisms.[12] To strengthen the evaluation, the cluster RCT (VRESIST C) was conducted following the before-and-after study (VRESIST B) to overcome confounding factors such as seasonal variations, individual hospital-specific changes, and the impact of COVID-19 on hospitalisations. By randomising hospitals into intervention and control groups, the study ensured that temporal trends and external influences affected both groups equally. This design reduced bias, enhanced generalisability, and strengthened causal inference, making it a more rigorous method for evaluating the true impact of AMS interventions in district hospitals in Vietnam.

The AMS interventions implemented in the studies incorporated recommendations from WHO, the Vietnam MoH and Australian AMS frameworks,[58-60] which were adapted to the local context. Additionally, a validated audit tool (Hospital NAPS) was used to assess antimicrobial prescribing.[25] Together, these elements made the VRESIST studies a robust, comprehensive assessment of the effectiveness of AMS interventions in district hospitals in Vietnam.

A six-month AMS intervention in VRESIST B (Chapter 3) led to a modest reduction in antimicrobial consumption of 4.0 (95%CI : 2.3, 6.2) DDD/100 bed-days per month over the intervention period. However, this effect was not seen in the RCT, where comparator sites were used. This difference may be attributed to external factors influencing the reduction observed in the before-and-after study. As for prescribing appropriateness, both studies showed an increase in inappropriate prescribing pre- and post-intervention: from 79% to 80% in VRESIST B, 78% to 82% in the intervention group of VRESIST C, and 72% to 81% in the control group in VRESIST C. The RCT design provided a more robust assessment, as the larger number of sites reduced the likelihood of confounding due to hospital-level differences. Additionally, the inclusion of control groups helped balance differences between groups and mitigated the impact of temporal factors as potential confounders. This design demonstrated a smaller increase in inappropriate prescribing in the intervention group compared to the control group—a distinction that was not apparent in the before-and-after study.

We postulate that the increase in inappropriate prescribing across all hospitals may partly be attributed to the timing of both VRESIST studies at the end of COVID-19 restrictions. During this period, a surge in hospital presentations occurred, with unnecessary antibiotic prescribing practices from the pandemic period likely persisting.[2] It is important to monitor longitudinal trends in prescribing appropriateness to identify and address these prescribing patterns.

Using the Hospital NAPS audit tool, subgroup analyses captured areas where prescribing practices improved, however, these findings should be interpreted with caution, as the smaller sample size may limit representativeness and may not fully reflect actual prescribing trends. For example, AMS interventions improved prescribing appropriateness in obstetrics and gynaecology patients in VRESIST B, and for paediatric and emergency department and Intensive care unit patients in VRESIST C. As for the reasons for inappropriateness, VRESIST B study demonstrated lower proportions of broad-spectrum antibiotic use and prolonged antimicrobial durations following AMS intervention. In contrast, VRESIST C study showed an improvement in dosing practices. A large proportion of prescriptions were also found to be non-compliant with guidelines, with minimal improvement following intervention in both VRESIST studies.

For the secondary outcome measures, no change was observed in formulary costs of antimicrobials post-intervention in the before-and-after study (Chapter 3), despite a reduction in total antimicrobial consumption. In contrast, the cluster RCT (Chapter 5) showed a modest reduction in formulary costs of USD $1300 (95%CI -$2314, -$284) per month in the intervention group, compared to the control group, even though no difference in antimicrobial consumption was detected. Modest reduction in costs need to be interpreted carefully, given the wide variability in drug costs.

Reassuringly, inpatient mortality rates did not differ between groups in the RCT, and in fact there was a mortality rate reduction in the before-and-after study. This reinforces the effectiveness of AMS interventions in optimising antimicrobial use while maintaining patient safety. However, this should be interpreted cautiously given the modest reduction in inappropriate prescribing and the studies' limited power to detect small differences. Studies included in the systematic review (Chapter 2) also reported no change in mortality outcomes.

As for the prevalence of MROs (Chapter 4), while no significant change was observed in ESBL or CPE prevalence following AMS interventions, a reduction in nasal MRSA carriage was noted from 5% to 1% [-4.0% (95% CI: -7.2, -0.7), p=0.04]. However, given the low overall prevalence of MRSA carriage in this setting, this reduction should be interpreted with caution, as it may be influenced by temporal factors rather than a direct effect of AMS interventions. Differences in patient characteristics between baseline and post-intervention groups may have contributed to a biased effect estimate, further complicating the interpretation of this finding.

Quantifying the relative contribution of AMS interventions in reducing MRO prevalence remains challenging, as MRO colonisation and infection rates are influenced by multiple factors, including antimicrobial use, hospital IPC practices, community prevalence, and environmental reservoirs.[61] A systematic review and meta-analysis reported reductions in infections and colonisation with multidrug-resistant Gram-negative bacteria, ESBL-producing organisms, MRSA, and *Clostridium difficile* infections following AMS interventions.[62] However, a Cochrane review found that evidence across studies remains inconclusive, with results varying based on study design, setting, and intervention type.[63] Antimicrobial use is a key determinant of MRO prevalence, with reductions in MRO rates typically observed only when antimicrobial consumption decreases. [64] In the VRESIST B study, this reduction was modest. Despite variations in study outcomes, there is strong consensus in the literature that AMS alongside IPC measures, particularly hand hygiene, is critical for reducing MRO prevalence.[62,63]

Summary of findings

In summary, VRESIST B and C only showed modest improvements in antimicrobial consumption, prescribing appropriateness and prevalence of MROs with the implementation of an AMS program. The short duration of the intervention may have limited its impact, although the VRESIST model focused upon building in-house capacity to sustain AMS efforts beyond the study period. Conducting follow-up assessments across all hospitals would help determine whether these interventions lead to long-term, sustainable improvements. Finally, these findings demonstrate that AMS interventions alone have limitations. Without structural changes, as explored in the next section, the potential for AMS to drive lasting improvements, remains constrained.

The VRESIST studies and systematic review identified key enablers and barriers to AMS in Vietnam, providing insights that could inform policy and implementation strategies in Vietnam and other similar LMIC settings.

Enablers for implementing AMS identified in VRESIST studies

The successful implementation of AMS interventions depends on multiple health system components working together. The WHO Health System Building Blocks framework[65] provides a structured approach to understanding key enablers that support AMS efforts, particularly in resource-limited settings like district hospitals in Vietnam. This framework identifies six core building blocks essential for strengthening health systems: leadership and governance, health workforce, information systems, service delivery, medicines and technologies, and financing.

In the context of this study, three of these building blocks—leadership and governance, health workforce, and service delivery—were particularly crucial in facilitating AMS implementation and

sustainability. By examining these enablers through the WHO framework, we can better understand how AMS interventions were successfully implemented in the VRESIST studies and how they can be scaled and sustained in similar settings in Vietnam and other LMICs.

Leadership and governance

A supportive policy environment is a key enabler of successful AMS implementation, aligning with the leadership and governance pillar of the WHO health system framework. Prior to commencing the two AMS intervention studies, the Vietnamese Ministry of Health (MoH) released "Decision 5631/QD-BYT" in 2020.[59] This national policy document provided high-level guidance for implementing AMS across all levels of the healthcare system, which was mandated nationwide. However, operational guidance for district-level health facilities had not yet been developed. The before-and-after study (VRESIST B) bridged this gap by developing hands-on guidance for district staff, making AMS implementation more practical and feasible. The AMS intervention studies were designed in alignment with this national policy, as well as integrating WHO recommendations and Australian AMS programs.[58,60]

Service delivery and health workforce

Effective stakeholder engagement was another critical enabler of AMS implementation in VRESIST B and C, aligning with the WHO service delivery and health workforce building block. Throughout the AMS studies, hospital administrators and healthcare workers (HCWs) demonstrated strong engagement. Hospital leaders valued the practical support provided by the study team, which helped them align with performance mandates under Decision 5631/QD-BYT. Hospital leadership engagement within AMS committees and teams provided additional motivation, encouraging stewardship efforts to not only implemented, but also sustained over time. Similarly, HCWs comprising doctors, nurses and pharmacists showed keen interest in AMS interventions, as

evidenced by high participation rates of between 50 to 80% in training workshops. Doctors actively engaged in audit and feedback sessions with insightful discussions and demonstrated a proactive attitude in integrating stewardship practices into their clinical workflows.

The engagement of hospital pharmacists was another key strength of the two VRESIST studies. In Australia, clinical pharmacists contribute significantly to antimicrobial decision-making given their training in pharmacology and stewardship principles. However, in Vietnamese district hospitals, the pharmacists are underutilised, largely due to variations in qualifications and AMS experience.[66] In the VRESIST studies, hospital clinical pharmacists – who generally hold Bachelor's or Master's degrees – were actively involved in AMS teams, particularly in the audit and feedback process. This approach not only provided hands-on AMS training but also strengthened pharmacists' roles within hospital AMS initiatives. Hospital administrators, doctors and pharmacists recognised this shift as a transformative step toward enhancing the role of pharmacists in AMS, similar to what's been reported in studies in Vietnam and other LMICs. [66,67] Finally, the VRESIST studies strengthened multidisciplinary collaboration, bringing together researchers, doctors, pharmacists, and nurses, to work toward a shared goal of improving hospital practices and patient care.

