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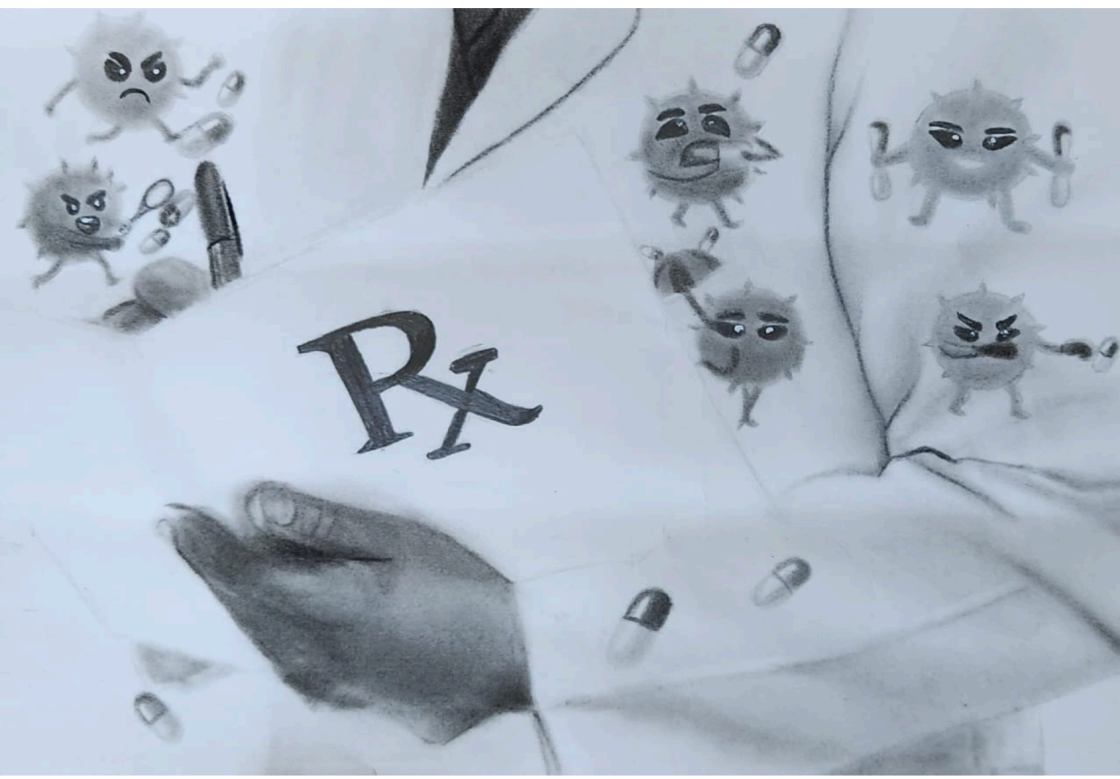
IMPLEMENTATION OF A CLINICAL DECISION SUPPORT ALGORITHM TO DE-IMPLEMENT UNNECESSARY ANTIBIOTIC PRESCRIPTIONS AMONG HIV-INFECTED ADULTS WITH UPPER RESPIRATORY TRACT INFECTIONS IN PRIMARY HEALTHCARE SETTINGS IN THE CITIES OF MAPUTO AND MATOLA, MOZAMBIQUE



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Implementation of a Clinical Decision Support Algorithm (CDSA) to De-implement Unnecessary Antibiotic Prescriptions among HIV-Infected Adults with Upper Respiratory Tract Infections in Primary Healthcare Settings in the Cities of Maputo and Matola, Mozambique

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I declare that this thesis was never presented to obtain any degree or in any other field, and it is the result of my fieldwork. This thesis is given in compliance with the requirements of Eduardo Mondlane University for a Doctoral degree (PhD).

Signed: ……C. Faiela…… (Candidate)

Date: December 2, 2025

DEDICATION

To my beloved family, the pillar of my life and encouragement.

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ABSTRACT

Antibiotics are commonly overused to treat upper respiratory tract infections (URTIs) in HIV-infected adults, even though viruses cause most URTIs. Therefore, antibiotic overuse for URTIs is considered an unwarranted and unnecessary practice, which needs to be de-implemented. Thus, the goal of this thesis is to evaluate the effectiveness and implementation of a clinical decision support algorithm (CDSA) to de-implement unnecessary antibiotic prescriptions among HIV-infected adults with URTI symptoms in primary healthcare facilities. The thesis comprises a total of four studies, culminating in five manuscripts. Study I (Paper I) aimed to explore and describe antibiotic prescribing for HIV-infected patients in primary healthcare facilities, using a cross-sectional design. Antibiotics were prescribed in 65.9% of prescriptions, either for treatment (69.8%) or prophylaxis (30.2%) of infections, and most were indicated for respiratory tract infections (30.5%). Study II (Paper III) aimed to explore the context of readiness for implementing the intervention in selected healthcare facilities, using a cross-sectional design with a mixed-methods approach. Thirty-nine healthcare providers (HCPs) among clinicians, laboratory technicians, and pharmacists were interviewed. Over 50% of clinicians did not possess or use any clinical guideline/algorithm, and 92.6% reported using clinical diagnosis alone to determine the choice in antibiotic use. All study facilities reported limited laboratory capacity to aid evidence to clinicians in antibiotic prescribing. HCPs described enthusiasm and willingness to utilize a new CDSA intervention. The lack of existing decision-support tools and limitations in laboratory diagnostic support justified the introduction of our CDSA, and the HCPs' enthusiasm and willingness supported their readiness. Study III (Papers II and IV) aimed to evaluate the effectiveness of the intervention on reducing unnecessary antibiotic prescriptions for URTIs among HIV-infected adults, using a two-arm cluster randomized controlled trial design. Three hundred seventy-nine patients were recruited, comprising 182 (48%) in the intervention group and 197 (52%) in the control group. Most appeared with common cold and flu-like symptoms. The intervention was associated with a significant reduction in antibiotic prescribing by 33.2% ($p < 0.001$) and a non-significant decrease in incidence of complications by 3.7% ($p = 0.096$). In both groups, most patients (78%) recovered completely within five days. Amoxicillin (47.8%), azithromycin (21.9%), and phenoxymethylpenicillin (14.1%) were the most prescribed antibiotics. Study IV (Paper V) aimed to evaluate implementation outcomes of the intervention using the RE-AIM framework, employing a hybrid type II effectiveness-implementation design. Among 387 HIV-infected

adults approached, 379 (97.9%) were successfully recruited, with 182 (48%) in the intervention and 197 (52%) in the control group. Among the recruited patients, the mean age was 44±12.3 years, and 286 (75.5%) were female. The intervention resulted in 33.2% fewer antibiotics prescribed compared to the control. All intervention sites (100%) and clinicians (100%) demonstrated a commitment to de-implementing antibiotics. The implementation protocol was delivered as planned, and participants (n=21) in focus group discussions (FGD) were satisfied with the intervention. The evidence presented in this thesis may support clinicians and decision makers in their efforts for rational antibiotic use in managing URTIs in primary healthcare facilities.

Keywords: Antibiotics; Antimicrobial resistance; De-implementation; Clinical decision support algorithm; Upper respiratory tract infections; HIV; Dynamic adaptation process; RE-AIM; Mozambique.

ABSTRACT IN PORTUGUESE

Os antibióticos são comumente excessivamente usados para tratar infecções do trato respiratório superior (ITRS) em adultos infectados pelo HIV, embora os vírus causem a maioria das ITRS. Portanto, o uso excessivo de antibióticos para ITRS é considerado uma prática injustificada e desnecessária, que precisa ser desimplementada. Assim, o objectivo desta tese é avaliar a efectividade e a implementação de um algoritmo de suporte à decisão clínica (ASDC) para desimplementar prescrições desnecessárias de antibióticos entre adultos infectados pelo HIV com sintomas de ITRS em unidades sanitárias primárias. A tese compreende um total de quatro estudos, culminando em cinco manuscritos. O Estudo I (Artigo I) teve como objectivo explorar e descrever a prescrição de antibióticos para pacientes infectados pelo HIV em unidades sanitárias primárias, usando um delineamento transversal. Os antibióticos foram prescritos em 65,9% das prescrições, seja para tratamento (69,8%) ou profilaxia (30,2%) de infecções, e a maioria foi indicada para infecções do trato respiratório (30,5%). O Estudo II (Artigo III) teve como objectivo explorar o contexto de prontidão para a implementação da intervenção em unidades de saúde selecionadas, utilizando um delineamento transversal com abordagem de métodos mistos. Trinta e nove profissionais de saúde (PS) foram entrevistados, incluindo 27 clínicos, seis técnicos de laboratório e seis farmacêuticos. Mais de 50% dos clínicos não possuíam ou utilizavam qualquer directriz/algoritmo clínico e 92,6% relataram utilizar apenas o diagnóstico clínico para determinar a escolha do uso de antibióticos. Todas as unidades do estudo relataram capacidade laboratorial limitada para auxiliar os clínicos na prescrição de antibióticos com evidências. Os PS descreveram entusiasmo e disposição para utilizar uma nova intervenção de ASDC. A falta de ferramentas de apoio à decisão e as limitações no suporte diagnóstico laboratorial justificaram a introdução do nosso ASDC. O entusiasmo e a disposição dos PS reforçaram sua prontidão. O Estudo III (Artigos II e IV) teve como objectivo avaliar a efectividade de um ASDC na redução de prescrições desnecessárias de antibióticos para ITRS entre adultos infectados pelo HIV, utilizando um delineamento de ensaio clínico randomizado controlado por conglomerados de dois braços. Trezentos e setenta e nove pacientes foram recrutados, 182 (48%) na intervenção e 197 (52%) no controle. A maioria apareceu com sintomas de resfriado comum e gripe. A intervenção foi associada a uma redução significativa na prescrição de antibióticos em 33,2% ($p < 0,001$) e uma diminuição não significativa na incidência de complicações em 3,7% ($p = 0,096$). Em ambos os grupos, a maioria dos pacientes (78%) se recuperou completamente em cinco dias.

Amoxicilina (47,8%), azitromicina (21,9%) e fenoximetilpenicilina (14,1%) foram os antibióticos mais prescritos. O Estudo IV (Artigo V) teve como objectivo avaliar os resultados da implementação da intervenção usando a estrutura RE-AIM, empregando um delineamento híbrido de efectividade-implementação do tipo II. Entre 387 adultos infectados pelo HIV abordados, 379 (97,9%) foram recrutados com sucesso, com 182 (48%) na intervenção e 197 (52%) no grupo controle. Entre os pacientes recrutados, a idade média foi de 44 ± 12,3 anos, e 286 (75,5%) eram do sexo feminino. A intervenção resultou em 33,2% menos antibióticos prescritos em comparação ao controle. Todos os locais de intervenção (100%) e clínicos (100%) demonstraram um compromisso com a desimplementação de antibióticos. O protocolo de implementação foi entregue conforme planejado, e os participantes (n = 21) nas discussões de grupo focal ficaram satisfeitos com a intervenção. As evidências apresentadas nesta tese podem orientar os clínicos e os decisores nos seus esforços para uso racional de antibióticos no tratamento de ITRS em unidades sanitárias primárias.

Palavras-chave: Antibióticos; Resistência aos antimicrobianos; Desimplementação; Algoritmo de apoio à decisão clínica; Infecções do trato respiratório superior; HIV; Processo de adaptação dinâmica; RE-AIM; Moçambique.

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LIST OF PAPERS

This thesis was based on the following peer-reviewed papers.

No	Paper	Impact factor
I.	**Faiela C** & Sevene E. (2022). Antibiotic prescription for HIV-positive patients in primary health care in Mozambique: A cross-sectional study. S Afr J Infect Dis, 37 (1), 340. doi: 10.4102/sajid.v37i1.340.	1.4
II.	**Faiela C**, Moon TD, Sidat M & Sevene E. (2024). De-implementation strategy to reduce unnecessary antibiotic prescriptions for ambulatory HIV-infected patients with upper respiratory tract infections in Mozambique: a study protocol of a cluster randomized controlled trial. Implement Sci, 19 (1), 51. doi: 10.1186/s13012-024-01382-8.	8.8
III.	**Faiela C**, Moon TD, Sidat M & Sevene E. Pre-implementation determinants of a clinical decision support algorithm for management of upper respiratory tract infections in primary healthcare settings in Mozambique: a mixed-methods study. *Submitted*.	Under review
IV.	**Faiela C**, Moon TD, Amorim G, Sidat M, & Sevene E. Effectiveness of a clinical decision support algorithm (CDSA) on reducing unnecessary antibiotic prescriptions for upper respiratory tract infections among ambulatory HIV-infected adults in Mozambique: a cluster randomized controlled trial. *Submitted*.	Under review
V.	**Faiela C**, Moon TD, Sidat M & Sevene E. De-implementation of unnecessary antibiotic use for upper respiratory tract infections in ambulatory HIV care in Mozambique: an implementation science study using the RE-AIM framework. *Submitted*.	Under review

LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
AMC	Amoxicillin-clavulanic acid
AMINO	Aminoglycoside family
AMR	Antimicrobial resistance
AMX	Amoxicillin
ART	Antiretroviral therapy
ASDC	Clinical decision support algorithm in Portuguese *(Algoritmo de suporte a decisão clínica)*
ASP	Antimicrobial Stewardship
AWaRe	Access, watch and reserve the WHO antibiotic classification
AZI	Azithromycin
BPG	Benzathine benzylpenicillin
CBC	Complete blood count
CD4	Cluster of differentiation 4, a glycoprotein found on the surface of immune cells
CDSA	Clinical decision support algorithm
CFX	Cefixime
CHL	Chloramphenicol
CI	Confidence interval
CIP	Ciprofloxacin
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease of 2019
CRP	C-reactive protein
CTX	Cotrimoxazole
DAP	Dynamic adaptation process
DOXY	Doxycycline
ERY	Erythromycin
FGD	Focus group discussion
FOCEP	Collaborative research ethics education program
GDP	Gross Domestic Product
GEN	Gentamicin
HCF	Healthcare facility
HCP	Healthcare provider
HIV	Human immunodeficiency virus
IDI	In-depth interview

IMASIDA	Survey of immunization, malaria, and HIV/AIDS indicators *(Inquérito de indicadores de imunização, malaria e HIV/SIDA in Portuguese)*
INE	National Institute of Statistics *(Instituto Nacional de Estatística in Portuguese)*
ITRS	Upper respiratory tract infections in Portuguese *(Infecções do trato respiratório superior)*
KAN	Kanamycin
Km2	Square kilometers
LRTI	Lower respiratory tract infection
MAC	Mycobacterium avium complex
MACRO	Macrolide family
MET	Metronidazole
MISAU	Ministry of Health *(Ministério de Saúde in Portuguese)*
NAL	Nalidixic acid
n.d.	No date
NHS	National Health System
NMF	National Medicines Formulary
PCP	Pneumocystis pneumonia
PCR	Polymerase chain reaction
PcV	Phenoxymethylpenicillin
PEN	Penicillin family
PI	Principal investigator
PRISM	Partnership Research in Implementation Science Mozambique project
PS	Healthcare provider in Portuguese *(Profissional de saúde)*
QUINO	Quinolone family
RE-AIM	Reach, effectiveness, adoption, implementation, and maintenance framework
RR	Relative risk
RTI	Respiratory tract infection
SD	Standard deviation
SPSS	Statistical package for social science
SULFO	Sulfonamide family
TB	Tuberculosis
TET	Tetracycline
TETRA	Tetracycline family

UEM	Eduardo Mondlane University *(Universidade Eduardo Mondlane in Portuguese)*
URTI	Upper respiratory tract infection
USA	United States of America
WHO	World Health Organization

GLOSSARY OF TERMS

Algorithm	A finite set of clear, step-by-step instructions designed to solve a problem or perform a task.
Antibiotic	A type of antimicrobial substance used to fight bacterial infections in humans and animals.
Antimicrobial resistance	The ability of a microorganism to survive and resist exposure to antimicrobial drugs threatening the effectiveness of successful treatment of infection.
Antimicrobial stewardship	Coordinated strategies that promote the appropriate and responsible use of antimicrobial medications, such as antibiotics, to improve patient outcomes, reduce the emergence of antimicrobial resistance, and limit toxicity and costs.
Associated deaths	Deaths that would not have occurred if the infections had been prevented entirely.
Attributable deaths	Deaths that would have been prevented if the drug-resistant bacteria causing the infections had not been drug-resistant.
Complication	Defined as worsening of symptoms that were deemed to result from not receiving antibiotics, such as sinusitis, pharyngotonsillitis, pneumonia, bronchitis, and asthma.
One Health	An integrated and unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems.
Primary healthcare	Known as a type of healthcare that enables support of a person's needs, from health promotion, treatment, rehabilitation, palliative care, and more, ensuring that healthcare is delivered in a way that is centered on people's needs and respects their preferences.

CHAPTER 1

CONTEXTUALIZATION

1. Introduction

Antibiotics are inappropriately overprescribed to treat upper respiratory tract infections (URTIs) among ambulatory adult patients (Sweet *et al*., 2023). Approximately 90% of all URTIs are of viral origin, self-limiting, and generally resolve without further complications, and prescribing antibiotics may not be required (Mortazhejri *et al*., 2020; Wong *et al*., 2020). Despite this, as many as over two-thirds of patients with URTI end up being prescribed antibiotics (Alvsåker *et al*., 2024; Peláez-Ballestas *et al*., 2003). Excessive or inappropriate antibiotic prescribing for URTIs is considered an unwarranted and unnecessary practice, and thus needs to be de-implemented (Raudasoja *et al*., 2022). De-implementation is recognized as a crucial research area that can eliminate unnecessary practices in health systems (Branch-Elliman *et al*., 2022).

Using unnecessary antibiotics contributes to the emerging global threat of antibiotic-resistant organisms, making future infections more difficult to treat (Ahmed *et al*., 2024). Antibiotic resistance may also render essential medicines ineffective, leading to untreatable infections, increased severe illness, disability, and death. It poses a major global health threat by undermining routine medical procedures, resulting in longer hospital stays, higher healthcare costs, and a heightened risk of widespread disease (Ahmed *et al*., 2024; Aslam *et al*., 2024).

Respiratory tract infections (RTIs) are the main reason for antibiotic prescribing in adult HIV-infected patients, who are subject to lifelong antiretroviral therapy (ART), and prescribing antibiotics would increase the number of medications. Thus, avoiding unnecessary antibiotic prescriptions will reduce the likelihood of drug interactions and adverse events (Klein *et al*., 2007; Shehab *et al*., 2008). Additionally, patients with weakened immune systems are more likely to experience adverse consequences from unnecessary antibiotic use, thereby increasing their susceptibility to infection (Revolinski *et al*., 2019).

Improving antibiotic prescribing requires complementary strategies, which include changing clinician behavior and educating patients about the role of antibiotics in medical care and their well-being (Cuevas *et al*., 2021). Several strategies to improve antibiotic prescribing among patients with URTI across a variety of clinical settings are being employed worldwide. These strategies include: 1) the use of clinical decision support algorithms (CDSA) by the clinician; 2) employment of rapid diagnostic testing or a biomarker to try and reduce uncertainty in diagnosis in real-time, and thus the need for empiric antibiotics; 3) education of healthcare providers, including feedback and

auditing concerning their prescribing practices; 4) establishing institutional antibiotic stewardship programs; and 5) creation of, and then deployment of essential medicines policies (Cuevas *et al*., 2021; Shao *et al*., 2015; Wei *et al*., 2017; Rambaud-Althaus *et al*., 2017; Zhang *et al*., 2017; Petel *et al*., 2018; Knowles *et al*., 2024).

CDSAs are among the most effective approaches to promote rational use of antibiotics and the reduction of their prescription, mainly when combined with education of healthcare providers and prescription audits (Dunsmore *et al*., 2023). The CDSAs for managing RTIs have shown significant implementation effectiveness (Avent *et al*., 2020). Many of these tools have been integrated into electronic prescribing platforms and are associated with reduced inappropriate antibiotic prescribing (McGinn *et al*., 2013; Rambaud-Althaus *et al*., 2017; Avent *et al*., 2020).

In Mozambique, the management of URTIs in primary healthcare settings is primarily empirical and often results in the prescription of antibiotics, despite compelling evidence of a viral origin. Hence, one potential solution to this problem is to utilize a CDSA that can help clinicians differentiate when a patient with URTI symptoms needs antibiotics versus those who do not, thus ideally reducing the number of unnecessary antibiotics being prescribed (Davidson *et al*., 2017; Branch-Elliman *et al*., 2022). With this thesis, we intended to evaluate the implementation of a CDSA in de-implementing unnecessary antibiotic usage in managing URTIs in HIV-infected patients.

2. Literature review

2.1 Use of antibiotics

Antibiotics can be used both to treat existing infections (therapeutic use) and to prevent infections (prophylactic use). Therapeutic use is for fighting active infections, while prophylactic use involves administering antibiotics before an infection is likely to occur. For example, cotrimoxazole has been frequently prescribed to HIV-infected individuals for the prophylaxis of certain opportunistic infections (Suthar *et al*., 2012). Inappropriate use, both for prophylactic and therapeutic purposes, has contributed to the emergence of bacterial resistance to previously sensitive antibiotics (Guillemot, 1999).

Antibiotic prescribing in primary care settings has been empirical and based on nonspecific clinical signs and symptoms, rather than on more accurate diagnostic tools readily available in secondary care, such as radiology, immunology, microbiology, and blood chemistry tests. Some of these empirical clinical assessments are objective, such as temperature, blood pressure, and

respiratory rate; others are more subjective, including pain, inflammation, and general malaise. Most of these assessments are incorporated into clinical decision rules and evaluated for their negative or positive prognostic utility (Cooke *et al*., 2020).

2.2 Respiratory tract infections

Acute respiratory tract infections are associated with an excessive and inappropriate use of antibiotics worldwide. Approximately 70% of infectious diseases are respiratory tract infections (RTIs), the most common being acute bronchitis, acute rhinosinusitis, and acute pharyngitis or pharyngotonsillitis (Del Poza Abad *et al*., 2013). Among other infections, although less frequent, otitis media, pneumonia, bronchitis, and adenoiditis contribute to increased RTI morbidity, especially in children (Silva *et al*., 2013) and HIV-infected adults (Brown *et al*., 2020).

RTIs are among the most common acute conditions leading to ambulatory consultation and antibiotic prescriptions, although 70% are viral in origin and a small proportion are bacterial infections (Cooke *et al*., 2020). Thus, antibiotic use in these situations is often considered wasteful and unwarranted (Marchete *et al*., 2011; Ladd, 2005). There is concern that the lack of new antibiotics will threaten global efforts to contain infections resulting from antimicrobial resistance, and therefore, countries should strive to preserve existing agents and not use them indiscriminately.

2.2.1 Upper respiratory tract infections

Upper respiratory tract infections (URTIs) are common in adults, and they experience an acute course two to five times per year. Acute URTIs refer to acute infections involving the nasal passages, sinuses, throat, and larynx (Yoon *et al*., 2017). The most common acute URTIs include the common cold (acute rhinitis/nasopharyngitis), sinusitis, pharyngitis and tonsillitis (sore throat), and laryngitis or epiglottitis (hoarseness). The common cold, primarily caused by rhinoviruses, is the most frequent URTI (Wat, 2004). However, these URTIs are diagnosed clinically based on predominant symptoms, according to the anatomical location with the most severe infiltration (Yoon *et al*., 2017).

Approximately 90% of all acute URTIs are caused by viruses, but antibiotics are prescribed for 50% to 70% of patients seeking medical care for these conditions (Neiderman *et al*., 1998). For example, in the United States of America (USA), over 60% of uncomplicated acute URTI cases in adults

are prescribed antibiotics, with a significant increase in broad-spectrum antibiotics (Wong *et al*., 2020). In the United Kingdom, approximately 50% of all general physician consultations for URTIs result in an antibiotic prescription, although the range varies from 20% to 80% (Gulliford *et al*., 2014). In the Netherlands, only 22.5% of URTI episodes in 2010 resulted in an antibiotic prescription (Van den Broek d'Obrenan *et al*., 2014).

The common cold is viral in origin, primarily caused by rhinoviruses, with symptoms like an abrupt onset of mild fever, nasal discharge, congestion, sneezing, sore throat, nonproductive cough, and muscle aches. The common cold typically resolves on its own, often requiring only symptomatic treatment in certain cases. Antiviral medications can shorten the duration of symptoms by approximately 24 hours but are only effective when administered within the first 36 hours of illness (Wong *et al*., 2006). The use of antibiotics for the common cold is ineffective in reducing complications such as bacterial infection and also increases medical costs by inducing adverse effects and antibiotic resistance (Wat, 2004). Avoiding the use of antibiotics for the common cold is a strategy that should be reinforced to prevent antibiotic overuse and misuse (Yoon *et al*., 2017; Gonzales *et al*., 2017). However, patients with bacterial and viral infections present with similar symptoms, and clinically differentiating between patients who require antibiotics and those who do not is a challenge in clinical practice (Wong *et al*., 2020).

Sinusitis involves inflammation of the sinuses, often causing nasal congestion and facial pain. Pharyngitis, or sore throat, can be viral or bacterial, while laryngitis involves inflammation of the voice box, leading to hoarseness (Carvalho *et al*., 2025).

Tonsillitis is characterized by pain when swallowing, fever, and general malaise. Pharyngitis is milder, with mild pain, a cough with secretions, no fever, and with or without voice hoarseness. Most patients with a sore throat due to an infectious cause have a virus (Wong *et al*., 2006). Symptoms that suggest a viral etiology for sore throat include conjunctivitis, cough, and runny nose. Approximately 5–15% of tonsillitis in adults, particularly in late winter, is caused by bacteria such as Streptococcus pyogenes, and 0.5–2% of patients may develop acute bacterial rhinosinusitis after a viral respiratory infection (Yoon *et al*., 2017; Kalra *et al*., 2016). Approximately 80% of these episodes occur in primary care settings (Kalra *et al*., 2016).

2.2.2 Lower respiratory tract infections

Lower respiratory tract infections (LRTIs) are infections that affect the lower airways and lungs, including conditions like pneumonia, bronchitis, and bronchiolitis. LRTIs can be caused by various pathogens, most commonly viruses and bacteria, and can range in severity from mild to life-threatening (Hussain *et al*., 2024). Acute LRTIs are those that last 21 days or less, typically characterized by cough as the primary symptom, accompanied by at least one other respiratory tract symptom (such as sputum production, dyspnea, wheezing, or chest discomfort/pain), and with no alternative explanation, excluding conditions like asthma or sinusitis (Woodhead *et al*., 2011).

Bronchitis is an inflammation of the bronchial mucosa, leading to a productive cough. Diagnosis is based on clinical evaluation, and no objective test exists. Sputum characteristics (green versus clear versus absent) are not useful in differentiating acute bronchitis from bacterial or viral causes. Over 90% of uncomplicated acute bronchitis cases have nonbacterial causes, and thus, antibiotics are generally not indicated for this condition (Wong *et al*., 2006). If pneumonia is suspected based on tachypnea, high fever, asymmetric breath sounds, or other symptoms, the diagnosis should be confirmed with a chest X-ray before prescribing antibiotics. However, approximately 10% of acute bronchitis cases can be caused by bacteria such as Bordetella pertussis, Mycoplasma pneumoniae, and Chlamydophila pneumoniae (Yoon *et al*., 2017).

To differentiate pneumonia from other respiratory infections, the patient must have an acute cough and one of the following signs or symptoms: new focal chest signs; dyspnea, tachypnea, or fever lasting >4 days. If pneumonia is suspected, a chest X-ray should be performed to confirm the diagnosis (Woodhead *et al*., 2005).

Antibiotic treatment in patients with LRTI should be considered in the following situations: suspected or definite pneumonia; selected exacerbations of chronic obstructive pulmonary disease (COPD); age > 75 years and fever; heart failure; insulin-independent diabetes mellitus; and severe neurological impairment (Woodhead *et al*., 2005).

In a cohort analysis examining clinically diagnosed patients with LRTI who were more likely to receive antibiotic prescriptions (i.e., patients with green sputum or significant comorbidities), no clear evidence of significant benefit from amoxicillin was found. Only patients with evidence of pneumonia on chest radiographs benefited from amoxicillin treatment (Bruyndoncky *et al*., 2017). However, chest radiography is not performed for most patients in primary care settings.

2.3 HIV and respiratory tract infections

There are clear associations between a weakened immune system and the risk of developing specific RTIs (Table 1). The most frequent RTIs in the HIV-infected patients are URTI and acute bronchitis (Benito *et al*., 2012). They occur at all strata of CD4 cell counts and for patients who are well controlled on ART have similar clinical outcomes to those of HIV-non-infected patients (Benito *et al*., 2012; Ojha *et al*., 2015). Recurrent bacterial pneumonia and pulmonary tuberculosis occur more frequently in patients with CD4 cell counts of less than 400 cells/μL. Pneumocystis pneumonia (PCP) and disseminated tuberculosis are usually diagnosed when CD4 cell counts drop below 200 cells/μL. Disseminated MAC, fungal pneumonia, and cytomegalovirus pneumonitis occur in patients with the most severe immunosuppression (CD4 cell counts less than 100 cells/μL) (Benito *et al*., 2012).

Bacterial pneumonia occurs more frequently in HIV-infected patients than in the general population. It occurs at any CD4 cell count, but it is common as HIV infection progresses. The spectrum of bacterial pathogens in community-acquired pneumonia is similar to that in the general population, and Streptococcus pneumoniae remains the most common (Benito *et al*., 2012). Staphylococcus aureus and Pseudomonas aeruginosa are seen more frequently in the advanced stage. Treatment is similar to that for HIV-non-infected patients. Cotrimoxazole for PCP prophylaxis may be effective in preventing bacterial pneumonia (Benito *et al*., 2012). Some RTIs may be prevented through vaccination of HIV-infected patients. For example, influenza and pneumococcal vaccination are indicated in HIV-infected patients (Larsen *et al*., 2021).

With the advent of antiretroviral therapy, many HIV-infected patients have improved their immune status, thus reducing the likelihood of occurrence of HIV-related opportunistic infections and improving their quality of life (Briongos-Figuero *et al*., 2011; Campos *et al*., 2009).

Table 1. Associations of RTIs with different strata of CD4. Most pulmonary infections occur with increasing frequency at lower CD4 cell counts.

CD4 cell counts when infection first occurs	RTIs
>500 cells/μL	Acute pharyngitis, bronchitis, sinusitis Pneumonia Pulmonary TB
200 – 500 cells/μL	Recurrent bacterial pneumonia Varicella zoster pneumonitis
100 – 200 cells/μL	PCP Disseminated TB
<100 cells/μL	Disseminated MAC CMV pneumonitis Herpes simplex pneumonitis

CD4: cluster of differentiation 4, a glycoprotein found on the surface of immune cells; RTIs: respiratory tract infections; TB: tuberculosis; PCP: Pneumocystis pneumonia; MAC: Mycobacterium avium complex; CMV: Cytomegalovirus.