Barriers to implementing AMS identified in VRESIST studies

The VRESIST studies identified several systemic, cultural, and resource-related barriers to AMS implementation in district hospitals. These challenges can also be understood through the WHO Health System Building Blocks Framework, particularly in relation to health technologies, essential medicines, service delivery, information and financing.

Limited Access to Microbiology Services (Health technologies barrier)

A limitation identified in the VRESIST studies was the lack of access to microbiology services at the district level. Without bacterial culture and susceptibility testing, clinicians could not confirm diagnoses or tailor antibiotic therapy, leading to empirical use of broad-spectrum antibiotics.[68] This may have prolonged treatment durations, increasing unnecessary antimicrobial exposure, and heightened selection pressure for resistance. Fear of patient deterioration can also drive defensive prescribing, especially when bacterial infection couldn't be confirmed or excluded.[69] While laboratory support is crucial for optimising antibiotic selection, many early gains in stewardship come from reducing unnecessary antibiotic use based solely on the lack of clinical indication.[70]

Drug Shortages and Antimicrobial Supply Chain Issues (Essential medicines barrier)

Inconsistent antimicrobial availability due to supply chain disruptions presented another significant challenge to AMS efforts in VRESIST studies. Drug shortages of first-line antibiotics forced clinicians in the district hospitals to prescribe suboptimal or inappropriately broad-spectrum alternatives, undermining the effectiveness of stewardship interventions.[71]

Factors affecting prescribing practices (Service delivery barrier)

Prescribers in VRESIST studies either used (a) experience-based (i.e., based upon the historical practice of doctors and their colleagues), or (b) guideline-based approaches (following study or national guidelines) in their daily prescribing practice.[24] Experience-based prescribing was reported in many district hospitals, where junior clinicians felt compelled to follow the prescribing habits of senior medical staff, even when these practices conflicted with AMS guidelines. This has also been reported in the literature.[72] This top-down approach hindered stewardship efforts, as established prescribing norms often took precedence over evidence-based interventions. When a guideline-based approach was used, the usage of multiple guidelines with differing recommendations still led

to variability in prescribing practices.[24] Guidelines also offered a wide range of antimicrobial choices that often did not align with best stewardship practices, contributing to inconsistent prescribing practices.

Challenges in Infection Prevention and Control (Service delivery and information barrier)

Effective infection prevention and control(IPC) is an important contributor to successful AMS, as reducing the need for antibiotics depends on preventing healthcare-associated infections (HAIs). The implementation and effectiveness of IPC policies at participating districts were not evaluated in VRESIST studies. Clinicians reported to use extended antibiotic prophylaxis, particularly in surgical and obstetrics patients, due to concerns over inadequate infection control measures (Doshi, personal communication). This has been reported in the literature before.[38,73] In the absence of effective IPC policies, hospitals face challenges in creating environments conducive to the confident application of AMS interventions. Measures such as hand hygiene, thorough room sterilisation, and the use of personal protective equipment are essential in reducing the transmission of pathogens within healthcare settings.

Impact of the COVID-19 Pandemic (Service delivery barrier)

During the conduct of the VRESIST studies, the COVID-19 pandemic disrupted routine healthcare service delivery. The pandemic created additional barriers to implementing AMS programs worldwide, including LMICs.[74] Healthcare resources were redirected towards pandemic response efforts, including COVID-19 case management, infection control, and vaccination campaigns,[75] naturally deprioritising AMS activities.

Conversely, a recent study on outpatient visits reported a significant decline in antibiotic prescribing from 96.0% in 2019 to 67.3% in 2021. During the same period, presentations with acute respiratory infections during that time also dropped from 47.3% in 2019 to 40.7% in 2021.[76] This reduction, driven by social distancing, public pandemic guidance, changes in healthcare seeking behaviour and changes to clinical guidelines showed that prescribing behaviours are amenable to change and could inform AMS strategies.[76]

Insurance and Government Health Structures (Financing barrier)

Public healthcare and health insurance systems can contribute to perverse incentives for inappropriate antibiotic use. In Vietnam, hospitals generate revenue from both insurance fees and out-of-pocket payments, fostering a profit-driven approach to patient care.[77] This financial model may incentivise doctors to prolong antibiotic courses or prefer intravenous administration to justify hospitalisations. A qualitative report following the VRESIST studies (McKinn et al., unpublished) found that doctors felt restricted in prescribing oral antibiotics, as doing so often triggered scrutiny from health insurance companies, questioning why the patient had not been discharged. Similarly, admitting patients for observation without prescribing medication was questioned. As a result, antibiotics were sometimes inappropriately prescribed to prevent health insurance reimbursement rejections. These financial and administrative pressures encourage prolonged antibiotic use, making it difficult to align clinical decision-making with AMS principles.

Policy implications

Direct policy implications of VRESIST studies' findings

The findings from this study provide important policy-relevant insights into AMS implementation in district hospitals in Vietnam. At a national level, preliminary findings from VRESIST B and C (Chapter

3,4 and 5) contributed to the development of the "Handbook for Guidance on Implementation of Antibiotic Use Management Program for District Hospitals (No. 2115/QD-BYT)".[78] The handbook also aligned with Decision 5631/QD-BYT document,[59] which mandated AMS implementation across all hospitals. The handbook applied the AMS intervention package used in VRESIST studies as it had demonstrated feasibility and engagement amongst key district hospital stakeholders. It was designed to be practical and adaptable, recognising constraints of district hospitals.

In particular, the handbook provided step-by-step recommendations on establishing AMS committees and teams, conducting education and training workshops, implementing audit-and-feedback mechanisms, and using data analysis to drive AMS improvements in district hospitals, as demonstrated in the VRESIST studies. This policy document was distributed nationwide in May 2023.

Generalisability, scalability and adaptation across healthcare settings

This research has significant policy implications for district hospitals across Vietnam especially. The inclusion of multiple district hospitals across both northern and southern Vietnam strengthens the generalisability of the findings within similar healthcare environments, making the study highly relevant for scaling up AMS initiatives in district hospitals nationwide. Adaptation and context-specific modifications may be necessary for effective implementation in different settings depending on resources available.

For instance, AMS strategies such as use of antimicrobial guidelines and audit-and-feedback mechanisms could be extended to commune health centres in Vietnam, which primarily provide outpatient and primary care services. The successful implementation of the Hospital NAPS audit tool in general practice and aged care settings in Australia, as well as in community hospitals in

Canada,[25,79,80] demonstrates the feasibility of applying AMS frameworks beyond hospital settings. Meanwhile, this AMS program also provides a strong foundation for tertiary hospitals, where better resources could enable stronger multidisciplinary AMS teams, more frequent audits and feedback, and structured education initiatives. Furthermore, we postulate that the VRESIST AMS intervention model could have broader applicability to other LMICs facing similar challenges in antimicrobial use, workforce shortages and limited diagnostic capacity.

Although the intervention required coordination and time investment—particularly during the initial implementation phase—it demonstrated that AMS programs are feasible in district hospitals in Vietnam when supported by a structured strategy. In this study, up to five full-time research staff provided centralised support across all sites, while local hospital staff contributed up to 10 hours per week during peak periods to conduct audits, deliver feedback, facilitate training, and collect monitoring data. Importantly, integrating activities into existing clinical workflows, engaging hospital leadership, and appointing AMS focal points enabled the intervention to be sustained with minimal disruption to routine care. These findings suggest that with appropriate planning, local ownership, and adaptation to available resources, similar AMS models can be implemented more broadly without requiring extensive external support.

Aligning VRESIST Findings with Vietnam's National Action Plan on AMR

The findings from the VRESIST studies provide evidence to support the implementation of a new national action plan on AMR. The new Vietnamese National Action Plan on AMR (2023–2030), with a vision extending to 2045, builds on the initial 2013–2020 strategy.[81] The National Action Plan sets actionable targets for raising AMR awareness, strengthening drug resistance and antimicrobial consumption monitoring, improving specialty training, enhancing IPC compliance, and expanding AMS programs across human and animal health. By 2045, the plan aims to establish a robust

surveillance system for AMR, antibiotic supply and consumption, and AMS implementation comparable to those in developed countries.

A key priority of this action plan is enhancing national surveillance systems, which is critical for tracking antimicrobial consumption, MRO colonisation, and infection rates. Findings from VRESIST B and C (Chapters 3 and 5) reinforced the importance of standardised surveillance and benchmarking systems, such as a national antimicrobial prescribing audit modelled after Hospital NAPS in Australia, to provide policymakers with data-driven insights for evaluating AMS effectiveness and ensuring hospital accountability.

Expanding access to microbiology services in district hospitals is another crucial policy priority as previously mentioned. Beyond improving individualised antimicrobial selection through culture and drug susceptibility testing, enhanced microbiological capacity will also enable systematic tracking of local resistance patterns, providing essential data to inform district-level AMS strategies[58], as highlighted in our study on MRO prevalence (Chapter 4). The National Action Plan acknowledges this gap, but its success will depend on sufficient funding and targeted investment in microbiological testing and workforce capacity.