2.4 Strategies for reducing antibiotic prescriptions

Patients with acute respiratory infections typically expect to receive an antibiotic. Because healthcare providers strive for patient satisfaction, they may feel pressured to prescribe an unnecessary antibiotic (Wong *et al*., 2006). If the diagnosis is a viral illness, the clinician needs to have a contingency plan to explain to the patient why an antibiotic will not be prescribed. Patients should be informed about the difference between bacterial and viral infections and why antibiotics will be ineffective for a viral illness (Cuevas *et al*., 2021). Targeted symptomatic relief can be provided with antipyretics, decongestants, antihistamines, and cough suppressants (Wat, 2004).

Several studies indicate that giving patients an antibiotic prescription and telling them not to take it unless their symptoms worsen or do not improve after several days has been shown to reduce antibiotic use (Dowell *et al*., 2001; Arroll *et al*., 2006; Wong *et al*., 2006; Saguil, 2016). Therefore, delayed antibiotic prescribing and the use of clinical scoring tools based on combinations of signs and symptoms significantly reduce antibiotic prescribing rates (Saguil, 2016). An educational intervention, such as educating patients on responsible antibiotic use, can help maintain patient satisfaction without antibiotic prescriptions (Wong *et al*., 2006).

2.4.1 Clinical decision support

2.4.1.1 Algorithms

There is evidence that algorithms can improve management and reduce antibiotic prescribing. Tabatabaei *et al*. (2012) evaluated the feasibility of a new algorithm in reducing misdiagnosis rates and inappropriate antibiotic use in the treatment of acute RTIs in pediatric patients. The study concluded that the use of the new algorithm is feasible and can help reduce diagnostic errors and the frequency of antibiotic prescribing in pediatric patients with RTIs.

Shao *et al*. (2015), using a quasi-experimental study in a primary healthcare setting, evaluated an algorithm to support the integrated management of childhood illnesses. The study reported a statistically significant improvement in adherence to the algorithm between the control group (routine practice) and the intervention group. The study concluded that using the new algorithm improved clinical outcomes and reduced antibiotic prescribing by 80%.

Rambaud-Althaus *et al*. (2017), using a randomized controlled trial design, evaluated the effect of algorithms that support the integrated diagnosis and treatment of common diseases among children in primary healthcare settings. They compared a control group with two different algorithm support methods: paper-based and electronic (smartphone). Although both the paper-based and smartphone-based algorithms showed a reduction in antibiotic prescriptions, they were unable to identify which patients whose pathologies required antibiotics. Therefore, compared to the control group, there was a considerable number of patients who needed antibiotics but did not receive them. Patient follow-up should be improved and is relevant to addressing resistance and combating health problems.

However, the algorithms used in these studies are distinct from the algorithm used in this research project. Furthermore, the studies described were conducted in primary healthcare settings and on pediatric patients. This thesis is a result of a research project conducted in primary healthcare settings, but on adult and HIV-infected patients.

2.4.1.2 Rapid diagnostic test

Misdiagnosis of viral illnesses such as influenza and the overuse of antibiotics can be reduced by using a rapid influenza test in outpatient settings. Bhavnani *et al*. (2007) evaluated a rapid influenza diagnostic test in outpatients in rural Thailand and found that a negative influenza test result was associated with a reduction in antibiotic prescribing. However, the level of the reduction was

modest, suggesting that comprehensive reductions will require more than improved diagnostics.

Rapid point-of-care testing to quickly determine the likelihood of a patient having a specific infection significantly reduces antibiotic prescribing (Saguil, 2016; Cooke *et al*., 2020). For example, the use of rapid antigen detection tests for streptococcal infection in throat swab samples, multi-viral polymerase chain reaction (PCR), and a specific influenza throat test may also be used. Tests to detect whether an infection is bacterial rather than viral, such as blood procalcitonin and C-reactive protein (CRP), are also used (Díez-Padrisa *et al*., 2010; Wu *et al*., 2017; Petel *et al*., 2018). A narrative review of the literature undertaken to ascertain the value of CRP point-of-care testing to guide antibiotic prescribing in adults presenting to ambulatory care with RTI symptoms reported that there is evidence of the use of CRP tests in reducing the index of antibiotic prescribing (Cooke *et al*., 2020).

2.4.2 Increasing the knowledge of healthcare providers

2.4.2.1 Education

Continuing education for healthcare providers can be effective; however, a gap exists between actual and reported practice, with physicians underestimating or underreporting antibiotic prescribing. Two studies have examined direct training interventions. Shrestha *et al*. (2006) evaluated a five-day training course on the new WHO prescribing guidelines for lung health in primary care settings. Sun *et al*. (2015) assessed the knowledge, attitudes, and practices of clinicians in China. Clinicians who participated in the training reported that they were less likely to prescribe antibiotics. However, a separate analysis of prescriptions revealed high levels of antibiotic prescribing. Esmaily *et al* (2010) evaluated a two-day training course for primary healthcare clinicians on prescribing principles and found no improvement in prescribing levels, although the intervention was not extensive.

Continuous education for clinicians on current treatment guidelines and communication skills training programs for healthcare providers are some strategies that can reduce antibiotic prescribing (Saguil, 2016). Clinical guidance to patients or parents about when antibiotics may be appropriate (e.g., videos, pamphlets, education, waiting room posters) and public education campaigns (e.g., outdoor advertising, public transportation, radio and television commercials) are strategies that can be integrated to reduce antibiotic prescribing (Saguil, 2016).

2.4.2.2 Education and feedback

To different degrees, Apisarnthanarak *et al*. (2006), Bantar *et al*. (2003), Kafle *et al*. (2009), and Opondo *et al*. (2011) combined education, support, and monitoring in multifaceted interventions. The components included theoretical and practical training sessions, tools (e.g., guidelines and job aids), management processes (e.g., order forms), regular supervision by senior colleagues, opportunities to discuss guideline implementation, facilitators/champions, and face-to-face and group discussions and feedback on performance. Three were conducted in hospital settings and one in primary healthcare. These interventions were educational but combined knowledge with restrictive and facilitative approaches. After the interventions, these authors reported a significant reduction in antibiotic prescribing rates and improved prescribing practices. However, the healthcare provider education strategy is most effective when combined with monitoring and feedback from seniors or specialists.

2.4.2.3 Audit and feedback

Successful interventions involved repeated feedback combined with face-to-face educational support strategies and monitoring, and similar approaches have demonstrated effectiveness in both hospitals and primary care settings. Awad *et al*. (2006), Eltayeb *et al*. (2005), Messina *et al*. (2015), and Shen *et al*. (2011) evaluated the effects of audit and feedback on prescribing behavior in hospitals and primary care settings. The interventions lasted between six months and one year. All interventions targeted appropriate antibiotic prescribing and included combinations of audit and feedback, expert review, regular reports to management/superiors, reminders, recommendations, and discussion of inappropriate prescribing, educational seminars, and in-person training courses. Awad *et al*. (2006) and Eltayeb *et al*. (2005) tested different intervention combinations and found that auditing and feedback alone were less effective than when combined with other educational and follow-up components. However, all authors reported a reduction in antibiotic prescribing rates and improved prescribing practices.

2.4.3 Stewardship or organization of the health service

2.4.3.1 Antimicrobial Stewardship

Comprehensive antibiotic stewardship campaigns using various approaches have resulted in significant reductions in antibiotic prescribing frequency and sales in hospitals and pharmacies. Kalel *et al*. (2017), Ma *et al*. (2016), Ozkurt *et al*. (2005), and Zhang *et al*. (2017) evaluated the effects of antibiotic stewardship programs in secondary and tertiary hospitals, while Markovi´c-Pekovi´c *et al*. (2017) evaluated the effects of the program in pharmacies. Interventions included the formation of interdisciplinary expert groups to provide supervision and guidance, knowledge dissemination, clinical training, academic engagement (e.g., participation in conferences and seminars), monitoring, feedback, data management and verification, the development of new guidelines and targets, and the implementation of financial penalties. In the study by Ma *et al*. (2016), doctors who failed to comply with the new regulations had their salaries docked, and in the study by Markovi´c-Pekovi´c *et al*. (2017), pharmacists were fined for selling antibiotics without a prescription. This latter study of pharmacists also included public awareness campaigns and policy coordination as part of a national management effort. However, the authors also found that pharmacists provided less oral or written advice about antibiotic sales, which they suggested could indicate an attempt to mask the practices. Increased sales restrictions may lead vendors to sell antibiotics in more covert or unsafe ways.

Magedanz *et al*. (2012) evaluated an antibiotic stewardship program, which included, in part, auditing and feedback focused on restricting certain antibiotic classes. The study concluded that there was a reduction in the prescribing of some restricted antibiotics, apparently driving an increase in the use of others.

2.4.3.2 Essential Medicines Policy

Essential drug policies have had mixed effects and highlighted the need to integrate antibiotic use action with other health system initiatives. Ding *et al*. (2016) and Wei *et al*. (2017) evaluated the effects of China's essential drug policy on antibiotic prescribing levels in hospitals, while Song *et al*. (2014) and Yao *et al*. (2015) studied its effects in primary care. Essential drug policies are multifaceted, involving: establishing an essential drug list, supply chain measures, and price controls. Results were mixed across regions, urban-rural settings, and different facilities, depending on implementation. Prescription

of some antibiotics increased or decreased depending on their inclusion on the lists, as did the cost of treatment. Some interventions coincided with other initiatives (e.g., hospital-level antibiotic stewardship program), which made it difficult to separate the effects, including broader health system reform (e.g., no-appointment policy) and delivery (e.g., health insurance programs), and may be responsible for changes in antibiotic prescribing patterns.
Yang *et al*. (2013) evaluated China's national essential medicines policy and found that while the availability and cost of essential medicines increased, there was no reduction in the number of antibiotics prescribed. This is likely due to the policy's focus on expanding access to quality services and affordable medicines for citizens, rather than explicitly focusing on prudent drug use.

2.5 Factors influencing antibiotic prescribing behavior

Factors influencing prescribing behavior fall into four main categories: patient-related factors, product-related factors, prescriber factors (including clinical experience, workload, attitudes, beliefs, and training), and environmental factors (such as guidelines, colleague influence, pharmaceutical promotion, and policy). These elements interact to create a complex decision-making process for prescribers.

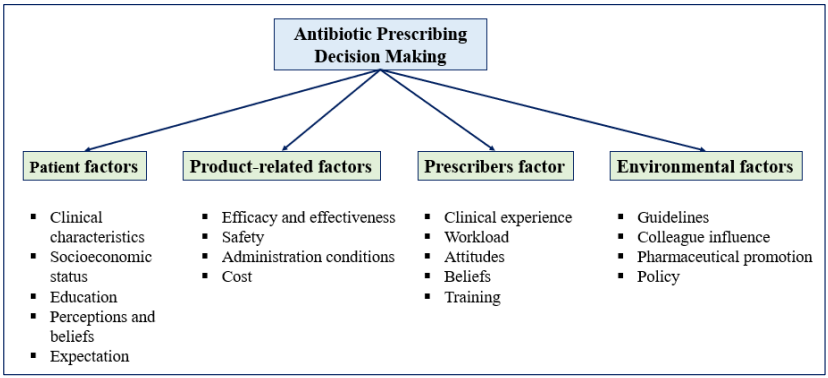

Figure 1. Factors influencing antibiotic prescribing behavior

2.5.1 Patient-related factors

Some studies reported that the practitioner's perception of patients' expectations influences antibiotic prescribing (Zhang *et al*., 2016; Lum *et al*., 2018; Laka *et al*., 2022). A study conducted in China reported that patients

often had an expectation of receiving antibiotics when they visited healthcare providers, and a perception of this expectation pressures clinicians to prescribe (Reynolds & McKee, 2009). Another study noted that clinicians commonly overprescribe antibiotics due to patient expectations and preferences (Chan *et al*., 2019). The expectations and preferences of patients who have previously received antibiotics affect the decision of clinicians (Swe *et al*., 2021).

The economic status of patients affects both the actual and perceived need for antibiotics (Reynolds & McKee, 2009). Patients do not want to waste money on another prescription; instead, they use their previous prescription to purchase drugs from a private or public pharmacy (Ahmadi & Zarei, 2017). Likewise, a study focusing on prescribing patterns and factors associated with antibiotic prescriptions in primary healthcare facilities reported that patients with lower financial capacity exerted less pressure on physicians to prescribe antibiotics (Chem *et al*., 2018). Conversely, two studies reported that patients with low income, individual unemployment status, and high uncertainty avoidance are likely to result in patient demand for physician prescription of antibiotics (Kotwani *et al*., 2010; Laka *et al*., 2021).

Patient social characteristics such as education, health literacy levels, and occupation have potentially impacted the perceived need for prescribing antibiotics (Chan *et al*., 2019). Patients who engage in self-diagnosis and self-medication requested specific antibiotics compared with patients who did not know antibiotics (Kotwani *et al*., 2010). Besides, patients' relationship with clinicians and the deliberate exaggeration or misinformation of symptoms affects the prescription of antibiotics (Guo *et al*., 2021). Some patients claiming antibiotic prescriptions believe that they know their body and only an antibiotic can help them, and that they need to recover quickly (Swider *et al*, 2024).

2.5.2 Product-related factors

Product efficacy/effectiveness, safety, administration conditions, and cost are product-related factors influencing antibiotic prescribing. The clinical effectiveness of a drug forms one of the most crucial factors for prescribing a drug to patients (Bandi *et al*., 2024). The literature highlights the clinicians' inclination for drugs with proven efficacy, demonstrated results, the onset of action, safety profile, compatibility with other drugs, and lacking complications with a least potential for resistance development (Abulhaj *et al*., 2013; Mikhael & Alhilali, 2014; Bandi *et al*., 2024). Due to these factors, clinicians choose to prescribe the products with the brand name to their patients for managing pathological conditions as the branded drug stands by its promise with an assurance of a predictable outcome in the form of relief

to the patient at an affordable price, unlike a generic substitute (Manju & Sharma, 2020; Chukwu *et al*., 2021).

2.5.3 Prescriber factors

The literature shows that clinicians who actively refresh their expertise through continuing medical training, workshops, seminars, and journals are less likely to prescribe antibiotics (Bharathiraja *et al*., 2005; Sharaf *et al*., 2021). In addition, diagnostic uncertainty combined with time constraints influenced physicians' antibiotic prescribing practices (Aabenhus *et al*., 2017). A survey conducted in the United Kingdom reported that time pressure, especially the limited time available for consultation, has an impact on increased antibiotic prescribing in primary healthcare (van der Zande *et al*., 2019). Another study reported that complacency, fear, and insufficient knowledge were additional factors influencing the prescribing of antibiotics by clinicians (Chem *et al*., 2018). However, clinicians who practice only outpatient medicine are more likely to prescribe antibiotics than those in inpatient settings (Cordoba *et al*., 2017; Chem *et al*., 2018).

2.5.4 Environmental factors

Antibiotic prescribing is affected by the presence of and adherence to evidence-based clinical guidelines and protocols for antibiotic use. Quantity and quality of service are associated with antibiotic prescribing practices and variability of prescribing antibiotics in primary health care physicians (Kasse *et al*., 2024). Weak regulation of health systems, the dissemination of medical information, and practice setting characteristics are some environmental factors that influence antibiotic prescribing (Khalfan *et al*., 2022; Kasse *et al*., 2024).

Pharmaceutical marketing tools play a crucial role in influencing physicians' prescribing behavior. Physicians' interactions with sales representatives in a competitive environment have been found to affect the physicians' prescribing behavior with a wide array of pharmaceutical marketing tools. Physicians have shown an inclination towards scientific promotion led by product detailing from the visual aid, mentioning the brand name, followed by the presentation of useful information in the form of brochures and booklets relating to the product (Bandi *et al*., 2024). They have also shown an inclination towards financial support for attending conferences of repute, workshops, preferably online, focusing on the latest developments for implementation in the practice for patient benefit, and accepting gifts based on the utility (Sharma *et al*., 2021; Bandi *et al*., 2024).