The findings in this thesis also underscore the importance of regularly updating national antimicrobial guidelines to align with real-time resistance patterns and stewardship principles. While the Vietnamese National Action Plan recognises this, effective implementation will require systematic guideline revisions, integration of local surveillance data, and active engagement of high-use specialties (e.g., surgery, paediatrics, and obstetrics & gynaecology) where unnecessary or prolonged antibiotic use is common. Moreover, updating guidelines alone is insufficient; adherence is equally essential to ensure that AMS policies translate into clinical practice. Educational initiatives,

including face-to-face outreach, small group discussions, and audit-and-feedback, have been shown in a systematic review to improve clinical guideline adherence among prescribers.[82]

This research reinforces the importance of positioning AMS not only as a strategy to combat AMR, but as a core component of patient safety and quality of care. Even in the absence of measurable short-term changes in AMR, AMS programs can improve clinical decision-making, reduce unnecessary exposure to antimicrobials, and minimise risks of adverse events.

Sustainability and Future Directions

While this study was conducted within a research-supported framework, most elements were designed to promote sustainability, including the use of local AMS committees and teams, integration of audit feedback and educational sessions into existing hospital workflows, as well as engagement with hospital leadership. Encouragingly, informal follow-up with participating sites has indicated that all hospitals have continued audit and feedback activities beyond the trial period by the AMS committees and teams, had better engagement with clinical pharmacists and had ongoing educational activities. At a broader level, findings from this study are being used to inform discussions with regional health authorities regarding the scale-up of AMS programs in additional district hospitals in other provinces.

The next phase of research will focus on supporting this scale-up, adapting the intervention for wider implementation across Vietnam's district-level facilities, and evaluating long-term sustainability within routine health system structures. These efforts align with national AMR policy priorities and aim to embed AMS more systematically across the health system.

Future research

Several important research questions emerge from this thesis. First, reassessing antimicrobial consumption, appropriateness of antimicrobial prescribing, MRO prevalence as well as secondary outcomes of mortality and costs across the 20 district hospitals (four in VRESIST B, 16 in VRESIST C) would provide valuable insights into the sustained effectiveness of the AMS program. Additionally, extending the intervention period beyond the initial four to six month period timeframe would be valuable for evaluating the longer-term effectiveness of AMS interventions.[83,84] Such an approach would contribute to a deeper understanding on how AMS programs can be embedded into routine clinical practice in resource-limited settings.

This thesis has mainly focused on persuasive strategies (Chapter 1- AMS interventions), such as audit and feedback, use of antimicrobial guidelines and educational initiatives. Exploring restrictive AMS strategies, such as requiring pre-approval for certain broad-spectrum antibiotics,[58] may be beneficial. However, this approach is not commonly implemented in lower levels of healthcare, especially in LMICs. This is due to a number of factors including limitation in human resources, potential delays in patient care and also potential breakdowns in communication and trust between infection specialists and clinical teams.[63] An example of a method used widely in Australian hospitals is antimicrobial approval systems which use a traffic light system, which serve as a visual representation of antimicrobial restrictions.[85] Green antimicrobials can be prescribed freely, yellow prescribed without restriction for certain conditions or for certain duration (usually 48 to 72 hours) before approval is required, and red antimicrobials requiring an approval from an Infectious Diseases physician or Clinical Microbiologist prior to use. This approach could be tested in within district hospitals in Vietnam.

Future studies could prospectively collect additional outcomes such as Days of Therapy (DOT), Length of Therapy (LOT) and length of stay into outcome assessments to provide a more nuanced understanding of antimicrobial usage patterns. These measures offer insights into the duration and intensity of antimicrobial exposure, facilitating more precise evaluations of AMS interventions.[12] This will require additional data collection tools, given the limitations of established information systems in Vietnamese district hospitals (described above). Measurements of cost-effectiveness[86] would further quantify the benefits of AMS programs in terms of both health outcomes and cost savings. Expanding outcome measurements to include the prevalence of hospital-acquired infections, such as *Clostridiodes difficile* infections and central line-associated bloodstream infection alongside MRO prevalence, would provide a more comprehensive evaluation of the impact of high antimicrobial consumption in hospitals, capturing both antimicrobial resistance trends and infection-related patient outcomes.[62,87]

As previously discussed, IPC practices are also important tools in combatting AMR. Assessing the impact of IPC interventions such as improvements in hand hygiene, the appropriate use of contact precautions and enhanced ward cleaning on the prevalence of hospital-acquired infections and MRO colonisation would provide useful insights. Moreover, holistic programs that combine both IPC measured with AMS interventions in Vietnam could further inform best practice. Evidence from other settings suggests that such an approach reduced hospital-acquired infections and improved patient safety.[58,88] Investigating the effects of IPC and AMS interventions both independently and in combination would help determine their relative effectiveness and contribute to the development of optimised, evidence-based strategies for resource-limited settings.

Finally, adopting a “One Health” perspective is imperative for future AMS research. Implementing One Health interventions across human, animal, and environmental health sectors can address the multifaceted nature of AMR, promoting coordinated efforts to mitigate its spread across different domains. An example of this in the literature was an intensive education and training initiative in a Ugandan district across health practitioners, animal health workers and community health workers, along with primary school pupils on AMR, AMS and IPC, which led to a reduction in unnecessary antibiotic prescriptions and improved hand hygiene.[89]

Conclusion of thesis

In conclusion, antimicrobial resistance remains an urgent global health challenge, and Vietnam is no exception. This thesis has provided critical insights into the extent of AMR in district hospitals in Vietnam and identified solutions tailored to the specific constraints and capacities of the district healthcare system. The VRESIST AMS framework comprising of AMS committees and teams, antimicrobial guideline development, targeted education, and audit-and-feedback mechanisms offer a practical approach for district hospitals and other healthcare settings.

The VRESIST studies found that AMS interventions demonstrated only modest improvements in antimicrobial consumption, prescribing appropriateness, MRO prevalence and antimicrobial formulary costs in Vietnamese district hospitals. A careful stepwise approach in scale up of AMS interventions in district hospitals is advisable to justify continued investment into its implementation. However, we postulate that sustained stewardship efforts in district hospital settings will yield greater effect and achieve successes comparable to those reported in hospitals across the country, as well as globally.

References for Chapter 6

1. World Health Organisation. Antimicrobial resistance fact sheet. 2023. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance (accessed 15/7/2024).

2. Torumkuney D, Kundu S, Vu GV, et al. Country data on AMR in Vietnam in the context of community-acquired respiratory tract infections: links between antibiotic susceptibility, local and international antibiotic prescribing guidelines, access to medicines and clinical outcome. *Journal of Antimicrobial Chemotherapy* 2022; **77**(Supplement_1): i26-i34.

3. World Health Organization. Antimicrobial resistance - Western Pacific -Viet Nam. 2024. https://www.who.int/vietnam/health-topics/antimicrobial-resistance (accessed 16/08/2022).

4. World Health Organisation. ATC/DDD Toolkit. 2024. https://www.who.int/tools/atc-ddd-toolkit (accessed 23/02/2022).

5. Dellit TH, Owens RC, McGowan JE, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clinical infectious diseases* 2007; **44**(2): 159-77.

6. Limato R, Lazarus G, Dernison P, et al. Optimizing antibiotic use in Indonesia: A systematic review and evidence synthesis to inform opportunities for intervention. *The Lancet Regional Health - Southeast Asia* 2022; **2**.

7. Pharmacy Practice and Development Division. The Report on Antibiotic Utilisation in Malaysian Hospitals 2008-2017. 2020. https://pharmacy.moh.gov.my/en/documents/report-antibiotic-utilisation-malaysian-hospitals-2008-2017.html (accessed 04/072023).

8. Dat VQ. Antibiotic use in public hospitals in Vietnam between 2018 and 2022: a retrospective study. *BMJ open* 2024; **14**(8): e087322.

9. Gandra S, Trett A, Klein EY, Laxminarayan R. Is Antimicrobial Resistance a Bigger Problem in Tertiary Care Hospitals Than in Small Community Hospitals in the United States? *Clinical Infectious Diseases* 2017; **65**(5): 860-3.

10. Klein EY, Van Boeckel TP, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proceedings of the National Academy of Sciences* 2018; **115**(15): E3463-E70.

11. Gisev N, Sluggett JK. Descriptive and Drug Utilization Studies. In: Babar Z-U-D, ed. Encyclopedia of Pharmacy Practice and Clinical Pharmacy. Oxford: Elsevier; 2019: 344-55.

12. Morris AM. Antimicrobial Stewardship Programs: Appropriate Measures and Metrics to Study their Impact. *Curr Treat Options Infect Dis* 2014; **6**(2): 101-12.

13. Baier J, Höpner J, Haase R, et al. Monitoring antibiotic consumption in pediatrics. How close to reality are days of therapy and recommended daily dose methods? *The Pediatric Infectious Disease Journal* 2022; **41**(4): e126-e32.

14. National Centre for Antimicrobial Stewardship and Australian Commission on Safety and Quality in Health Care. Antimicrobial prescribing practice in Australian Hospitals Results of the 2019 Hospital: National Antimicrobial Prescribing Survey. 2021. https://www.safetyandquality.gov.au/sites/default/files/2021-04/report_-_2019_hospital_naps.pdf (accessed 22/11/2024).

15. Magill SS, O'Leary E, Ray SM, et al. Antimicrobial Use in US Hospitals: Comparison of Results From Emerging Infections Program Prevalence Surveys, 2015 and 2011. *Clinical Infectious Diseases* 2020; **72**(10): 1784-92.

16. World Health Organization. The WHO AWaRe (access, watch, reserve) antibiotic book. 2022. https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.04 (accessed 02/07/2024).

17. World Health Organisation. WHO Thirteenth General Programme of Work 2019-2023 : Target ≥60% of total antibiotic consumption being Access group antibiotics. https://www.who.int/data/gho/indicator-metadata-registry (accessed 03/07/2024).

18. Naylor NR, Zhu N, Hulscher M, Holmes A, Ahmad R, Robotham JV. Is antimicrobial stewardship cost-effective? A narrative review of the evidence. *Clinical Microbiology and Infection* 2017; **23**(11): 806-11.

19. Rüttimann S, Keck B, Hartmeier C, Maetzel A, Bucher HC. Long-term antibiotic cost savings from a comprehensive intervention program in a medical department of a university-affiliated teaching hospital. *Clinical Infectious Diseases* 2004; **38**(3): 348-56.

20. Carrique-Mas JJ, Choisy M, Van Cuong N, Thwaites G, Baker S. An estimation of total antimicrobial usage in humans and animals in Vietnam. *Antimicrobial Resistance & Infection Control* 2020; **9**: 1-6.

21. Vo DC, Mai TA, Nguyen TT, Nguyen DT, Vo TH. The use of an antibiotic order form in a tertiary hospital: Influence on physicians' prescribing patterns. *Journal of Pharmacy & Pharmacognosy Research* 2021; **9**(4): 474-83.

22. Muller A, Monnet DL, Talon D, Hénon T, Bertrand X. Discrepancies between prescribed daily doses and WHO defined daily doses of antibacterials at a university hospital. *British journal of clinical pharmacology* 2006; **61**(5): 585-91.

23. Ministry of Health Vietnam. Instructions for Use of Antibiotics - Decision No. 708/QD-BYT. Hanoi, Vietnam, 2015. https://kcb.vn/thu-vien-tai-lieu/tai-lieu-huong-dan-su-dung-khang-sinh.html (accessed 31/03/2022).

24. Pham GN, Dang TTH, Nguyen T-A, et al. Health system barriers to the implementation of the national action plan to combat antimicrobial resistance in Vietnam: a scoping review. *Antimicrobial Resistance & Infection Control* 2024; **13**(1): 12.

25. James R, Nakamachi Y, Morris A, et al. The feasibility and generalizability of assessing the appropriateness of antimicrobial prescribing in hospitals: a review of the Australian National Antimicrobial Prescribing Survey. *JAC-antimicrobial resistance* 2022; **4**(1).

26. James R, Upjohn L, Cotta M, et al. Measuring antimicrobial prescribing quality in Australian hospitals: development and evaluation of a national antimicrobial prescribing survey tool. *Journal of Antimicrobial Chemotherapy* 2015; **70**(6): 1912-8.

27. National Centre for Antimicrobial Stewardship. The National Antimicrobial Prescribing Survey. 2024. https://www.ncas-australia.org/National_Antimicrobial_Prescribing_Survey (accessed 08/04/2022).

28. Di KN, Tay ST, Sri La Sri Ponnampalavanar S, Pham DT, Wong LP. Physician's Perspectives on Factors Influencing Antibiotic Resistance: A Qualitative Study in Vietnam. *Healthcare (Basel)* 2022; **11**(1).

29. Chaw P, Höpner J, Mikolajczyk R. The knowledge, attitude and practice of health practitioners towards antibiotic prescribing and resistance in developing countries—A systematic review. *Journal of clinical pharmacy and therapeutics* 2018; **43**(5): 606-13.

30. Vu Minh D, Nguyen Thi Hong Y, Nagraj S, et al. Determinants of antibiotic prescribing in primary care in Vietnam: a qualitative study using the Theoretical Domains Framework. *Antimicrobial Resistance & Infection Control* 2024; **13**(1): 115.

31. Roberts JA, Kruger P, Paterson DL, Lipman J. Antibiotic resistance--what's dosing got to do with it? *Crit Care Med* 2008; **36**(8): 2433-40.

32. Bassetti S, Tschudin-Sutter S, Egli A, Osthoff M. Optimizing antibiotic therapies to reduce the risk of bacterial resistance. *European Journal of Internal Medicine* 2022; **99**: 7-12.

33. Minh NNQ, Toi PV, Qui LM, et al. Antibiotic use and prescription and its effects on Enterobacteriaceae in the gut in children with mild respiratory infections in Ho Chi Minh City, Vietnam. A prospective observational outpatient study. *PloS one* 2020; **15**(11): e0241760.

34. Nguyen PT, Tran HT, Fitzgerald DA, Graham SM, Marais BJ. Antibiotic use in children hospitalised with pneumonia in Central Vietnam. *Archives of Disease in Childhood* 2020; **105**(8): 713-9.

35. Van Tuong P, Xiem CH, Anh NC, Quang N. Assessment of Antibiotic Prophylaxis in Surgical Patients and Association Factors at Thu Duc District Hospital, Ho Chi Minh City, Vietnam in 2018. *Health Serv Insights* 2021; **14**: 11786329211029354.

36. Nguyen HT, Bui QTH, Vo TV, Pham HTT, Vo TD. Antibiotic use in gastrointestinal surgery patients at a Vietnamese national hospital. *BMC Gastroenterol* 2022; **22**(1): 480.

37. Nguyễn THT, Bùi KT, Phùng TH, Phạm QA. Thực trạng sử dụng kháng sinh trên người bệnh phẫu thuật và một số yếu tố ảnh hưởng tại khoa ngoại tổng hợp bệnh viện Thanh Nhàn, Hà Nội năm 2015. *Tạp chí y tế công cộng* 2016; **13**(40).

38. World Health Organisation and UNICEF. Combatting Antimicrobial Resistance through Water, Sanitation and Hygiene and Infection Prevention and Control in Healthcare. 2020. https://www.washinhcf.org/resource/combatting-amr-through-wash-and-ipc-in-healthcare/ (accessed 21/01/2025).

39. Dat VQ, Vu HN, Nguyen The H, et al. Bacterial bloodstream infections in a tertiary infectious diseases hospital in Northern Vietnam: aetiology, drug resistance, and treatment outcome. *BMC infectious diseases* 2017; **17**(1): 493.

40. Ngoc-Nga P-T, Nhut-Thang N, Hong-Ha N, Trung-Son L, To HTN, Bich-Van T-T. Drug Susceptibility and Prevalence of ESBL in Escherichia coli Isolates from Infection Patients in Can Tho General Hospital.

41. Tran DM, Larsson M, Olson L, et al. High prevalence of colonisation with carbapenem-resistant Enterobacteriaceae among patients admitted to Vietnamese hospitals: Risk factors and burden of disease. *J Infect* 2019; **79**(2): 115-22.

42. Yen NTP, Nhung NT, Phu DH, et al. Prevalence of carbapenem resistance and its potential association with antimicrobial use in humans and animals in rural communities in Vietnam. *JAC-antimicrobial resistance* 2022; **4**(2): dlac038.

43. Tran H, Nguyen B, Tran H, Tran H. A cross-sectional study of the antibiotic resistant prevalence of ESBL-producing Enterobacteriaceae in Vietnam. *Journal of Health Sciences* 2022.

44. Massart N, Camus C, Benezit F, Moriconi M, Fillatre P, Le Tulzo Y. Incidence and risk factors for acquired colonization and infection due to extended-spectrum beta-lactamase-producing Gram-negative bacilli: a retrospective analysis in three ICUs with low multidrug resistance rate. *Eur J Clin Microbiol Infect Dis* 2020; **39**(5): 889-95.

45. Pérez-Galera S, Bravo-Ferrer JM, Paniagua M, et al. Risk factors for infections caused by carbapenem-resistant Enterobacterales: an international matched case-control-control study (EURECA). *EClinicalMedicine* 2023; **57**: 101871.

46. Tumbarello M, Sali M, Trecarichi EM, et al. Bloodstream Infections Caused by Extended-Spectrum-β-Lactamase- Producing Escherichia coli: Risk Factors for Inadequate Initial Antimicrobial Therapy. *Antimicrobial Agents and Chemotherapy* 2008; **52**(9): 3244-52.

47. Nakayama T, Ueda S, Huong BTM, et al. Wide dissemination of extended-spectrum β-lactamase-producing Escherichia coli in community residents in the Indochinese peninsula. *Infection and drug resistance* 2015: 1-5.

48. Singh SR, Teo AKJ, Prem K, et al. Epidemiology of Extended-Spectrum Beta-Lactamase and Carbapenemase-Producing Enterobacterales in the Greater Mekong Subregion: A Systematic-Review and Meta-Analysis of Risk Factors Associated With Extended-Spectrum Beta-Lactamase and Carbapenemase Isolation. *Frontiers in Microbiology* 2021; **12**.

49. Van Nguyen K, Zhang T, Thi Vu BN, et al. Staphylococcus aureus nasopharyngeal carriage in rural and urban northern Vietnam. *Transactions of The Royal Society of Tropical Medicine and Hygiene* 2014; **108**(12): 783-90.