In the case of developing countries, the literature has indicated a positive correlation between the credibility of marketing and promotion tools in comparison to the extent to which they influence prescription behavior. Studies have reported that over 50% of physicians perceived that pharmaceutical marketing strategies influence their prescribing behavior (Sharma *et al*., 2021; Bandi *et al*., 2024). Like the developed world, physicians from the developing world have shown an inclination towards scientific promotional literature, including clinical trial results, quality in the service provided, promotional items, or tangible rewards being presented, and conference participation towards improving knowledge and skills (Sharma *et al*., 2021; Ali *et al*., 2022).

Likewise, studies have shown that the major tools that clinicians agree to are mostly motivated by the visits of medical representatives, as they are the most important source of information (Ali *et al*., 2022; Bandi *et al*., 2024). Although this holds for the developed world as well, in the developing world, clinicians expect value addition from pharmaceutical representatives, and they expect them to be trained enough to handle their product queries with standards of market knowledge, product knowledge, and to maintain the corporate reputation (Bandi *et al*., 2024).

2.6 The burden of antimicrobial resistance

Antimicrobial resistance (AMR) is a "Silent Pandemic" and represents an established public health threat, a status recognized by the World Health Organization (WHO), which is responsible for millions of deaths worldwide (Ahmed *et al*., 2024; Naghavi *et al*., 2024). Global estimates indicate that the number of deaths directly attributable to AMR reached over 1.14 million, and associated with AMR, 4.71 million deaths in 2021 (Naghavi *et al*., 2024). Without adequate measures to control AMR, the WHO report on antibiotic resistance projects that this figure could surge to around 10 million deaths annually by the year 2050 (Ahmed *et al*., 2024).

The threat of AMR extends far beyond clinical outcomes, posing a significant danger to global economic stability. International bodies, including the World Bank, have forecasted that without effective containment, AMR could reduce the annual global Gross Domestic Product (GDP) by as much as 3.8% by 2050, pushing millions into extreme poverty (Pokharel *et al*., 2019; Aslam *et al*., 2024). This economic burden manifests through increased healthcare expenditures, prolonged hospital stays, and losses in labor productivity, straining even the most resilient health systems (Pokharel *et al*., 2019; Naghavi *et al*., 2024).

The WHO Global Action Plan provides a roadmap, calling for a multisectoral response to combat AMR (WHO, 2015; Aslam *et al*., 2024; Jamil *et al*., 2025). This plan emphasizes the need to improve public awareness (Strategic Objective 1), strengthen the evidence base through surveillance (Strategic Objective 2), and optimize the use of antimicrobial medicines (Strategic Objective 4). Mozambique's national action plan against AMR was reviewed in 2023, assessing the current burden of AMR, and exploring how vaccines can help mitigate it, as well as identifying key actions (One Health Trust, n.d.). Fulfilling these objectives in Mozambique requires targeted research that can generate the necessary evidence, local data, and insights for interventions, especially given the country's unique challenges in combating AMR (WHO, 2015).

AMR existed in nature before humans began using antimicrobials, and its development is driven by natural selection. Resistant bacteria thrive in environments exposed to antimicrobials. Enzyme activity plays a significant role in many forms of AMR, as resistant bacteria transfer genes to the next generation (Aslam *et al*., 2024). The complex relationship between antimicrobials, resistance, and microbial dynamics underscores the value of responsible and judicious use to ensure their continued efficacy. Nevertheless, AMR is experiencing a sharp rise, exacerbated by the obsolete standard antibiotic treatment regimens, posing the risk of patients in critical conditions requiring palliative care, and yet the prescribed drugs are no longer clinically effective (WHO, 2019a; Aslam *et al*., 2024). WHO studies on clinical and preclinical drug development highlighted a limited pipeline for new antibiotics, raising concerns about the global efforts to control drug-resistant infections (WHO, 2019b). The pillars to promote and support antimicrobial stewardship to address AMR likely encompass aspects of awareness, education, monitoring, and enforcement to ensure responsible antibiotic use (Aslam *et al*., 2024).

The nature of AMR progression necessitates the adoption of the "One Health" concept, a comprehensive approach recognizing the interconnectedness of human, animal, plant, and environmental health (Velázquez-Meza *et al*., 2022). This approach informs comprehensive mitigation strategies by targeting the drivers of resistance across each dimension. In human health, this involves optimizing clinical prescribing practices, including appropriate drug selection, dosing, and duration, and addressing patient behaviors such as self-medication, expectations, and beliefs (McEwen & Collignon, 2018). In animal and plant health, it requires regulating antibiotic use in animal production, agriculture, and aquaculture for growth promotion and preventing diseases, as well as selecting appropriate drugs, dosing, and duration

(McEwen & Collignon, 2018; Velázquez-Meza *et al*., 2022). Environmental health addresses the environment as a critical reservoir for resistant genes, focusing on strategies like the proper disposal of unused medications to prevent the contamination of soil and water systems with selective antibiotic residues (McEwen & Collignon, 2018). However, AMR can be reduced when antimicrobials are used only as a treatment, rarely for prophylaxis, and never as growth promoters (Velázquez-Meza *et al*., 2022).
From the perspective of human health to combat AMR, this thesis focuses on optimizing clinical prescribing practices through the utilization of a CDSA, aimed at de-prescribing unnecessary antibiotics. For the successful implementation of this intervention, clinicians need to change their prescribing behavior.

2.7 Theory of change of prescribing behavior

The theory of change serves as a valuable tool, given that by utilizing it, we can assess the effectiveness of implemented activities and determine their impact on health outcomes (Rogers, 2014). Moreover, it allows us to identify areas for improvement and replicate successful strategies in other locations (Breuer, 2015).
This thesis draws on the theory of change to improve prescribing behavior, ultimately reducing antibiotic prescribing and enhancing the quality of life for adult HIV-infected patients (Figure 2). Through multifaceted activities, we seek to address key cognitive, behavioral, and health outcomes.
By conducting training on the use of the CDSA and other intervention elements, including the distribution of intervention tools (i.e., CDSA, questionnaires, informed consent, case record notebook), clinicians will absorb the intervention elements and increase their knowledge and confidence in the management of URTI symptoms, because they will be better equipped for the implementation of the intervention. Likewise, the collaboration with stakeholders will facilitate the linkage and exchange of information about the intervention, thereby increasing knowledge and confidence. On the other hand, conducting prescription audit and feedback will improve knowledge of the use of the CDSA and the other intervention elements, thereby increasing confidence in the management of URTI symptoms. In addition, in the meantime, documentation of all intervention logs will allow for assessment of cognitive, behavioral, and health outcomes.
Ultimately, improved knowledge and increased confidence of clinicians will result in the de-prescription of antibiotics and encouragement of patients regarding the delay of antibiotic prescription, thereby reducing antibiotic

prescribing and, in turn, enhancing the quality of life for HIV-infected patients.

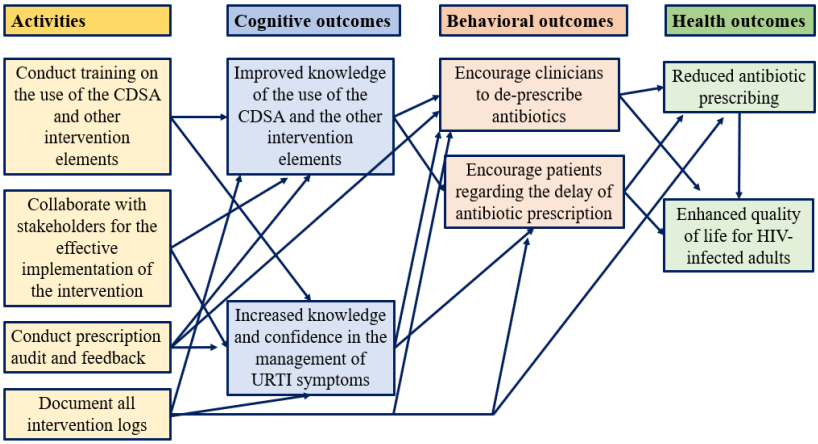

Figure 2. Diagram of the theory of change

CHAPTER 2

RATIONAL AND OBJECTIVES

1. Motivation

The primary motivations to conduct this research project are to combat escalating AMR, which threatens to make antibiotics ineffective, and to mitigate the high burden of infectious diseases in Mozambique. Inappropriate and excessive antibiotic use, including self-medication and non-prescription dispensing, fuels AMR and leads to adverse drug reactions.

There is evidence of the prevalence of self-medication with antibiotics in Mozambique, a practice that contributes significantly to irrational consumption (Torres et al., 2020). In addition, antibiotics, despite being prescription-only medicines, are frequently dispensed without professional oversight, further contributing to inappropriate use. Clinicians also contribute to overuse by frequently prescribing antibiotics for non-bacterial infections or empirical use in situations where they may not be needed, such as the common cold and influenza (Alsan et al., 2015; Refaei et al., 2024).

Mozambique has a national action plan to combat AMR under the "One Health" approach, highlighting the government's commitment to promoting the rational use of antibiotics (MISAU & MASA, 2019). Implementing interventions to optimize rational antibiotic use can improve patient outcomes, protect the effectiveness of antibiotics, and align with Mozambique's national strategy to tackle AMR and enhance public health. On the other hand, these interventions can reduce adverse drug reactions, improve patient safety, and ensure the long-term availability of effective antibiotic treatments.

This work will gather evidence that will be used to strengthen the rational use of antibiotics in managing URTIs in primary healthcare facilities across Mozambique.

2. Rational and problem

Despite strong evidence of viral origin, antibiotics are still inappropriately overprescribed to treat URTI symptoms. The inappropriate use of antibiotics and lack of structured antimicrobial stewardship programs have fostered the emergence of antibiotic resistance, which makes infections harder, more expensive, and sometimes impossible to treat, increasing the risk of severe illness, complications, prolonged hospital stays, and death (Aslam et al., 2024). Other consequences include disruptions to the gut microbiome, an increased risk of side effects such as diarrhea and rashes, and higher healthcare costs. In addition, given that antibiotics are unsubsidized drugs, the emergence of resistant bacteria leads to an increased need for new antibiotics, which significantly contributes to the rising costs of medical care to both

patients and the National Health System. Meanwhile, the discovery of new antibiotics has been slow (Aslam et al., 2024). There is a risk that, without adopting rational antibiotic use strategies, there will be no effective drugs to treat bacterial infections in the future (WHO, 2019; Ahmed et al., 2024).

Mozambique, like many African countries, faces a high burden of infectious diseases, exacerbated by the rise of AMR. On the other hand, there is a significant knowledge gap regarding AMR trends and patterns, with sparse information available on resistance rates and limited implementation of robust surveillance systems. Notably, a lack of affordable and reliable diagnostic tools hinders effective treatment and monitoring of resistance. Without effective interventions, AMR threatens to undo decades of progress in controlling infectious diseases, leading to treatment failures and increased mortality. Addressing AMR burden requires strengthening diagnostic capacity, improving infection prevention and control, and implementing strategies to rationalize antibiotic use (WHO, 2015).

HIV-infected patients are subject to lifelong antiretroviral therapy (ART), and the development of an RTI requires a combination with an antibiotic or other medicines, increasing the number of medications. Combining medications can lead to drug interactions, which can decrease the effectiveness of one drug, contributing to therapeutic failure, or increase the pharmacological effect, leading to the emergence of adverse drug events (Secoli, 2001). This situation can worsen the clinical condition of HIV-infected patients, increasing the risk of morbidity and mortality (Mateus et al., 2022).

3. Contribution

The purpose of implementing our intervention is to promote the rational use of antibiotics among clinicians attending HIV-infected adults with URTI symptoms in primary healthcare settings where limited laboratory diagnostic support is a serious problem. HIV-infected patients will benefit from appropriate antibiotic prescribing, potentially reducing the number of medications they are exposed to, thereby reducing the risk of drug interactions, adverse drug events, and costs associated with antibiotics.

For healthcare providers, the CDSA will support them when making decisions to prescribe antibiotics. It will allow clinicians to manage their patients with URTI symptoms in situations of limited laboratory support and promote practice change, de-prescribing antibiotics if deemed unwarranted. The research may contribute to improving the quality of prescriptions, reducing inappropriate antibiotic use, and, in turn, contributing to the combat of antimicrobial resistance.

For the National Health System, the CDSA could be recommended and

used for the management of URTIs in both HIV-infected and HIV-non-infected patients. It could also be validated for use in all primary healthcare facilities in the country. However, the findings will allow for appropriate recommendations to the health authorities, healthcare providers, and patients with URTI symptoms.
De-implementation has been understudied in primary healthcare settings in Mozambique. Findings from this thesis will add to the evidence base around how to de-implement unnecessary antibiotic use in primary healthcare settings.

4. Objectives

4.1 Aim and objectives

This thesis aimed to evaluate the effectiveness and implementation of a clinical decision support algorithm (CDSA) to de-prescribe unnecessary antibiotics among HIV-infected adults with upper respiratory tract infection (URTI) symptoms in primary healthcare settings in the cities of Maputo and Matola, Mozambique.

4.2 Specific objectives

- Paper I (Study 1): To explore and describe antibiotic prescribing to HIV-infected patients managed in primary healthcare settings in the cities of Maputo and Matola, Mozambique.
- Paper II (Comprehensive study protocol): To describe the frameworks and methods guiding the implementation of the strategy to de-implement unnecessary antibiotic use.
- Paper III (Study 2): To explore and understand the pre-implementation contexts of the study sites and to identify potential and/or actual determinants that could influence the successful implementation of the intervention.
- Paper IV (Study 3): To evaluate the effectiveness of a CDSA on reducing unnecessary antibiotic prescriptions for URTIs among HIV-infected adults in primary healthcare settings.
- Paper V (Study 4): To evaluate the process of implementation of the CDSA to de-implement unnecessary antibiotic prescriptions among ambulatory HIV-infected adults with URTI symptoms using the RE-AIM framework.

CHAPTER 3

MATERIAL AND METHODS

1. Study design

For this thesis, we employed a hybrid type II effectiveness-implementation multifaceted study utilizing a cluster randomized controlled trial design with a mixed methods approach, guided by the Dynamic Adaptation Process (DAP) and RE-AIM frameworks. DAP is a framework that allows iterative adaptations or changes to be made according to the real context, and this was used to guide the implementation process. It provides a four-phase process for implementing an evidence-based practice: the pre-implementation (exploration) phase, the adaptation (preparation) phase, the implementation phase, and the post-implementation phase (Aarons et al., 2012). Afterwards, we used RE-AIM, a planning and evaluation framework, to evaluate the implementation of our research project (Figure 3).

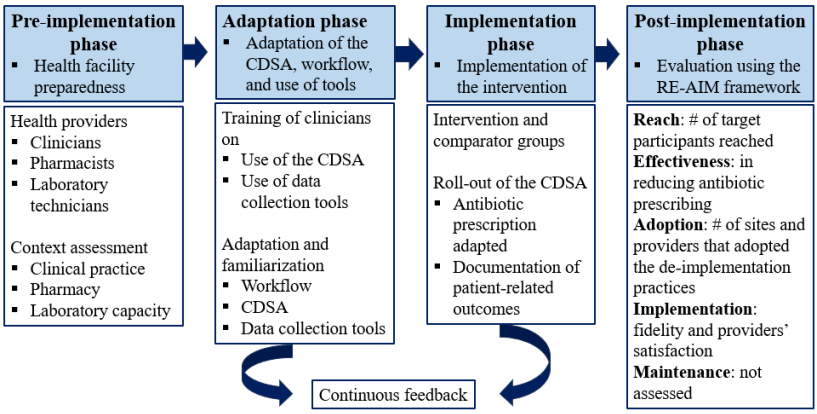

Figure 3. The Dynamic Adaptation Process (DAP) that guided the implementation of the research project

The topics and questions of each study are summarized in Table 2, and all were based on primary data.