50. Nicolas-Chanoine MH, Vigan M, Laouénan C, Robert J. Risk factors for carbapenem-resistant Enterobacteriaceae infections: a French case-control-control study. *Eur J Clin Microbiol Infect Dis* 2019; **38**(2): 383-93.

51. Tacconelli E, De Angelis G, Cataldo MA, Pozzi E, Cauda R. Does antibiotic exposure increase the risk of methicillin-resistant Staphylococcus aureus (MRSA) isolation? A systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy* 2007; **61**(1): 26-38.

52. Vũ ĐH, Đặng TLA, Nguyễn HAB, et al. Đánh giá hiệu quả can thiệp của chương trình quản lý kháng sinh với fosfomycin truyền tĩnh mạch tại Bệnh viện Thanh Nhàn. *Tạp chí dược học (BYT)* 2019; **59**.

53. Trần MD, Nguyễn NK, Nguyễn NH. ĐÁNH GIÁ HIỆU QUẢ CAN THIỆP CỦA HOẠT ĐỘNG DƯỢC LÂM SÀNG TRONG VIỆC SỬ DỤNG NHÓM KHÁNG SINH CARBAPENEM TẠI KHOA HỒI SỨC TÍCH CỰC - CHỐNG ĐỘC BỆNH VIỆN ĐA KHOA TỈNH NINH THUẬN. *Tạp chí Y học Việt Nam* 2022; **515**(1).

54. Nguyen-Thi H-Y, Nguyen D-A, Huynh P-T, Le NDT. Impact of antimicrobial stewardship program on vancomycin usage: costs and outcomes at hospital for tropical diseases in Ho Chi Minh City, Vietnam. *Risk Management and Healthcare Policy* 2021: 2637-46.

55. Nguyen HQ, Nguyen-Thi H, Huynh P, Le N, Nguyen N-Q, Hsia Y. Effectiveness of an enhanced antibiotic stewardship programme among paediatric patients in a tertiary hospital in Vietnam. *Journal of Hospital Infection* 2022; **127**: 121-8.

56. Hoa NQ, Thi Lan P, Phuc HD, Chuc NTK, Stalsby Lundborg C. Antibiotic prescribing and dispensing for acute respiratory infections in children: effectiveness of a multi-faceted intervention for health-care providers in Vietnam. *Global Health Action* 2017; **10**(1): 1327638.

57. Cai HTN, Tran HT, Nguyen YHT, et al. Challenges and lessons learned in the development of a participatory learning and action intervention to tackle antibiotic resistance: experiences from northern Vietnam. *Frontiers in public health* 2022; **10**: 822873.

58. World Health Organisation. Antimicrobial Stewardship programmes in health-care facilties in Low- and Middle-income countries - a WHO practical toolkit. 2019. https://www.who.int/publications/i/item/9789241515481 (accessed 10/01/2023).

59. Son NT. Decision No. 5631/QD-BYT 2020 Guidance on management of the antibiotic use in hospitals. 2020. https://english.luatvietnam.vn/decision-no-5631-qd-byt-of-the-ministry-of-health-on-promulgating-the-guidance-on-management-of-the-antibiotic-use-in-hospit-196563-doc1.html (accessed 15/03/2022).

60. Australian Commission on Safety and Quality in Health Care. Antimicrobial Stewardship in Australian Health Care. Sydney, Australia: ACSQHC, 202322/11/2024).

61. Styczynski A, Herzig C, Luvsansharav U-O, McDonald LC, Smith RM. Using Colonization to Understand the Burden of Antimicrobial Resistance Across Low- and Middle-Income Countries. *Clinical Infectious Diseases* 2023; **77**(Supplement_1): S70-S4.

62. Baur D, Beryl Primrose G, Burkert F, et al. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis. *The Lancet Infectious Diseases* 2017; **17**(9): 990-1001.

63. Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017; **2**(2): Cd003543.

64. Peragine C, Walker SAN, Simor A, Walker SE, Kiss A, Leis JA. Impact of a Comprehensive Antimicrobial Stewardship Program on Institutional Burden of Antimicrobial Resistance: A 14-Year Controlled Interrupted Time-series Study. *Clinical Infectious Diseases* 2019; **71**(11): 2897-904.

65. World Health Organisation. Monitoring the building blocks of health systems: a handbook of indicators and their measurement strategies. Geneva, Switzerland, 2010. https://iris.who.int/bitstream/handle/10665/258734/9789241564052-eng.pdf (accessed 21/01/2025).

66. Van TM, Pham NH, Hoang TLH, et al. First-Time Use of Clinical Pharmacists to Improve Appropriate Antibiotic Prescribing in a Medical ICU in Viet Nam. *Infection Control & Hospital Epidemiology* 2020; **41**(S1): s236-s.

67. Jantarathaneewat K, Camins B, Apisarnthanarak A. The role of the clinical pharmacist in antimicrobial stewardship in Asia: A review. *Antimicrobial Stewardship & Healthcare Epidemiology* 2022; **2**(1): e176.

68. York M. Challenges encountered when building laboratory capacity in limited-resource hospitals in Vietnam. *Clinical Microbiology Newsletter* 2012; **34**(21): 169-75.

69. Mabaya G, Evans JM, Longo CJ, Morris AM. A Behavioral Analysis of Factors That Influence Antibiotic Prescribing in Hospitals: A Metasynthesis of Reviews. *Open forum infectious diseases* 2024; **12**(1).

70. Mendelson M, Morris AM, Thursky K, Pulcini C. How to start an antimicrobial stewardship programme in a hospital. *Clinical Microbiology and Infection* 2020; **26**(4): 447-53.

71. Pandey AK, Cohn J, Nampoothiri V, et al. A systematic review of antibiotic drug shortages and the strategies employed for managing these shortages. *Clinical Microbiology and Infection* 2024; **31**(3): 345-53.

72. Charani E, Smith I, Skodvin B, et al. Investigating the cultural and contextual determinants of antimicrobial stewardship programmes across low-, middle-and high-income countries—A qualitative study. *PloS one* 2019; **14**(1): e0209847.

73. Nguyen D, MacLeod WB, Phung DC, et al. Incidence and predictors of surgical-site infections in Vietnam. *Infection control and hospital epidemiology* 2001; **22**(8): 485-92.

74. Mustafa ZU, Mallhi TH, Khan YH, Hayat K, Salman M. Drivers of antimicrobial resistance during and after COVID-19 pandemic in low-middle-income countries. Frontiers Media SA; 2024. p. 1521798.

75. Hoang V. The COVID-19 pandemic in Vietnam - success, crisis, and endemic: Key thresholds and lessons. *J Glob Health* 2022; **12**: 03065.

76. Trinh ST, Chan JTN, Vu DTV, et al. Impact of the COVID-19 Pandemic on Healthcare Seeking and Antibiotic Prescribing for Acute Respiratory Infection in Vietnamese Primary Healthcare Centres: Analysis of Routinely Collected Electronic Prescription Data [Preprint]. 2024.

77. Cai J. A robust health system to achieve universal health coverage in Vietnam. *The Lancet Regional Health–Western Pacific* 2023; **37**.

78. Ministry of Health Vietnam. Handbook for Guidance on Implementation of Antibiotic Use Management Program for District Hospitals - No. 2115/QD-BYT. In: Management DoMEaT, editor. Hanoi, Vietnam; 2023.

79. Monaghan T, Biezen R, Buising K, Hallinan C, Cheah R, Manski-Nankervis J. Clinical insights into appropriate choice of antimicrobials for acute respiratory tract infections. *Australian Journal for General Practitioners* 2022; **51**: 33-7.

80. Royal Melbourne Hospital and the National Centre for Antimicrobial Stewardship. Infections and antimicrobial prescribing in Australian residential aged care facilities. Results of the 2022 Aged Care National Antimicrobial Prescribing Survey: Canberra: Department of Health and Aged Care, 2024. https://www.amr.gov.au/sites/default/files/2024-05/infection-and-antimicrobial-prescribing-in-australian-residential-aged-care-facilities-results-of-the-2022-aged-care-naps.pdf (accessed 11/01/2025).

81. Ministry of Health Vietnam. Decision No. 1121/QD-TTg dated September 25, 2023 on approval of The national strategy for prevention and control of drug resistance in Vietnam for the period of 2023 - 2030 with a vision towards 2045. 2023. https://lawnet.vn/en/vb/Decision-1121-QD-TTg-2023-The-national-strategy-for-prevention-and-control-of-drug-resistance-8DDD4.html (accessed 10/01/2025).

82. Foxlee ND, Townell N, Heney C, McIver L, Lau CL. Strategies Used for Implementing and Promoting Adherence to Antibiotic Guidelines in Low- and Lower-Middle-Income Countries: A Systematic Review. *Trop Med Infect Dis* 2021; **6**(3).

83. Ronda M, Gumucio-Sanguino VD, Shaw E, et al. Long-Term Effects of a Stepwise, Multimodal, Non-Restrictive Antimicrobial Stewardship Programme for Reducing Broad-Spectrum Antibiotic Use in the ICU. *Antibiotics (Basel, Switzerland)* 2024; **13**(2).

84. Avent ML, Cosgrove SE, Price-Haywood EG, van Driel ML. Antimicrobial stewardship in the primary care setting: from dream to reality? *BMC Family Practice* 2020; **21**(1): 134.