Table 2. Summary of the four studies related to this thesis

Study	Topic	Research question	Study design	Participants	Data collection	Analysis
1	Antibiotic prescribing to HIV-infected patients	What are the specific patient demographics and clinical conditions that are more likely to be associated with antibiotic prescriptions among HIV-infected patients in the cities of Maputo and Matola?	Prospective cross-sectional, quantitative approach	HIV-infected patients, regardless of their illness condition (children and adults)	Prescription review	Descriptive and analytical statistics "SPSS"
2	Pre-implementation determinants of the CDSA-based intervention for the management of URTIs	What are the pre-implementation determinants of the CDSA-based intervention for the management of URTIs?	Prospective cross-sectional, mixed methods approach	Healthcare providers	Document review In-depth interview; Prescription review.	Descriptive statistics "SPSS" and "Excel"
3	Effectiveness of the CDSA on reducing antibiotic prescriptions	How effective is the CDSA in reducing antibiotic prescribing among HIV-infected adults with URTI symptoms?	Two-arm parallel cluster randomized controlled trial, quantitative approach	HIV-infected adults with URTI symptoms	Structured questionnaire and case record notebooks.	Descriptive and analytical statistics "SPSS"
4	Evaluating implementation outcomes using the RE-AIM framework	To what extent does the use of a tailored, multi-component implementation strategy improve the uptake and sustained use of the CDSA in HIV-infected adults with URTI symptoms?	Hybrid type II effectiveness-implementation, mixed methods, RE-AIM framework	HIV-infected adults with URTI symptoms Healthcare providers	Structured questionnaire and case record notebooks. Focus group discussion.	Descriptive and analytical statistics "SPSS" and "Excel"

2. Study settings

This research project was conducted within the primary healthcare facilities in the cities of Maputo and Matola, in Mozambique (Figure 4). Maputo is the nation's capital city, and Matola is the capital of Maputo Province, located around 20 kilometers (km) outside the city of Maputo. The city of Maputo occupies an area of 346 km2 with a population of 1,130,319 inhabitants and a population density of 3,768 inhabitants/km2. Approximately 7% of the population is illiterate, and its GDP growth rate is 3.5%. The health

network consists of 38 healthcare facilities (HCF), 31 of which are primary, 4 secondary, and 3 quaternary (MISAU, 2024). The city of Matola occupies an area of 375 km2 with a population of 1,245,799 inhabitants and a population density of 3,322.1 inhabitants/km2. The illiteracy rate is 13.3%, and its GDP growth rate is 3.8%. The health network is composed of a total of 23 HCFs, 21 of which are primary level, 1 secondary level, and 1 tertiary level (INE, 2021). The prevalence of HIV is 16.9% for Maputo City and 22.9% for Maputo Province, which includes the city of Matola (MISAU et al., 2018).

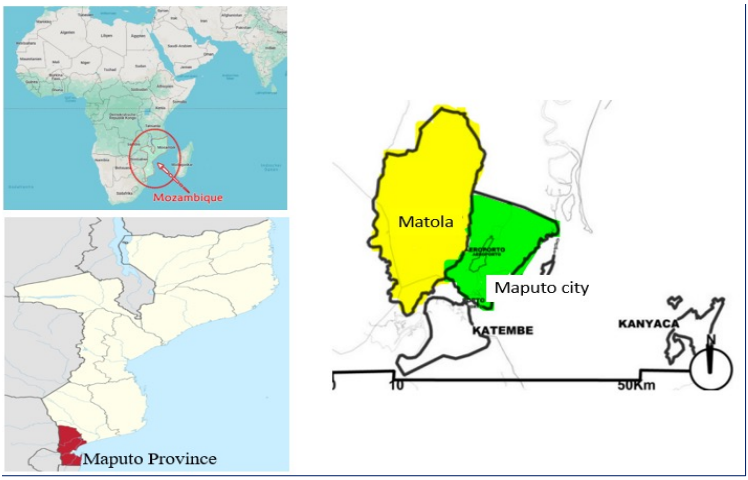

Figure 4. Location of the study area

The two cities were selected for convenience due to easy accessibility. Eligible facilities were urban primary healthcare types A and B. Rural and urban primary healthcare type C were excluded. Primary HCFs types A and B were included in this research project because they have more diversified infrastructures and staff with diverse qualifications, with an emphasis on the existence of at least a general physician, which is not commonly observed in rural and urban type C primary HCFs (Diploma Ministerial no 127/2002, de 31/07/2002, Ministério de Saúde). Both cities are subdivided into 10 administrative units, containing a total of 31 eligible urban types A and B primary healthcare facilities. The primary HCFs in these catchment areas offer outpatient care for all ages, including HIV care and treatment clinics; family planning; maternal and child health services; youth and adolescent care; health counseling and screening; and a pediatric immunization program.

None of these facilities offer inpatient services; thus, if required, patients are referred to a nearby reference hospital with inpatient capacity.

2.1 Randomization of study sites

A two-stage cluster sampling method was used to select our study sites. The first stage involved the random selection of administrative units, hereafter referred to as primary clusters, and the second stage involved the random selection of healthcare facilities, hereafter referred to as secondary clusters. First, a random sequence was generated to assign six of the primary clusters equally to either the intervention or control groups (three each). Second, within each selected primary cluster, one primary healthcare facility (secondary cluster) was then randomly selected to participate in the study. All participants within a given facility received the same group assignment. Due to resource constraints, only six primary clusters were included, and to prevent contamination between facilities, only one health facility was selected per cluster. The allocation sequence was generated by a statistician, who also assigned the selected facilities to either the intervention or control.

3. Population, sample, and sampling

3.1 Study 1

3.1.1 Study sites, population, and sampling

For the study 1, using a convenience sampling, we selected a total of eight primary healthcare facilities according to established criteria, which included the existence of prescribers in the screening and consultation rooms, attendance of more than 600 HIV-infected patients per month, and a pharmacy dispensing medication to HIV-infected patients. All selected HCFs had antiretroviral therapy (ART) service, patient counseling service, and voluntary testing service, and appropriate follow-up.

The primary care for HIV-infected patients in the study area is provided by general practitioners, clinical technicians (i.e., técnicos de medicina in Portuguese), and nurses. All HIV-infected patients of all ages who presented consecutively at the HCF for medical care with a complaint were included in the study, based on the following inclusion criteria: (1) HIV-infected patient in follow-up or diagnosed on the same day of consultation, (2) absence of severe pathology that would interfere with the ability to consent and (3) accepting freely to sign the consent.

3.2 Study 2

The participants of the present study included clinicians, pharmacists, and laboratory technicians who met the following inclusion criteria: 1) Providers of primary healthcare to HIV-infected patients, 2) Dispensers of prescribed medications for HIV-infected patients, and 3) Laboratory technicians who perform laboratory tests in the healthcare facility participating in the study. The sample size was decided by convenience, considering the different categories of healthcare providers (HCPs) to be included and the expected number to achieve saturation.

3.3 Study 3

Eligible participants were adult HIV-infected individuals who presented to the outpatient clinics with symptoms of an acute URTI, such as nasal discharge or congestion, sore throat, cough, sneezing, chills, or disturbances in smell and taste, with or without fever. Patients were excluded if they exhibited symptoms of lower respiratory tract infection, had a fever of ≥39ºC, severe mental illness, or advanced HIV disease.

Our preliminary study, examining the primary outcome, showed that among HIV-infected patients in primary healthcare settings, 65.9% were prescribed antibiotics (Faiela & Sevene, 2022). For our sample size calculation, we set alpha equal to 0.05 and power at 80% to detect differences in proportion greater than or equal to 15% between the intervention and control groups. Thus, our calculations resulted in a sample size of 345 participants to be assigned to either the intervention or control groups in a 1-to-1 ratio. Allowing for an attrition rate of 10%, we aimed to recruit a total of 380 (190 for each group) HIV-infected patients with URTIs to ensure refusals or loss of patients' follow-up or their information.

3.4 Study 4

Eligible participants were HIV-infected adults aged 18 years and older with URTI symptoms. Patients with lower respiratory tract infection symptoms, those with a fever of 39ºC or over, severe mental illness, or advanced HIV status were excluded from the study. Eligible health providers were 1) clinicians (general physicians, nurses, and técnicos de medicina, a cadre of health providers with 18 – 24 months of clinical training beyond high school) providing healthcare to HIV-infected adults; 2) medication dispensers for HIV-infected patients; 3) laboratory technicians performing laboratory tests

for HIV-infected patients; and 4) clinical managers involved in the supervision of clinical activities. For the analysis of health provider satisfaction with the intervention, we included only the health workers from the intervention sites listed above.

4. Study procedures, data management, and analysis

4.1 Study 1

4.1.1 Data collection

Data were collected in 2013 as part of the master's degree, and based on self-completion of a questionnaire by the clinicians. The questionnaire was structured with questions related to prescriber identification, patient socio-demographic data, signs and symptoms, laboratory tests, diagnosis, and drug prescription. The questionnaires were placed in the screening and consultation rooms of the HCF so that the clinician prospectively would fill them out whenever he or she treated an HIV-infected patient after giving a free informed consent. For cases requiring additional tests, the clinician withheld the questionnaire to complete with the results that were obtained. The researchers were responsible for training the clinicians to fill out the questionnaires, monitoring the filling, collecting the questionnaires, cleaning up the data (completeness, incongruous data, unreadable data), and data entry in the database created on the Statistical Package for Social Sciences (SPSS) version 20.

4.1.2 Data analysis

Data were analyzed using SPSS version 20. Data analysis was performed descriptively by drawing up frequency tables. The descriptive analysis was based on the characterization of the pattern of antibiotic prescription in general, by socio-demographic and clinical features. Univariate analysis was performed for the following variables: antibiotic prescription, antibiotic class, prescriber gender, patient age, category, and time of service. For the age variable, the measures of central tendency and dispersion were also calculated. For bivariate analysis, Pearson's chi-squared test with a 95% confidence interval was used to verify if there was an association between patient characteristics (socio-demographic and clinical) and an antibiotic prescription, and $p \leq 0.05$ was considered statistically significant. For variables (age and clinical diagnosis) where expected frequencies below five were found, Fisher's exact test was used.

4.2 Study 2

4.2.1 Data collection and measures

In-depth interviews with healthcare providers

We conducted face-to-face in-depth interviews with identified HCPs, guided by one of three interview scripts, one designed for clinicians, one for pharmacists, and one for laboratory technicians. Interviews took place between October and December 2023 and lasted approximately 15-20 minutes each. Informed consent was provided before the conduct of any interviews. For the clinicians and pharmacists, interview scripts included a combination of close-ended and open-ended questions designed to explore 1) the current flow of HIV-infected patients with URTI symptoms within the primary health facility; 2) current clinicians' practices toward management of respiratory illness; 3) laboratory capacity toward supporting management of HIV-infected patients with respiratory illness; 4) general antibiotic prescribing practices of the facility staff; and 5) the existence of any prior initiatives or opportunities for implementing an antimicrobial stewardship program (ASP). This includes the participants' willingness to work as a team to change work processes and the availability of medicines within the facility. To assess participants' willingness to work as a team to change work processes, we asked about their perceptions of interactions/communications between clinicians and pharmacists within a given facility. We classified the interaction as an "effective interaction" if the HCP stated they felt they could ask for help from their counterpart and if they felt there was strong cooperation amongst colleagues in cases of clinical doubt. For the laboratory technicians, interview scripts were composed of closed-ended questions designed to elicit the current laboratory capacity for diagnosing the etiology of different infections. All interview forms included sociodemographic information of the participants. The interviews were conducted in the Portuguese language (Mozambique's national language), on a day that was convenient to each participant.

Past pharmacy prescription reviews

To assess indicators of prescription quality and to describe antibiotic prescription patterns, quantitative data were collected from copies of past medical prescriptions stored at the health facility's pharmacy. One hundred prescriptions were randomly selected at each facility for review, half from

summer (September to December 2023) and the other half from winter (May to August 2023). We assessed the overall facilities' compliance with the WHO reference indicators for quality prescriptions: average number of medicines per prescription, antibiotic prescription rate, prescriptions with an injectable antibiotic, prescriptions with medications prescribed by generic name, and prescriptions with medicines listed in the National Medicines Formulary. We considered facilities in good compliance if the indicator was within the WHO reference range or a rate over 90%. We described antibiotics by their type and class, spectrum of action, and prescription level.
Five antibiotic prescription levels (Levels 0-4) based on the Mozambican National Medicine Formulary (NMF) were assessed. Level 0 prescriptions are those that can be prescribed or dispensed by the lowest classification of healthcare provider. Each increase in level represents a medication that requires a higher cadre of health professionals to be involved in its prescribing, with Level 3, for example, requiring a general medical physician to prescribe, and Level 4 requiring a physician specialist.

4.2.2 Data management and analysis

Interview forms were designed and stored in REDCap (Research Data Capture) version 10.6.12, a secure electronic data capture tool accessible through a computer or tablet, and stored on a server at the Faculty of Medicine at the University Eduardo Mondlane (UEM). All forms were de-identified, with access limited to only the study researchers. In addition, we stored our literature search results on normative documents, the de-identified past prescription reviews, and the pharmacy inventory reviews within our project-specific REDCap database.
For statistical analysis, data were exported to SPSS version 25. Descriptive statistics were used to describe the sample characteristics, in which absolute and relative frequency were used for categorical variables, while mean and standard deviation were used for numerical variables. Qualitative data were transcribed and exported to an EXCEL matrix for coding and analysis. Qualitative analysis was performed manually following a combination of content and thematic analysis. We used content analysis because it can determine the presence of certain themes or concepts within the data, allowing researchers to quantify their occurrence (Columbia University, 2016; Delve & Limpaecher, 2023). Content analysis was initiated by organizing and categorizing the content based on pre-defined themes (the same ones that guided the collection process), and ultimately quantified.

4.3 Study 3

4.3.1 Intervention and control

Eligible patients allocated to the intervention arm were managed using the CDSA (Figure 5). Per the CDSA, patients were not to receive antibiotics if their URTI symptoms lasted less than 10 days, unless there was an additional symptom suggesting a suspicion of bacterial infection. Bacterial infection was suspected in the following situations: (i) higher-grade fever than usually observed with the common cold, with the presence of yellow or greenish nasal discharge, pain or difficulty swallowing, or an intense sore throat; (ii) URTI symptoms lasting longer than 10 days; (iii) URTI symptoms continuing to get worse rather than improve over several days (5 days after the first visit). Twice per month, the study coordinator at each intervention site would review all antibiotic prescriptions provided to participants in the prior two weeks. Clinicians were provided feedback on the use of the CDSA in all cases where the CDSA was not followed and where no clinically appropriate justification was provided.

In the control sites, clinicians were instructed to continue managing patients according to their usual practices. Twice per month, antibiotic prescribing data from these clinicians were recorded, but no feedback was shared with them during the study period.

For both arms, patients were enrolled in the study at the time they presented to the clinic with URTI symptoms (t0 = day 0). They were then subsequently monitored through a phone call at three different time points after the initial medical visit to ascertain improvement of symptoms (t1 = day 5, t2 = day 10, and t3 = day 15). Participants were instructed that they could visit the healthcare facility for a follow-up clinical examination in person, at any time, if necessary.