85. National Centre for Antimicrobial Stewardship. Antimicrobial formulary and restrictions. 2024. https://www.ncas-australia.org/antimicrobial-formulary-and-restrictions (accessed 25/01/2025).

86. Coulter S, Merollini K, Roberts JA, Graves N, Halton K. The need for cost-effectiveness analyses of antimicrobial stewardship programmes: A structured review. *International journal of antimicrobial agents* 2015; **46**(2): 140-9.

87. Al-Omari A, Al Mutair A, Alhumaid S, et al. The impact of antimicrobial stewardship program implementation at four tertiary private hospitals: results of a five-years pre-post analysis. *Antimicrobial resistance and infection control* 2020; **9**(1): 95.

88. Gentilotti E, De Nardo P, Nguhuni B, et al. Implementing a combined infection prevention and control with antimicrobial stewardship joint program to prevent caesarean section surgical site infections and antimicrobial resistance: a Tanzanian tertiary hospital experience. *Antimicrobial resistance and infection control* 2020; **9**(1): 69.

89. Musoke D, Kitutu FE, Mugisha L, et al. A One Health Approach to Strengthening Antimicrobial Stewardship in Wakiso District, Uganda. *Antibiotics (Basel, Switzerland)* 2020; **9**(11).

Dissemination of research

The findings of this thesis have been widely disseminated to stakeholders in both Vietnam and Australia, including representatives from the Vietnam Ministry of Health, Vietnamese and Australian research partners, University of Sydney representatives, and the Australian Department of Foreign Affairs and Trade (DFAT). Additionally, the research has been shared at relevant conferences.

The table below outlines the conferences and meetings where I have personally presented my research findings.

Date	**Venue**	**Conference/ Meeting**	**Attendees**	**Details**
1st November 2022	Hanoi, Vietnam	VRESIST End-of-project Closing workshop	VRESIST research team, VRESIST research partners from district hospitals, National Institute of Hygiene and Epidemiology (NIHE) partners, Vietnam Ministry of Health representatives, University of Sydney representatives, DFAT representatives	Presentation of preliminary findings of VRESIST B and C findings
3rd April 2023	Adelaide, Australia	Australian Society of Infectious Diseases	Infectious Diseases physicians and Microbiologists from all over Australia and New Zealand	Poster presentation of findings of VRESIST B Before-and-after study demonstrating feasibility of AMS implementation in four district hospitals in Vietnam
31st May 2023	Sydney, Australia	Antimicrobial Resistance and Lung Disease Roundtable discussion	Senior research collaborators from Vietnam, DFAT representatives	Presentation of VRESIST Cluster RCT findings and future research plans and suggestions

Date	Venue	Conference/ Meeting	Attendees	Details
29th August 2023	Sydney, Australia	Australian Vietnam Innovation Symposium – celebrating 50 years of Vietnam and Australia relations	University of Sydney representatives, Consulate-general of Vietnam, ambassador of Vietnam and academics involved in Vietnam research	Poster presentation of VRESIST B findings and informal discussions about cluster RCT findings
7th September 2023	Sydney, Australia	Australia Awards Fellowships – The University of Sydney Vietnam Institute: Strengthening health security capacity in Vietnam program	Educational presentation to Fellows from Vietnam comprising of senior officials, mid-career professionals	Three presentations and a half day workshop on AMR and AMS in Vietnam and Australia - Presented findings of VRESIST B and C - Facilitated group presentations on global health projects
18th June 2024	Sydney, Australia	Global Health Security Conference	Physicians, scientists and experts in public health, agriculture, international relations, government, sociology and anthropology	- Oral presentation of findings from cluster RCT (VRESIST C) of AMS implementation in 16 district hospitals in Vietnam - Poster presentation of knowledge, attitudes and practices of healthcare workers before and after the implementation of AMS in four district hospitals in Vietnam

DFAT: Department of Foreign Affairs and Trade (DFAT)

Appendices

Appendix A. Systematic review data collection form (Chapter 2)

Appendix B. Newcastle – Ottawa quality assessment scale (Chapter 2)

Appendix C. National Antimicrobial Prescriber Survey (NAPS) audit form (Chapters 3 and 5)

Appendix D. CONSORT statement for Cluster RCT (Chapter 5)

Appendix E. Posters presented at conferences

Appendix A: Systematic review data collection form (Chapter 2)

Systematic review data collection form

Study title	
Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*	
Location *(e.g. all over Vietnam, or one province, or one district)*	
Date form completed *(dd/mm/yyyy)*	

Study eligibility

Study Characteristics	Eligibility criteria	Eligibility criteria met. Yes No Unclear	Location in text or source
Type of study	☐ Randomised Controlled Trial ☐ Quasi-randomised Controlled Trial ☐ Before and After Study (Controlled/Uncontrolled) ☐ Interrupted Time Series ☐ Cohort study ☐ Case series (with at least 20 participants) ☐ Descriptive study ☐ Qualitative study ☐ Official report/website:(specify)_____ ☐ Other: _____	☐ ☐ ☐	
Participants	☐ Hospitals/Health care facilities/pharmacies/ community settings Specify: _____ ☐ Individuals Specify: _____ ☐ Multi-country study which includes Vietnam	☐ ☐ ☐	
Study design	☐ Antibiotic consumption ☐ Presence of Antimicrobial stewardship program/intervention ☐ Impact of AMS interventions ☐ Other: _____		
Types of intervention	Is an intervention present? ☐ Yes ☐ No **If yes, tick all that apply:** ☐ Clinician education and training ☐ Patient and public education ☐ Institution of antibiotic guidelines for management of common infections ☐ Providing of resources for AMS activities to be carried out ☐ Formation of antimicrobial stewardship teams or committees in hospital settings ☐ Appointment of antimicrobial champions ☐ Restrictions/ pre-authorisation on antimicrobials ☐ De-labelling of antimicrobial allergies ☐ Audit and feedback of antimicrobial prescriptions ☐ Laboratory biochemical marker use/ microbiological techniques	☐ ☐ ☐	

Study Characteristics	Eligibility criteria	Eligibility criteria met. Yes No Unclear	Location in text or source
	☐ Antibiotic dosing and de-escalation strategies ☐ Others: please specify _____ _____		
Types of comparison	☐ Nil comparator ☐ No AMS intervention ☐ Comparison between AMS interventions Specify which: _____	☐ ☐ ☐	
Types of outcome measures reported (tick all that apply)	☐ No outcome measures ☐ Presence of AMS interventions ☐ Antibiotic consumption ☐ Appropriateness of prescribed antimicrobials for infections being treated ☐ Healthcare associated costs ☐ Length of stay in hospital ☐ Incidence of antimicrobial resistant organism carriage ☐ Consumer knowledge on antimicrobial resistance and appropriate usage of antibiotics ☐ Healthcare worker knowledge on antimicrobial resistance and improved prescribing of antibiotics ☐ Incidence of hospital-acquired infections ☐ Sustainability of AMS interventions ☐ Other: (Specify)_____	☐ ☐ ☐	
Language	☐ English ☐ Vietnamese ☐ Other	☐ ☐ ☐	
INCLUDE ☐	EXCLUDE ☐		
Reason for exclusion			

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Characteristics of included studies

Methods

	Descriptions as stated in report/paper	**Location in text or source** *(page & ¶/fig/table/other)*
Aim of study *(e.g. efficacy, observational)*		
Design		
Unit of allocation *(by individuals, cluster/ groups, hospital departments)*		

Participants

	Description	Location in text or source*)*
Population description *(from which study participants are drawn)*		
Setting *(including location and social context)*	☐ Hospital (specify) :_____ ☐ Pharmacy (specify): _____ ☐ Community (specify): _____ ☐ Private sector (specify): _____ ☐ Other :_____	
Number of participants		
Other demographics - Gender - Race, ethnicity - Professional qualifications - Policies/Procedures in place in setting		
Subgroups reported		

Intervention groups

Copy and paste table for each intervention and comparison group

Intervention/Control

	Intervention group	Comparator group
Group name (*e.g. AMS Committee group*)		
Number in group *(specify whether no. people or clusters or prescriptions*		
Description (include sufficient detail for replication, e.g. type of intervention, how it was carried out, Duration of treatment period, how often, mode of delivery and providers)		
Duration of treatment period, how often and duration of intervention activity		
Delivery *(mode of intervention) and provider of intervention*		

Outcomes

Copy and paste table for each outcome.