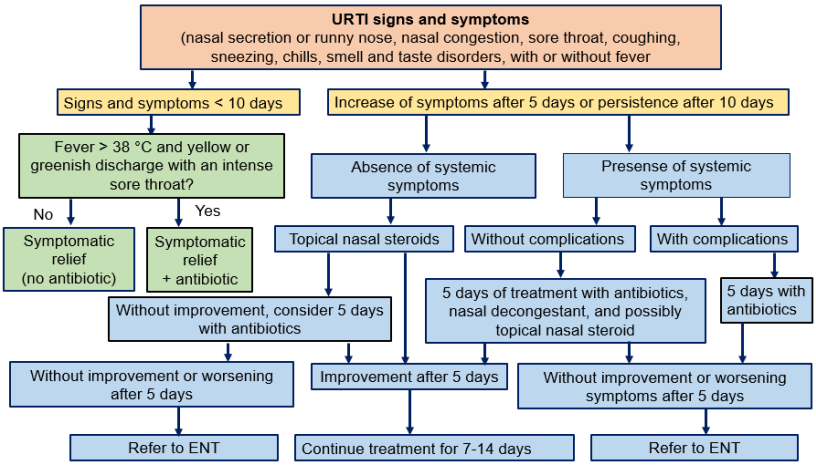

Figure 5. Clinical Decision Support Algorithm for Management of URTIs. *Modified from Bird et al. (2013): Algorithm for management of rhinosinusitis and adapted for our context.*

4.3.2 Data collection and measures

We used a structured questionnaire to collect patient-related sociodemographic and clinical information from June 2024 to September 2024. We also utilized a case record notebook where additional information had been registered. The on-site coordinator was responsible for collecting data in synchrony with the clinicians. Twice per month, data quality checks were performed by the study principal investigator (PI) for completeness, accuracy, consistency, validity, and uniqueness.

The effectiveness of the CDSA was analyzed by comparing antibiotic prescribing rates, complication rates, and mean time for complete recovery between the intervention and control groups. Our primary outcome was the antibiotic prescribing rate. Complication rates and the time for complete recovery from the first medical visit were the secondary outcomes. Complications were defined as worsening of symptoms that were deemed to result from not receiving antibiotics, such as sinusitis, pharyngotonsillitis, pneumonia, bronchitis, and asthma. These were documented for the first time at one of the follow-up visits. The antibiotic prescribing rate was calculated as the number of patients who received at least one antibiotic prescription on Day 0, among all participants enrolled. Antibiotics were classified

according to the spectrum of action, prescription level as per study 2, and the WHO AWaRe 2023 classification. We included the AWaRe classification to check for a prescribing trend of antibiotics with a safety profile regarding adverse effects and the potential risk of resistance development. According to the AWaRe classification, antibiotics are classified as Access, Watch, and Reserve, taking into account the impact of different antibiotics on antimicrobial resistance (WHO, 2023). Complication rate was measured as the proportion of complications among patients who were recruited and completed at least one follow-up visit. The mean time to complete recovery was calculated as the average time the patients took to recover completely from their symptoms.

4.3.3 Data management and analysis

Data collection forms and other patient registries were created in both paper and electronic format in REDCap (Research Electronic Data Capture). Study clinicians filled out the data collection forms during the initial visit, while the on-site study coordinator completed the forms during follow-up visits. These were then submitted to the study PI, who input data from the forms into the REDCap system. Data were then exported to SPSS (Statistical Package for Social Sciences) version 25 for statistical analysis (Maré et al., 2022).
Descriptive and analytical statistics were used to analyze the data. Descriptive analysis involved constructing tables of absolute and relative frequencies. Analytical statistics were used for bivariate analysis. Pearson's chi-square test was employed to compare outcomes between intervention and control sites, using a 5% significance level. The same test was used to assess baseline comparability between the two arms and to evaluate differences in recovery time rates. To quantify the intervention's impact, relative risk (RR) was calculated, along with the effectiveness ratio (1–RR), and 95% confidence intervals were reported for RR.

4.4 Study 4

4.4.1 Data collection, measures, and analysis

Quantitative data were collected from June to September 2024, whereas qualitative data were collected between October and December 2024. A structured questionnaire and a case record notebook were used to collect quantitative data. The on-site study coordinator was responsible for collecting data in close coordination with the clinicians. Data quality checks were

performed by the PI twice per month for completeness and accuracy and to address inconsistencies. Quantitative data were collected to evaluate the reach, effectiveness, adoption, and implementation of the intervention.

Reach

The "reach" outcome included two categories: recruitment rate and attrition rate. The recruitment rate was calculated as the proportion of patients recruited among those approached to participate in the study. The attrition rate was calculated as the proportion of patients who did not attend any of the follow-up visits among those recruited. These data were collected from the structured questionnaire. For analysis, we compared the reach outcomes between the intervention and control groups.

Effectiveness

For "effectiveness," we measured the antibiotic prescribing rate as the primary outcome, the incidence of complications, and the mean time for complete recovery from the first medical visit as the secondary outcomes. The antibiotic prescribing rate was calculated as the number of patients who received at least one antibiotic prescription among those recruited on the day of enrollment (day 0). Antibiotic prescribing data were collected from the structured questionnaire in the section on prescribed medication. The complications and the time for complete recovery from the first medical visit were collected from the structured questionnaire in the section on follow-up visits. The complication rate was measured as the proportion of patients who experienced complications among those recruited and who completed the first follow-up visit (day 5). The mean time for complete recovery was calculated as the average time it took for patients to recover from their symptoms completely. For analysis, Pearson's chi-square test was used to compare the effect of the intervention between the intervention and control sites, with a significance level of 5%. To ascertain the magnitude of the intervention's effect, the relative risk (RR) was calculated, and the effectiveness ratio (1–RR) was used to estimate the intervention's effectiveness.

Adoption

The "adoption" outcome was measured as the number of sites and intervention agents (i.e., clinicians) who effectively followed the CDSA and were committed to promoting the de-implementation of unnecessary antibiotics. To get this information, we reviewed the symptomatology, including the

duration of symptoms and antibiotic prescriptions, for each participant, and these data were collected from the structured questionnaire. The analysis was performed for the intervention group at two levels (facility level and health provider level).

Implementation

For the "implementation" outcome, we evaluated the intervention fidelity and the degree of health worker satisfaction with the intervention. To evaluate implementation fidelity, we reviewed fidelity logs and monitored the implementation protocol to ensure it was delivered as intended. The information to evaluate the degree of satisfaction was collected from a survey with health providers in the intervention group. The degree of satisfaction was measured using a 5-point Likert scale, and for analysis, it was reduced to a binary category: dissatisfied (very dissatisfied, dissatisfied, neutral) and satisfied (very satisfied, satisfied).

To explore a deeper understanding of the implementation outcome, we collected qualitative data through focus group discussions (FGDs). The researchers approached the selected participants for FGDs with the help of the on-site study coordinator. The participants were invited to participate in the FGD after being informed of the study's purpose and the anonymous nature of the activities. After convening the group, eligible participants were again informed of the purpose of the FGD through a written participant information sheet, which included an informed consent form. Concurrently, the informed consent documents were read aloud to the participants, who were invited to ask questions to ensure comprehension before being asked to sign them. The time and place for FGDs were suggested by the participants and agreed with the research team.

Three FGDs were conducted, one at each health facility selected for the study. The FGD generated discussions and debates about the topic from the participants' perspectives. Each FGD involved 5 - 9 participants with similar characteristics, including male and female clinicians, pharmacists, laboratory technicians, and clinical managers. The FGDs were conducted in Portuguese (Mozambique's official language) by two researchers, a moderator, and an observer, who took notes on group dynamics and nonverbal communication. The FGDs occurred at each health facility and lasted roughly 40 - 50 minutes. It was structured around five thematic sections: (i) CDSA effectiveness, (ii) implementation barriers, (iii) implementation enablers, (iv) maintenance and dissemination of the use of the CDSA, and (v) pharmacy and laboratory perspectives regarding the implementation of the CDSA. All sections consisted of open-ended questions.

To analyze the qualitative data, we developed a matrix in which rows

corresponded to participants' responses and columns to the questions posed. Responses were organized according to both predefined themes—based on the focus group discussion (FGD) guide—and themes that emerged during the analysis. The data were analyzed manually using a combination of content and thematic analysis, beginning with the organization and categorization of data under the predefined and emerging themes. Relevant quotes from participants were placed in the corresponding cells.

5. Limitations of the research project

The study was conducted in a primary healthcare setting where access to accurate diagnosis was limited because of a lack of laboratory support. For the implementation of our intervention, we only selected six healthcare facilities due to limited resources. The study area (Maputo and Matola cities) was chosen by convenience sampling. However, the study sites were selected by random sampling. Contamination may have occurred due to earlier activities in the pre-implementation and adaptation phases. But we feel that this did not affect the implementation process because the control group did not have access to the CDSA and other intervention elements. The patient recruitment rates between the intervention and control groups differed slightly but did not impact the overall interpretation of our findings. The maintenance dimension, one of the five pillars of the RE-AIM framework, was not assessed due to the limited timeframe for the Doctoral program. Therefore, we focused on the other four dimensions: reach, effectiveness, adoption, and implementation.

In addition, it is always difficult to interview healthcare providers about their work, as they tend to say what is right rather than what is actually done. To circumvent this limitation, healthcare providers were informed that they would not be identified under any circumstances and that codes would protect their identities. Acute URTIs are more common in winter. To mitigate the seasonal impact of URTIs, the intervention was implemented during the winter months.

Although these limitations were observed in the implementation of the research project, we were able to mitigate and provide scientific evidence that may be used to combat AMR within our healthcare settings.

6. Ethical considerations

Administrative authorization was obtained from the Ministry of Health, the Municipality of Maputo City, and the Provincial Health Services of Maputo (for Matola City). The Mozambican National Bioethics Committee for Health (Comité Nacional de Bioética para Saúde, CNBS) approved the research project on 14 August 2023 (register number 52/CNBS/2023). Participants were enrolled in the research after providing informed consent. The research project was conducted following the Declaration of Helsinki (2008).

CHAPTER 4

RESULTS

This section presents the main findings gathered through the entire research project from the four study objectives as follows:

1. STUDY 1 (Paper I)

1.1 Study participants' characteristics and antibiotic prescribing rates

Data were collected from 31 prescribers who recorded prescription information on 369 medical visits of HIV-infected patients (Table 3). Most of the prescribers were women (54.8%), aged 20 to 35 years (45.1%), medical technicians (41.9%), and with more than 10 years of experience (53.4%). For the attendees, the majority were women (63.7%), aged between 25 to 49 years (74%), with a mean age of 37 ± 11.7 years, and on ART (71.3%).
Antibiotics were prescribed in 65.9% (n = 243) of medical visits. Most antibiotics were prescribed to female patients (62.9%), adults aged 25 to 49 years (76.3%), HIV disease stages I and II (66.9%), and on ART (68.6%). Children (0 to 14 years) and the elderly (65+ years) received antibiotics less frequently (1.6% and 0.8%, respectively) compared with young and adults (15 to 64 years). Prescribers' category ($p = 0.374$) and length of service ($p = 0.200$) did not significantly influence the antibiotic prescribing rates (Table 3). Among patient visits with antibiotics prescribed, 48.2% received one antibiotic, 12% received two different types of antibiotics, 3.3% received three different types of antibiotics, and 2.4% received four different types of antibiotics (Figure 6). Overall, the antibiotic combinations were 17.6%. Among the antibiotic combinations, 69.4% were from two distinct classes, 24.2% of three distinct classes, and 6.4% of four distinct classes (Table 4). The association between penicillin and sulfonamide (29.2%), and macrolide associated with quinolone and metronidazole (12.3%) were the most frequent associations.

Table 3. Antibiotic prescribing per patient and clinician characteristics

Characteristics		Antibiotic Prescribing			
		Yes, n = 243 (%)	No, n = 126 (%)	Total, n (%)	*P* value
Patient sex (n = 369)					0.642
	Male	91 (37.1)	43 (34.7)	134 (36.3)	
	Female	154 (62.9)	81 (65.3)	235 (63.7)	
Patient age (n = 369)	Mean ± SD	---	---	37 ± 11.7	0.063
	0-14 years	4 (1.6)	6 (4.8)	10 (2.7)	
	15-24 years	22 (9)	8 (6.5)	30 (8.1)	
	25-39 years	124 (50.6)	63 (50.8)	187 (50.7)	
	40-49 years	63 (25.7)	23 (18.5)	86 (23.3)	
	50-64 years	30 (12.2)	19 (15.3)	49 (13.3)	
	65+ years	2 (0.8)	5 (4)	7 (1.9)	
ART (n = 369)					0.107
	Yes	168 (68.6)	95 (76.6)	263 (71.3)	
	No	77 (31.4)	29 (23.4)	106 (28.7)	
Patient HIV stage (n = 369)					0.445
	Stage I (n = 124)	88 (35.9)	36 (29.0)	124 (33.6)	
	Stage II (n = 124)	76 (31)	48 (38.7)	124 (33.6)	
	Stage III (n = 104)	70 (28.6)	34 (27.4)	104 (28.2)	
	Stage IV (n = 17)	11 (4.5)	6 (4.8)	17 (4.6)	
Diagnosis (n = 369)					<0.0001
	Cardiovascular system (I)	3 (1.2)	22 (17.4)	25 (6.8)	
	Infectious and parasitic disease (A)	2 (0.8)	3 (2.4)	5 (1.4)	
	Genitourinary tract (N)	39 (16.0)	3 (2.4)	42 (11.4)	
	Bone-muscular system and connective tissue (M)	6 (2.5)	4 (3.2)	10 (2.7)	
	Skin and subcutaneous tissue (L)	22 (9.1)	29 (23)	51 (13.8)	
	Respiratory tract (J)	74 (30.5)	7 (5.6)	81 (21.8)	
	General symptoms (R)	16 (6.6)	23 (18.3)	39 (10.6)	
	Gastrointestinal tract (K)	37 (15.2)	23 (18.3)	60 (16.3)	
	Nervous system (G)	2 (0.8)	12 (9.5)	14 (3.8)	
	No information	42 (17.3)	---	42 (11.4)	
Clinician sexy (n = 31)					---
	Male	---	---	14 (45.2)	
	Female	---	---	17 (54.8)	
Clinician age (n = 31)					---
	20 – 35 years	---	---	14 (45.1)	
	36 – 49 years	---	---	10 (32.3)	
	50 – 65 years	---	---	7 (22.6)	
Clinician category (n = 31)					0.374
	General practitioner	53 (22)	34 (27)	87 (23.6)	
	Medical technician	107 (44)	58 (46)	165 (44.7)	
	Nurse	83 (34)	34 (27)	117 (31.7)	
Clinician experience (n = 31)					0.200
	0-10 years	119 (49)	53 (41.9)	172 (46.6)	
	> 10 years	124 (51)	73 (58.1)	197 (53.4)	

Table 4. Associations of distinct classes of antibiotics

Number of classes	Association of classes of antibiotics	n (%)	Total, n (%)
2			43 (69.4)
	Penicillin + Sulfonamide	19 (29.2)	
	Penicillin + Tetracycline†	3 (4.6)	
	Penicillin + Macrolide	2 (3.1)	
	Aminoglycoside + Macrolide	1 (1.5)	
	Aminoglycoside + Metronidazole	1 (1.5)	
	Aminoglycoside + Tetracycline	1 (1.5)	
	Macrolide + Quinolone	1 (1.5)	
	Macrolide + Sulfonamide	5 (7.7)	
	Macrolide + Metronidazole	1 (1.5)	
	Quinolone + Metronidazole	1 (1.5)	
	Quinolone + Sulphonamide	2 (3.1)	
	Sulfonamide + Metronidazole	6 (9.2)	
3			15 (24.2)
	Penicillin + Tetracycline + Sulfonamide†	1 (1.5)	
	Penicillin + Sulfonamide + Quinolone	1 (1.5)	
	Penicillin + Aminoglycoside + Chloramphenicol	1 (1.5)	
	Aminoglycoside + Tetracycline + Metronidazole	2 (3.1)	
	Macrolide + Quinolone + Metronidazole	8 (12.3)	
	Macrolide + Quinolone + Sulphonamide	2 (3.1)	
4			4 (6.4)
	Aminoglycoside + Tetracycline + Metronidazole + Sulfonamide†	1 (1.5)	
	Macrolide + Quinolone + Sulfonamide + Metronidazole†	3 (4.6)	

† Associations not recommended because of increased risk of adverse reactions: Sulfonamide + Metronidazole and Penicillin + Tetracycline.

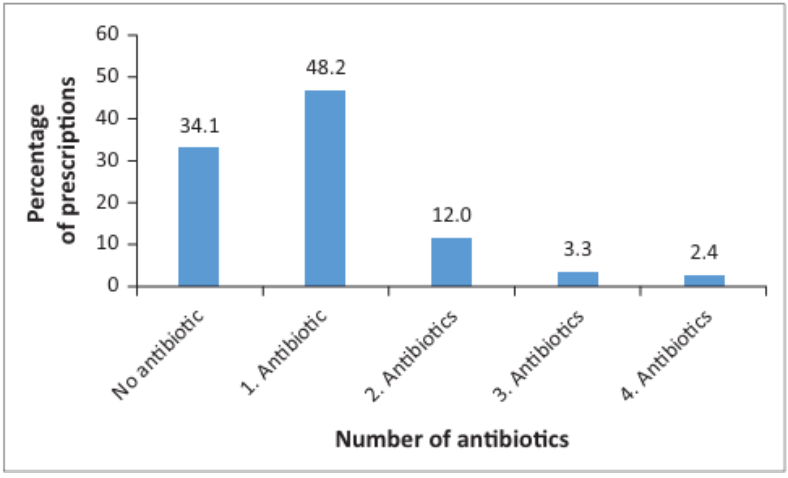

Figure 6. Number of antibiotics prescribed in each prescription

1.2 Pattern of antibiotic prescribing

A total of 334 antibiotics were prescribed, 69.8% (n = 233) for treatment and 30.2% (n = 101) for prophylaxis of infections (Table 5). For treatment, penicillin (29.2%), sulfonamides (19.7%), and quinolones (16.3%) were the most commonly prescribed classes of antibiotics. For prophylaxis, only sulfonamides and macrolides were prescribed, with the first-class being prescribed more frequently (93.1%). Of all prescribed sulfonamides (n = 139), 67.1% were used for prophylaxis of infections.

Table 5. The choice for prescribing a class of antibiotics

Class of antibiotics	Treatment n (%)	Prophylaxis n (%)	Total n (%)
Penicillin	68 (29.2)	---	68 (18.4)
Aminoglycoside	6 (2.6)	---	6 (1.8)
Macrolide	31 (13.3)	8 (6.9)	39 (14.3)
Quinolone	38 (16.3)	---	38 (14.4)
Sulfonamide	46 (19.7)	93 (93.1)	139 (37.9)
Tetracycline	10 (4.3)	---	10 (3)
Others	34 (14.6)	---	34 (10.2)
Total	233 (100)	101 (100)	334 (100)

We assessed the existence of an association between antibiotic prescription and patient socio-demographic and clinical characteristics (Table 3). The diagnosis was the only variable that had a significant association ($p < 0.0001$). Most of the penicillin (68.0%) prescribed was used to treat respiratory tract infections (Table 6). Amoxicillin and a combination of amoxicillin and clavulanic acid were the most prescribed penicillin (62.3%), followed by phenoxymethylpenicillin (21.7%) and benzyl penicillin (10.1%). Aminoglycosides were specially prescribed to treat genitourinary tract infections (66.6%), with kanamycin being the most prescribed aminoglycoside (85.7%). Macrolides were mainly used to treat infections of the genitourinary tract (44.8%), skin and subcutaneous tissue (26.3%), and respiratory tract (21.1%), with erythromycin (57.9%) being the most commonly prescribed macrolide. Tetracyclines were used to treat genitourinary (50%) and respiratory (40%) tract infections, with doxycycline being the most commonly prescribed tetracycline (70%).

Table 6. Antibiotic prescribing following diagnosis

Diagnosis (ICD-10)	PEN n (%)	AMINO n (%)	MACRO n (%)	TETRA n (%)	QUINO n (%)	SULFO n (%)	Other class n (%)
Cardiovascular system (I)	---	---	---	---	---	3 (2.1)	---
Infectious and parasitic diseases (A)	1 (1.5)	---	1 (2.6)	---	---	---	---
Genitourinary tract (N)	8 (11.6)	4 (66.6)	17 (44.8)	5 (50)	24 (64.1)	10 (7.1)	17 (50)
Musculoskeletal system and connective tissue (M)	---	---	1 (2.6)	---	1 (2.6)	4 (2.8)	----
Skin and subcutaneous tissue (L)	4 (5.8)	---	10 (26.3)	---	---	14 (10.6)	---
Respiratory tract (J)	46 (68)	1 (16.7)	8 (21.1)	4 (40)	6 (15.4)	30 (21.4)	1 (3)
General symptoms (R)	6 (8.7)	---	---	---	---	11 (7.8)	---
Gastrointestinal tract (K)	2 (2.9)	---	1 (2.6)	1 (10)	7 (17.9)	25 (17.7)	15 (44)
Nervous system (G)	1 (1.5)	1 (16.7)	---	---	---	1 (0.7)	1 (3)
Unknown	---	---	---	---	---	42 (29.8)	---

PEN: Penicillin; AMINO: aminoglycoside; MACRO: macrolide; TETRA: tetracycline; QUINO: quinolone; SULFO: sulfonamide

2. STUDY 2 (Paper III)

2.1 Characteristics of healthcare providers

We interviewed 39 HCPs out of 41 approached (two did not consent), including 27 clinicians, six laboratory technicians, and six pharmacists. Across all healthcare provider cadres included, the majority of participants were female (74.4%) and young between the ages of 18-35 years of age (71.8%), with a mean age of 32 years ± 4.5 (Table 7). For clinicians and pharmacists, roughly 66% of each group had been in their positions for more than 2 years, while for laboratory technicians, we saw the opposite, with roughly 66% having been in their positions for 2 years or less. Of the clinicians interviewed, 81.5% were técnicos de medicina. Most clinicians (74.1%) worked in the HIV care and treatment sector.

Table 7. Characteristics of healthcare providers

Feature	Clinician n = 27	Pharmacist n = 6	Laboratory Technician n = 6	Total N = 39
Sex				
Female	21 (77.8%)	4 (66.7%)	4 (66.7%)	29 (74.4%)
Male	6 (22.2%)	2 (33.3%)	2 (33.3%)	10 (25.6%)
Age Mean ± SD				32 ± 4.5
18 – 35 years	21 (77.8%)	2 (33.3%)	5 (83.3%)	28 (71.8%)
36 – 45 years	5 (18.5%)	4 (66.7%)	1 (16.7%)	10 (25.6%)
46 – 60 years	1 (3.7%)	--	--	1 (2.6%)
Years of experience				
≤ 2 years	9 (33.4%)	2 (33.3%)	4 (66.7%)	15 (38.5%)
3 – 10 years	13 (48.1%)	4 (66.7%)	1 (16.7%)	18 (46.1%)
11 – 20 years	4 (14.8%)	--	1 (16.7%)	5 (12.8%)
21 – 30 years	1 (3.7%)	--	--	1 (2.6%)
Job Category				
Clinical Assistant	1 (3.7%)	--	--	1 (2.6%)
Clinical Technician	22 (81.5%)	--	--	22 (56.4%)
General Physician	4 (14.8%)	--	--	4 (10.2%)
Pharmacist	--	1 (16.7%)	--	1 (2.6%)
Pharmacist Technician	--	5 (83.3%)	--	5 (12.8%)
Laboratory Technician	--	--	6 (100%)	6 (15.4%)
Facility Work Sector				
HIV care and treatment	20 (74.1%)	--	--	20 (51.3%)
General outpatient consultation	2 (7.4%)	--	--	2 (5.1%)
Triage Services	5 (18.5%)	--	--	5 (12.8%)
Pharmacy	--	6 (100%)	--	6 (15.4%)
Laboratory	--	--	6 (100%)	6 (15.4%)

2.2 Document review

Only three types of documents exist (such as guidelines/algorithms) that are designed to orient clinicians on the management of respiratory illnesses generally, or of opportunistic respiratory infections among adult HIV-infected patients more specifically. These included: 1) a guideline that includes two algorithms for the management of acute and chronic respiratory infections in HIV-infected adults and adolescents, 2) a guideline that is specific to the management of tuberculosis (TB), latent TB, and multidrug-resistant TB, and 3) a document with flowcharts and protocols for managing suspected COVID-19 patients at differing points within the health facility, that were created for use during the height of the COVID-19 pandemic. None of these documents provides specific guidance for clinicians caring for HIV-infected ambulatory patients with URTI symptoms.

2.3 Results of in-depth interview with HCPs

Clinicians' practices toward the management of respiratory illness

For assessing clinicians' practices, we asked them about their practices toward the management of patients with respiratory illness, and less than half (44.4%) reported having access to or utilizing any normative document (guideline/algorithm), either in paper or electronic format, for the management of respiratory tract infections (Table 8). The only document remotely useful that clinicians mentioned having access to was a guideline that includes two different algorithms for the management of acute and chronic opportunistic respiratory tract infections in HIV-infected adults and adolescents. However, only 48.1% of respondent clinicians used that guideline to manage RTIs.

> *"To manage respiratory tract infections in HIV-infected patients, my decision is based on the patient's clinical condition and duration of symptoms. When I suspect a lung infection, I request laboratory tests to rule out TB. While waiting for the results to come back, I prescribe according to the patient's condition" (IDI, Clinician 18/Female)*

Furthermore, we asked clinicians about their decision-making process for treating URTI symptoms with antibiotics. Most (92.6%) reported using clinical signs and symptoms as the sole determinant for deciding whether to treat with antibiotics. In comparison, 7.4% reported using a combination of clinical diagnosis and laboratory test results.

> *"To decide what to prescribe for URTI, I only use clinical diagnosis." (IDI, Clinician 3/Female)*
> *"To decide what to prescribe for URTI, I use clinical diagnosis and laboratory results if I have already ordered them." (IDI, Clinician 10/Female)*

We also questioned clinicians regarding the introduction of a tool that could help them make clinical decisions in managing URTIs. All of them (100%) declared themselves available and eager to contribute to the upcoming intervention (Table 8).

"Any complementary tool that would support us in managing URTIs is welcome. I am personally available to contribute to such an intervention." (IDI, Clinician 25/Female)

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Table 8. Results of the interview with clinicians and laboratory technicians

Theme	Content	Yes n (%)	No n (%)	Turnaround time
Clinicians' practices	Use of guidelines or algorithms for treating RTIs (n=27)	13 (48.1)	14 (51.9)	--
	Possession of a normative document (guideline or algorithm) for the treatment of RTIs (n=27)	12 (44.4)	15 (55.6)	--
Opportunities for Antimicrobial Stewardship Initiatives	Willingness to adhere to an intervention that would support clinical decisions in managing URTIs (n=27)	27 (100)	---	
	Knowledge of the existence of a prescription audit system (n=27)	5 (18.5)	22 (81.5)	--
	Knowledge of someone responsible for antibiotic management (n=27)	20 (74.1)	7 (25.9)	--
	Knowledge of the existence of a continuing clinical education program (n=27)	26 (96.3)	1 (3.7)	--
	Effective interaction between colleagues (n=27)	27 (100)	---	--
Laboratory capacity	HIV test (n=6)	6 (100)	---	--
	CD4 (n=6)	4 (67.3)	2 (33.3)	2-18 days
	Viral load (n=6)	---	6 (100)	8-28 days
	Blood count (n=6)	5 (83.3)	1 (16.7)	2-18 days
	C-reactive protein (n=6)	1 (16.7)	5 (83.3)	8-14 days
	Culture and antibiotic sensitivity test (n=6)	---	6 (100)	21-60 days
	Gram stain test (n=6)	1 (16.7)	5 (83.3)	7 days
	X-ray (n=6)	1 (16.7)	5 (83.3)	3-7 days

Laboratory capacity to support the management of HIV-infected patients with respiratory illness

When examining the patient, the clinician may request laboratory tests to support clinical decisions on what to prescribe. We asked laboratory technicians about laboratory capacity to support clinicians. The majority (83.3%) of laboratory technicians declared that their laboratory could perform a complete blood count (CBC) test. However, none could reportedly perform a blood culture and antibiotic sensitivity testing, and only 16.7% could perform a C-reactive protein (CRP) test (Table 7). Those not able to perform the tests on-site do have the option of sending samples to another reference laboratory; however, the turnaround time could be anywhere from 2-18 days for a CBC and 21-60 days for blood culture and antibiotic sensitivity testing. If the clinician requires a chest X-ray examination, 83.3% of participating health facilities will refer the patient to another facility, with a reported turnaround time of between 1-7 days.

"We can perform a blood count test. However, we cannot perform a C-reactive protein test. For this test, we refer the patient to perform it at the Mozambican National Institute of Health. The patient may come back with the results after two weeks. We also do not perform a culture and antibiotic sensitivity test. For this one, we send samples to Maputo Central Hospital, and the patient gets the result roughly after 30 days. It is not frequent to ask for a chest X-ray test. When it is needed, we send the patient to get it at Machava General Hospital or Matola Provincial Hospital, and after one day, the patient can come back with the report." (IDI, Laboratory technician 5/Male).

2.4 Prescription review

Antibiotic prescribing practices

In our review of pharmacy prescriptions to assess quality indicators and compliance with WHO indicators, we found an antibiotic prescribing rate of 65%. Less than half (49.3%) of prescriptions had one antibiotic prescribed, 6.2% had two antibiotics, and 9.3% had three antibiotics prescribed (Figure 7).

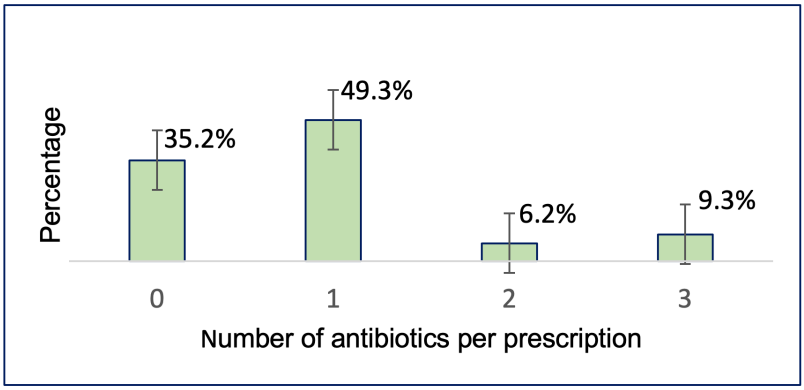


Figure 7. Number of antibiotics per prescription

Roughly 65% of prescriptions had the prescriber's name documented. Nearly 100% of prescriptions had the date, dosage, patient's name, and duration of treatment documented. Further, we observed good compliance with the

core WHO indicators for prescriptions with generic names (99.3%) and with medicines listed in the NMF (100%). In contrast, the antibiotic prescribing rate of 65% is roughly three times the recommendation from WHO, and the average number of medications per prescription of 2.5 is greater than the WHO recommendation of between 1.6-1.8 medicines (Table 9). We also observed good compliance with additional prescribing quality indicators for all except prescriptions with documentation of the prescriber's name (65%).