	Description as stated in report/paper	Location in text or source *(page. & ¶/fig/table/other)*
Outcome name		
Time points measured and reported*(specify whether from start or end of intervention)*		

Outcome definition *(with diagnostic criteria if relevant)*					
Person measuring/ reporting					
Is outcome/tool validated? *(include reference)*	☐ Yes	☐ No	☐ Unclear	If yes, reference:	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*	☐ Yes	☐ No	☐ Not reported		
Assumed risk estimate *(e.g. baseline or population risk noted in Background)*	☐ Yes	☐ No	☐ Not reported		
Power *(e.g. power & sample size calculation, level of power achieved)*	☐ Yes	☐ No	☐ Not reported		

Other

Study funding sources *(including role of funders)*	☐ Yes	☐ No	☐ Not reported Specify: _____	
Possible conflicts of interest *(for study authors)*	☐ Yes	☐ No	☐ Not reported Specify: _____	

Risk of Bias assessment - RCTs

Domain	Risk of bias Low	High	Unclear	Not Applicable	Support for judgement *(include direct quotes where available with explanatory comments)*
Random sequence generation (*selection bias)*	☐	☐	☐	☐	
Allocation concealment *(selection bias)*	☐	☐	☐	☐	
Blinding of participants and personnel *(performance bias)*	☐	☐	☐	☐	
Blinding of outcome assessment *(detection bias)*	☐	☐	☐	☐	
Incomplete outcome data *(attrition bias)*	☐	☐	☐	☐	
Selective outcome reporting? *(reporting bias)*	☐	☐	☐	☐	
Other source of bias (specify)	☐	☐	☐	☐	

Risk of bias assessment for non-RCTs (Newcastle-Ottawa quality assessment scale)

Note : A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Domain	Details	Support for judgement *(include direct quotes where available with explanatory comments)*	Location in text or source *(page & ¶/fig/table/other)*
CASE CONTROL STUDIES			
Is the case definition adequate?	☐ Yes, with independent validation ★ ☐ Yes, e.g. record linkage or based on self-reports ☐ No description		
Representativeness of the cases	☐ Consecutive or obviously representative series of cases ★ ☐ Potential for selection biases or not stated		
Selection of controls	☐ Community controls ★ ☐ Hospital controls ☐ No description		
Definition of controls	☐ No history of disease ★ ☐ No description of source		
Comparability of cases and controls on the basis of the design or analysis	☐ Study controls for _____ (select the most important factor) ★ ☐ Study controls for any additional factor _____ ★		
Ascertainment of exposure	☐ Secure medical record★ ☐ Structured interview (blind) ★ ☐ Interview not blinded to case/control status ☐ Written self-report or medical record only ☐ No description		
Same method of ascertainment for cases and controls	☐ Yes★ ☐ No		
Non-response rates	☐ Same rate for both groups★ ☐ Non-responders described ☐ Rate different and no designation		

Note : A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Domain		Support for judgement *(include direct quotes where available with explanatory comments)*	Location in text or source *(page & ¶/fig/table/other)*
COHORT STUDIES			
Representativeness of the exposed cohort	☐ Truly representative of the average _____ in the community★		

	☐ Somewhat representative of the average _____ in the community★ ☐ Selected group of users, specify: _____ ☐ No description of the derivation of the cohort		
Selection of the non-exposed cohort	☐ Drawn from the same community as the exposed cohort ★ ☐ Drawn from a different source ☐ No description of the derivation of the non-exposed cohort		
Ascertainment of exposure	☐ Secure medical record ★ ☐ Structured interview★ ☐ Written self-report ☐ No description		
Demonstration that outcome of interest was not present at start of study	☐ Yes★ ☐ No		
Comparability of cohorts based on the design or analysis	☐ Study controls for _____ (select the most important factor) ★ ☐ Study controls for any additional factor _____ ★		
Assessment of outcome	☐ Independent blind assessment★ ☐ Record linkage★ ☐ Self-report ☐ No description		
Was follow-up long enough for outcomes to occur? (at least 3 months)	☐ Yes★ ☐ No		
Adequacy of follow up of cohorts	☐ Complete follow up – all subjects accounted for ★ ☐ Subjects lost to follow up unlikely to introduce bias - small number lost - < 10 %★ ☐ Lost to follow up rate >10% ☐ No description of those lost to follow up ☐ No statement		

Risk of Bias unable to be ascertained using above methods: ☐ Yes ☐ Unsure

Specify reason: _____

Domain		Support for judgement	Location in text or source *(page & ¶/fig/table/other)*

		(include direct quotes where available with explanatory comments)	
CROSS SECTIONAL STUDIES			
Selection (Max 5 stars)			
Representativeness of the exposed cohort	☐ Truly representative of the average _____ in the community★ (1) ☐ Somewhat representative of the average _____ in the community★ (1) ☐ Selected group of users, specify: _____ (0) ☐ No description of the sampling strategy (0)	Convenience sampling of women and farmers	
Sample size	☐ Justified and satisfactory (including sample size calculation) ★ (1) ☐ Not justified/no information provided (0)		
Non-response rate	☐ Proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded. ★ (1) ☐ Unsatisfactory recruitment rate, no summary data on non-respondents/no information provided (0)		
Ascertainment of exposure	☐ Secure healthcare registers/hospital records/Medical records only/scripts. ★★ (2) ☐ Patient recall/Non-validated screening/surveillance tool, but tool is available or described. ★ (1) ☐ No description of measurement tool(0)		
Comparability of subjects in different outcome groups **(Max 1 star)**	☐ Data/ results adjusted for relevant predictors/risk factors/confounders ★ (1) ☐ Data/results not adjusted for all relevant confounders/risk factors/information not provided. (0)		
Assessment of outcome (MAX 3 stars)	☐ Independent blind assessment★★ ☐ Record linkage★ ★ ☐ Self-report★ ☐ No description		
Statistical test	☐The statistical test used to analyse the data is clearly described and appropriate. ★ (1) ☐The statistical test is not appropriate, not described or incomplete. (0)	No stats	
Notes:			
Risk of Bias unable to be ascertained using above methods: ☐ Yes ☐ Unsure Specify reason:			

Results and statistical analysis

	Description as stated in report/paper		Location in text or source *(page & ¶/fig/table/other)*
Results (Primary outcome)	Intervention	Comparison	
Results (Secondary outcome)	Intervention	Comparison	
Any other results reported *(e.g. odds ratio, risk difference, CI or P value)*			
No. missing participants & reasons			
Unit of analysis *(by individuals, cluster/groups*			
Statistical methods used and appropriateness of these *(e.g. adjustment for correlation)*			
Reanalysis required? *(specify, e.g. correlation adjustment)*	☐ Yes ☐ No ☐ Unclear		
Data can be used for meta-analysis?	☐ Yes ☐ No ☐ Unclear		

Other information

	Description as stated in report/paper	**Location in text or source** *(page & ¶/fig/table/other)*
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further information *(from whom, what and when)*	☐ Yes ☐ No Specify: _____	

Appendix B: Newcastle – Ottawa quality assessment scale (Chapter 2)

Newcastle – Ottawa Quality Assessment Scale (adapted for cross sectional studies)

Selection: (Maximum 5 stars)

1) Representativeness of the cases:

a) Truly representative of the HCC patients (consecutive or random sampling of cases). 1 score

b) Somewhat representative of the average in the HCC patients (non-random sampling) . 1 score

c) Selected demographic group of users. 0 score

d) No description of the sampling strategy. 0 score

2) Sample size:

a) Justified and satisfactory (≥ 400 HCC included). 1 score

b) Not justified (<400 HCC patients included). 0 score

3) Non-Response rate

a) The response rate is satisfactory (≥95%). 1 Score

b) The response rate is unsatisfactory (<95%), or no description. 0 Score

4) Ascertainment of the screening/surveillance tool:

a) Validated screening/surveillance tool. 2 scores

b) Non-validated screening/surveillance tool, but the tool is available or described. 1 score

c) No description of the measurement tool. 0 score

Comparability: (Maximum 1 stars)

1) The potential confounders were investigated by subgroup analysis or multivariable analysis.

a) The study investigates potential confounders. 1 score

b) The study does not investigate potential confounders. 0 score

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:

a) Independent blind assessment. 2 scores

b) Record linkage. 2 scores

c) Self report. 1 score

d) No description. 0 score

2) Statistical test:

a) The statistical test used to analyse the data is clearly described and appropriate. 1 score

b) The statistical test is not appropriate, not described or incomplete. 0 score

Appendix C: Hospital National Antimicrobial Prescribing Survey (NAPS) audit form (Chapters 3 and 5)

Antibiotic Prescribing Survey

VRESIST B, NAPS Form, Version 1.0, 01/03/2021

- please see instruction sheet on how to fill out this table for each individual patient.

Date:	PID:	DOB:	Gender:	Weight:	Creatinine:	Ward:	CrCl (to be calculated by Research team):

Start date	Antimicrobial	Route	Dose	Freq	Indication documented	Documented or presumed indication?	Stop date documented	Guideline compliance (1 -4)*	Surgical prophylaxis >24	Allergy mismatch	Microbiology mismatch	Incorrect route	Incorrect dose/frequency	Incorrect duration	Spectrum too broad	Spectrum too narrow	Indication does not require any antimicrobial	Appropriateness (1 -5)+

*** Guideline compliance**
1: Compliant with local guidelines
2: Non-compliance with guidelines
3: Directed therapy
4: No guidelines available
5: Not assessable

+ Appropriateness:
1: Optimal
2: Adequate
3: Suboptimal
4: Inadequate
5: Not assessable

Allergies	Microbiology	Surgical procedure	Notes:

Appendix D: CONSORT statement for Cluster RCT (Chapter 5)

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	186
	1b	Structured summary of trial design, methods, results, and conclusions	See table 2	187-188
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	189
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	190
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	191-193
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		**N/A**
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	191
	4b	Settings and locations where the data were collected		191
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	191-193
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Whether outcome measures pertain to the cluster level, the individual participant level or both	196

	6b	Any changes to trial outcomes after the trial commenced, with reasons		**N/A**
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	197
	7b	When applicable, explanation of any interim analyses and stopping guidelines		N/A
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		191
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	191
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	N/A
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	191
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial	191

			(such as complete enumeration, random sampling)	
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	191
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		191
	11b	If relevant, description of the similarity of interventions		191-193
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	198
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		198
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	Supplementary Figure S5.2
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up		199
	14b	Why the trial ended or was stopped		N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	Table 5.1, Supp Table S5.4

Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	199
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	199-201
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		200
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		201
Harms	19	All important harms or unintended effects in each group		N/A
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		204
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	205
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		206
Other information				
Registration	23	Registration number and name of trial registry		188

Protocol	24	Where the full trial protocol can be accessed, if available		Request author
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders		188

Appendix E. Posters presented at conferences

Poster presentation at Global Health Security Conference - Abstract

Title: Effect of Antimicrobial Stewardship interventions on Knowledge, Attitudes and Practices among Healthcare workers in District Hospitals in Vietnam

Introduction:

Recommended Antimicrobial Stewardship (AMS) interventions have had limited implementation at lower levels of health system in Vietnam.

Context and Aim:

The V-RESIST feasibility study aimed to assess the impact of a multi-faceted AMS intervention on knowledge, attitudes and practices of healthcare workers in district hospitals in Vietnam.

Method:

An AMS program which included establishing AMS committees, educational initiatives, antimicrobial guidelines and audit and feedback on antimicrobial prescribing was implemented in four district hospitals in Hanoi and Ca Mau provinces in Vietnam. Changes in the knowledge, attitude, and practice of healthcare workers were evaluated using a hospital-wide cross-sectional survey before and after the AMS program.

Findings:

The survey, which included an average of 25% doctors (n=423), revealed a significant increase in guideline use among doctors prescribing antibiotics after the intervention (92.4% vs. 97.6%; diff = 5.21%; 95%CI = 0.7 - 9.7%), with a notable 11.1% increase in local guideline use (95%CI =1.0% - 21.3%). More doctors reported that they no longer prescribed antibiotics for the treatment of viral infections (i.e. upper respiratory tract infections, bronchitis, and gastroenteritis). Post- intervention, healthcare workers believed that the most important AMS intervention was to establish prospective feedback to clinicians (37.8% vs 46.0%; diff = 8.2%; 95%CI =2.7% - 13.7%). Pharmacists are more likely to feel confident in contacting doctors about antibiotic prescriptions after the intervention (OR=4.62; 95%CI=1.5-14.0). More pharmacists believed they could contribute towards an AMS program by upholding the antimicrobial approval system (21.0% vs 67.6%,; diff = 46.6%; 95%CI = 31.8% - 61.5%).

Conclusions:

AMS interventions significantly improve healthcare staff knowledge, attitude, and prescription practices in district hospitals in Vietnam, underscoring the importance of scaling up these interventions.

2. Poster presentation for Australian Society of Infectious Diseases (ASID) Conference

Title: Feasibility of an antimicrobial stewardship programme to reduce inappropriate antimicrobial use in four district hospitals in Vietnam

Abstract as included in Chapter 3

Appendix F. Standards for Reporting Implementation Studies (STARI) checklist

Standards for Reporting Implementation Studies: the StaRI checklist for completion

The StaRI standard should be referenced as: Pinnock H, Barwick M, Carpenter C, Eldridge S, Grandes G, Griffiths CJ, Rycroft-Malone J, Meissner P, Murray E, Patel A, Sheikh A, Taylor SJC for the StaRI Group. Standards for Reporting Implementation Studies (StaRI) statement. *BMJ* 2017;356:i6795

The detailed Explanation and Elaboration document, which provides the rationale and exemplar text for all these items is: Pinnock H, Barwick M, Carpenter C, Eldridge S, Grandes G, Griffiths C, Rycroft-Malone J, Meissner P, Murray E, Patel A, Sheikh A, Taylor S, for the StaRI group. Standards for Reporting Implementation Studies (StaRI). Explanation and Elaboration document. *BMJ Open* 2017 2017;7:e013318

Notes: A key concept of the StaRI standards is the dual strands of describing, on the one hand, the implementation strategy and, on the other, the clinical, healthcare, or public health intervention that is being implemented. These strands are represented as two columns in the checklist.

The primary focus of implementation science is the implementation strategy (column 1) and the expectation is that this will always be completed.	The evidence about the impact of the intervention on the targeted population should always be considered (column 2) and either health outcomes reported or robust evidence cited to support a known beneficial effect of the intervention on the health of individuals or populations.

The StaRI standards refers to the broad range of study designs employed in implementation science. Authors should refer to other reporting standards for advice on reporting specific methodological features. Conversely, whilst all items are worthy of consideration, not all items will be applicable to, or feasible within every study.

Checklist item		Reported on page #	Implementation Strategy	Reported on page #	Intervention
			"Implementation strategy" refers to how the intervention was implemented		"Intervention" refers to the healthcare or public health intervention that is being implemented.
Title and abstract					
Title	**1**	186	Identification as an implementation study, and description of the methodology in the title and/or keywords		
Abstract	**2**	187-188	Identification as an implementation study, including a description of the implementation strategy to be tested, the evidence-based intervention being implemented, and defining the key implementation and health outcomes.		
Introduction					
Introduction	**3**	189	Description of the problem, challenge or deficiency in healthcare or public health that the intervention being implemented aims to address.		
Rationale	**4**		The scientific background and rationale for the implementation strategy (including any underpinning	190	The scientific background and rationale for the intervention being implemented (including evidence

			theory/framework/model, how it is expected to achieve its effects and any pilot work).		about its effectiveness and how it is expected to achieve its effects).
Aims and objectives	**5**	190	The aims of the study, differentiating between implementation objectives and any intervention objectives.		
Methods: description					
Design	**6**	191	The design and key features of the evaluation, (cross referencing to any appropriate methodology reporting standards) and any changes to study protocol, with reasons		
Context	**7**	191	The context in which the intervention was implemented. (Consider social, economic, policy, healthcare, organisational barriers and facilitators that might influence implementation elsewhere).		
Targeted 'sites'	**8**	N/A	The characteristics of the targeted 'site(s)' (e.g locations/personnel/resources etc.) for implementation and any eligibility criteria.	191	The population targeted by the intervention and any eligibility criteria.
Description	**9**	N/A	A description of the implementation strategy	192-194	A description of the intervention
Sub-groups	**10**	N/A	Any sub-groups recruited for additional research tasks, and/or nested studies are described		
Methods: evaluation					
Outcomes	**11**	N/A	Defined pre-specified primary and other outcome(s) of the implementation strategy, and how they were assessed. Document any pre-determined targets	196	Defined pre-specified primary and other outcome(s) of the intervention (if assessed), and how they were assessed. Document any pre-determined targets
Process evaluation	**12**	196	Process evaluation objectives and outcomes related to the mechanism by which the strategy is expected to work		
Economic evaluation	**13**	N/A	Methods for resource use, costs, economic outcomes and analysis for the implementation strategy	197	Methods for resource use, costs, economic outcomes and analysis for the intervention
Sample size	**14**	197	Rationale for sample sizes (including sample size calculations, budgetary constraints, practical considerations, data saturation, as appropriate)		
Analysis	**15**	198	Methods of analysis (with reasons for that choice)		
Sub-group analyses	**16**	198	Any a priori sub-group analyses (e.g. between different sites in a multicentre study, different clinical or demographic populations), and sub-groups recruited to specific nested research tasks		

Results					
Characteristics	**17**	N/A	Proportion recruited and characteristics of the recipient population for the implementation strategy	199	Proportion recruited and characteristics (if appropriate) of the recipient population for the intervention
Outcomes	**18**	N/A	Primary and other outcome(s) of the implementation strategy	199-200	Primary and other outcome(s) of the Intervention (if assessed)
Process outcomes	**19**	200	Process data related to the implementation strategy mapped to the mechanism by which the strategy is expected to work		
Economic evaluation	**20**	N/A	Resource use, costs, economic outcomes and analysis for the implementation strategy	200	Resource use, costs, economic outcomes and analysis for the intervention
Sub-group analyses	**21**	N/A	Representativeness and outcomes of subgroups including those recruited to specific research tasks		
Fidelity/ adaptation	**22**	N/A	Fidelity to implementation strategy as planned and adaptation to suit context and preferences	201	Fidelity to delivering the core components of intervention (where measured)
Contextual changes	**23**	N/A	Contextual changes (if any) which may have affected outcomes		
Harms	**24**	N/A	All important harms or unintended effects in each group		
Discussion					
Structured discussion	**25**	201	Summary of findings, strengths and limitations, comparisons with other studies, conclusions and implications		
Implications	**26**	N/A	Discussion of policy, practice and/or research implications of the implementation strategy (specifically including scalability)	201-207	Discussion of policy, practice and/or research implications of the intervention (specifically including sustainability)
General					
Statements	**27**	188	Include statement(s) on regulatory approvals (including, as appropriate, ethical approval, confidential use of routine data, governance approval), trial/study registration (availability of protocol), funding and conflicts of interest		