Table 9. Quality prescription indicators

Prescription quality indicators	Total	WHO reference
WHO core quality indicators		
Average number of medicines per prescription	2.5	1.6 – 1.8
Antibiotic prescription rate	65%	20 – 26.8%
Prescriptions with an injectable antibiotic	--	13.4 – 24.1%
Prescriptions with medicines prescribed by generic name	99.3%	100%
Prescriptions with medicines listed in the National Medicines Formulary	100%	100%
Additional quality indicators		
Average number of antibiotics per prescription	1.0	--
Prescriptions with the documented patient's name	99.8%	--
Prescriptions with the documented prescriber's name	65.5%	--
Prescriptions with documentation of the date	100%	--
Prescriptions with documentation of the dosage	100%	--
Prescriptions with documentation of the duration of the treatment	100%	--

Across the prescriptions that we reviewed (regardless of disease condition), we found that a total of 16 different antibiotics were among those most prescribed, of which 12 were broad-spectrum. Amoxicillin (30.5%), metronidazole (18.7%), azithromycin (13.7%), and ciprofloxacin (12.5%) were the most frequently prescribed (Table 10). Of the antibiotics prescribed, five were level 1 antibiotics (can be prescribed by a clinical agent/nurse), five were level 2 (prescribed by a clinical technician), and six were level 3 (prescribed by a general practitioner). According to AWaRe classification, among the most prescribed antibiotics, two were in the category of "access" antibiotics (amoxicillin and metronidazole), and the other two were classified as "watch" (azithromycin and ciprofloxacin).

Table 10. Pattern of antibiotic prescribing

Antibiotic name	Class	Spectrum of action	AWaRe 2023	Prescription level	Summer n (%)	Winter n (%)	Total n (%)
NAL	Quinolone	Narrow	---	2	2 (0.8)	2 (0.7)	4 (0.8)
AMX	Penicillin	Broad	Access	1	101 (38.3)	62 (23.0)	163 (30.5)
AMC	Beta-lactamase inhibitor	Broad	Access	3	2 (0.8)	1 (0.4)	3 (0.6)
AZI	Macrolide	Broad	Watch	3	26 (9.8)	47 (17.4)	73 (13.7)
BPG	Penicillin	Narrow	Access	1	9 (3.4)	3 (1.1)	12 (2.2)
CFX	Third-generation-cephalosporin	Broad	Watch	3	1 (0.4)	1 (0.4)	2 (0.4)
CIP	Fluoroquinolone	Broad	Watch	3	31 (11.7)	36 (13.3)	67 (12.5)
CHL	Amphenicol	Broad	Access	2	2 (0.8)	---	2 (0.4)
CTX	Sulphonamide-trimethoprim combination	Broad	Access	1	17 (6.4)	21 (7.8)	38 (7.1)
DOXY	Tetracycline	Broad	Access	2	1 (0.4)	5 (1.8)	6 (1.1)
ERY	Macrolide	Broad	Watch	2	9 (3.4)	13 (4.8)	22 (4.1)
GEN	Aminoglycoside	Broad	Access	3	6 (2.2)	---	6 (1.1)
KAN	Aminoglycoside	Narrow	Watch	3	---	1 (0.4)	1 (0.2)
MET	Imidazole	Broad	Access	1	45 (17.0)	55 (20.4)	100 (18.7)
PcV	Penicillin	Narrow	Access	1	11 (4.2)	21 (7.8)	32 (6.0)
TET	Tetracycline	Broad	Access	2	1 (0.4)	2 (0.7)	3 (0.6)

NAL: nalidixic acid; AMX: amoxicillin; AMC: amoxicillin-clavulanic acid; AZI: azithromycin; BPG: Benzathine-benzylpenicillin; CFX: cefixime; CIP: ciprofloxacin; CHL: chloramphenicol; CTX: cotrimoxazole; DOXY: doxycycline; ERY: erythromycin; GEN: Gentamicin; KAN: kanamycin; MET: metronidazole; PcV: phenoxymethylpenicillin; TET: tetracycline

Coordination among HCPs in the management of URTIs

We asked clinicians about their interactions with colleagues when they had uncertainties about their treatment decisions. One hundred percent (100%) of clinicians declared that they effectively interact with their colleagues, both amongst other prescribers as well as with the pharmacists.

When asked about prescription audits, a higher proportion of clinicians (83.9%) declared that they were unaware of a prescription audit system at their health facility. On the other hand, most of them (77.4%) claimed that the pharmacist was in charge of antibiotic management.

> *"When a colleague comes to me with a question related to a prescription or diagnosis, I explain and discuss the matter with the colleague until we find a decision that benefits the patient." (IDI, Clinician 19/Female)*

Clinicians' knowledge about the availability of medicines at any given moment, and thus what options are available to them for prescribing, depends on the state of communications between clinicians and pharmacists within a given facility. We asked the pharmacists about their interaction with clinicians, and all (100%) declared that they effectively interact with clinicians and that when they have doubts about a prescription, they ask the clinician who prescribed it for clarification.

> *"If we receive an unclear prescription, we interact with the clinician who prescribed it to ask for clarification or discuss the issue". (IDI, Pharmacist 3/Male)*

In addition, pharmacists were questioned about the existence of a list of essential medicines and the importance given to it. All of them (100%) reported that they have the list and use it to update clinicians on the medicines available in the pharmacy and to guide them in deciding what to prescribe. They also reported that they use the list to manage medicine stocks. All pharmacists questioned mentioned that when they receive a prescription for an antibiotic not available in the health facility, they advise the patient to look for it in private pharmacies.

> *"We use the list of essential medicines to inform clinicians about the stock of medicines and what they can prescribe". (IDI, Pharmacist 4/Female)*
> *"If we receive a prescription for a medicine out of stock, we send the patient to get it in private Pharmacies". (IDI, Pharmacist 2/Female)*

3. STUDY 3 (Paper IV)

3.1 Study participants

Among 387 patients approached, 379 (97.9%) were successfully recruited into the study. Two patients (0.5%) were excluded from enrolment due to their refusal to provide consent, and 6 (1.6%) were excluded as they were subsequently determined to have a lower respiratory tract infection. Of the patients recruited, 182 (48%) were allocated to the intervention arm and 197 (52%) to the control arm. Of these, 174 (95.6%) patients in the intervention arm and 197 (100%) patients in the control arm participated in at least one follow-up visit (Figure 8).

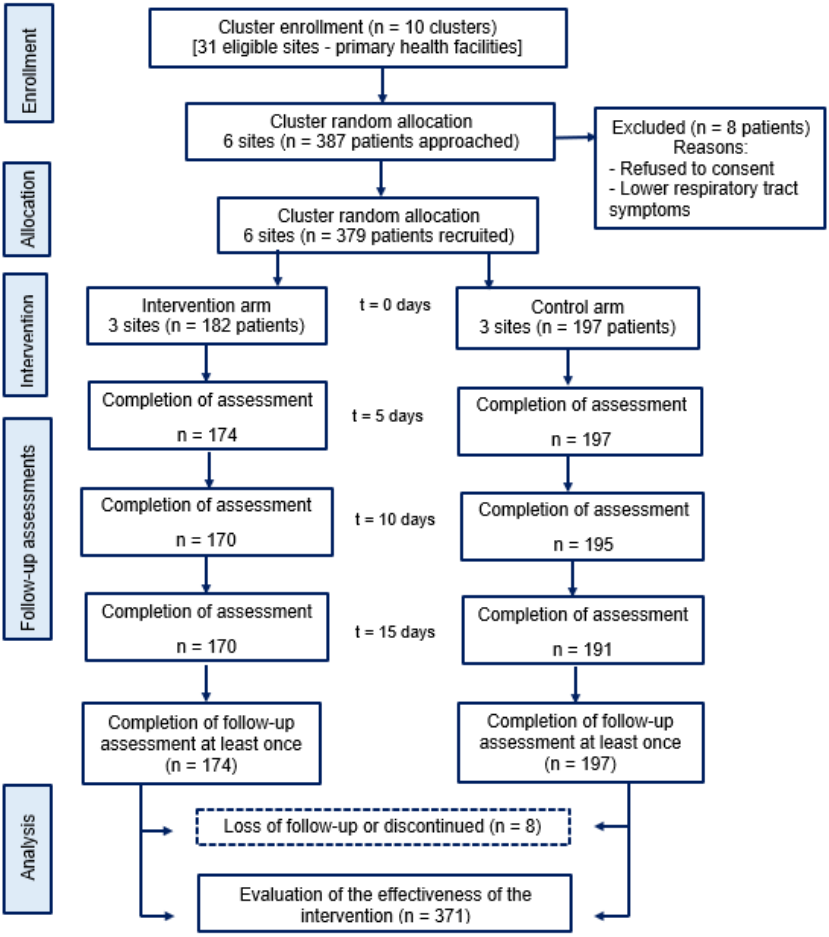


Figure 8. Study flow diagram

The study participants were adults aged 18 years or older, with a mean age of 44 ± 12.3 years, and the majority were female (75.5%). Over half of the participants (57%) were single and had a secondary level of education or higher (59.9%) (Table 11). The majority of participants presented to HCF with common cold and flu-like symptoms, with no fever (84.4%) or only a low-grade fever (13%), a cough lasting less than 10 days (74.9%), headache (60.2%), rhinorrhea (59.6%), nasal congestion lasting less than 10 days (53.8%), and sore throat (49.1%). Of our enrolled participants, roughly two-thirds (65.8%) were enrolled at HCFs in the city of Maputo.

When comparing sociodemographic characteristics of the participants in the intervention group versus the control group, we found no major differences except for a statistically significantly higher proportion of control participants with a secondary education or higher (66.9% vs. 52.5%, p<0.001). Additionally, a higher proportion of participants in the control group presented with a low-grade fever (29.7% vs 6.6%) or a high-grade fever (4.7% vs. 1.8%) (p<0.001) as compared to those in the intervention group. As part of the study, each intervention site received at least one thermometer for use during the study. As such, a significantly larger proportion of participants in the intervention group had their body temperature recorded compared to the control group (91.7% vs. 32.4%).

Table 11. Sociodemographic and clinical characteristics of the study participants

Characteristic (n=379)	Intervention	Control	Total	p-value
Sex				0.875
Male	44 (24.2%)	49 (24.9%)	93 (24.5%)	
Female	138 (75.8%)	148 (75.1%)	286 (75.5%)	
Age				0.051
18-35 years	35 (19.2%)	60 (30.5%)	95 (25.1%)	
36-45 years	65 (35.7%)	51 (25.9%)	116 (30.6%)	
46-59 years	62 (34.1%)	65 (32.9%)	127 (33.5%)	
≥60 years	20 (11.0%)	21 (10.7%)	41 (10.8%)	
Marital Status				0.276
Married	67 (36.8%)	70 (35.5%)	137 (36.6%)	
Divorced	6 (3.3%)	4 (2.0%)	10 (2.7%)	
Single	106 (58.2%)	113 (57.4%)	219 (57.0%)	
Widower	3 (1.6%)	10 (5.1%)	13 (3.7%)	
Level of Education (n=361)				<0.001
Illiterate	6 (3.4%)	14 (7.6%)	20 (5.5%)	
Primary	78 (44.1%)	47 (25.5%)	125 (34.6%)	
Secondary/technical	88 (49.7%)	105 (57.1%)	193 (53.5%)	
Higher	5 (2.8%)	18 (9.8%)	23 (6.4%)	
Fever (n=231)				<0.001
Low grade	11 (6.6%)	19 (29.7%)	30 (13%)	
High grade	3 (1.8%)	3 (4.7%)	6 (2.6%)	
No fever	153 (91.6%)	42 (65.6%)	195 (84.4%)	
Clinical signs/symptoms				
Rhinorrhoea	113 (62.1%)	113 (57.4%)	226 (59.6%)	0.349
Sore throat	80 (44%)	106 (53.8%)	186 (49.1%)	0.055
Cough < 10 days	139 (76.4%)	145 (73.6%)	284 (74.9%)	0.534
Cough > 10 days	11 (6%)	12 (6.1%)	23 (6.1%)	0.985
Nasal congestion < 10 days	89 (48.9%)	115 (58.4%)	204 (53.8%)	0.065
Nasal congestion > 10 days	5 (2.7%)	5 (2.5%)	10 (2.6%)	0.899
Chills	66 (36.3%)	67 (34%)	133 (35.1%)	0.646
Runny nose	61 (33.5%)	45 (22.8%)	106 (28%)	0.021
Headache	114 (62.6%)	112 (56.9%)	226 (59.6%)	0.251

3.2 Antibiotic prescribing rates

Overall, 40.4% of ambulatory HIV-infected patients presenting with a URTI were prescribed an antibiotic. When comparing the study arms, antibiotic prescribing was higher in the control group (56.3%) than in the intervention group (23.1%), representing a 33.2% reduction in antibiotic prescribing ($p < 0.001$) (Figure 9). Patients managed with the CDSA (intervention arm) had a 59% lower likelihood of antibiotic prescription compared to the control group (RR = 0.41; 95% CI: 0.31–0.55).

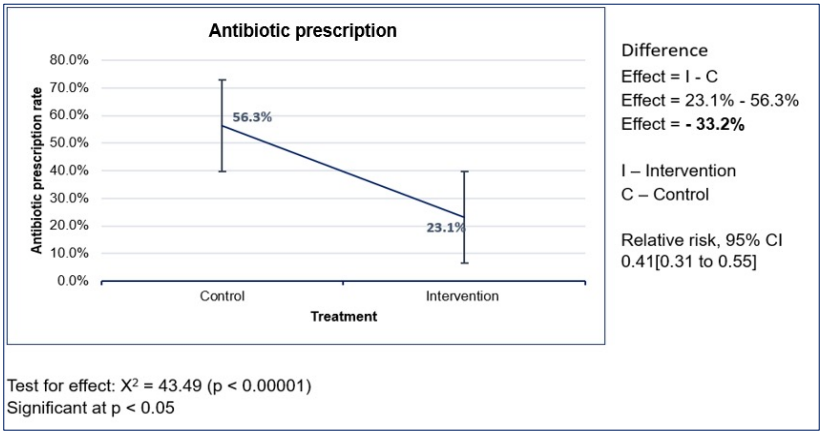


Figure 9. Comparison of antibiotic prescribing rates between intervention and control groups on the day of recruitment (Day 0). A reduced frequency is observed in the intervention arm. Pearson's chi-square test was used to test the significance of the reduction ($p < 0.001$). RR was less than 1, meaning that the intervention had a protective effect.

3.3 Pattern of antibiotic prescribing

In a review of medications prescribed throughout the study, we found that nine types of antibiotics were among those most prescribed, of which eight were broad-spectrum. Amoxicillin (47.8%), azithromycin (21.9%), and phenoxymethylpenicillin (14.1%) were the most commonly prescribed antibiotics. Six of the nine antibiotics are classified as "access" antibiotics and three as "watch" antibiotics according to the AWaRe classification. Among the most prescribed antibiotics, amoxicillin and phenoxymethylpenicillin are classified as "access" and azithromycin as "watch" (Table 12). Regarding the prescription level according to the national medicine formulary, four were level 1 antibiotics, two were level 2, and three were level 3.

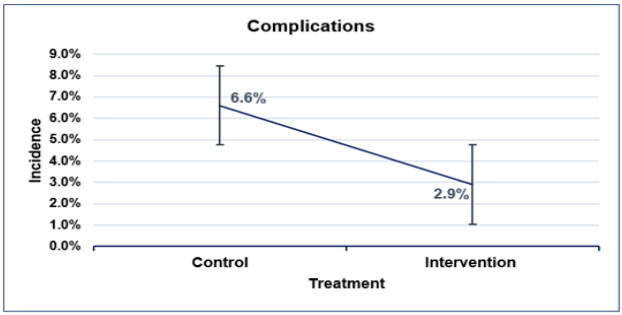
Table 12. Pattern of antibiotic prescribing on the days of recruitment and follow-up.

Antibiotic name	Spectrum of action	Prescription level*	AWaRe 2023	Day 0	Day 5	Day 10	Day15	Total
AMX	Broad	1	Access	88 (51.5%)	9 (32.1%)	1 (25%)	----	98 (47.8%)
AMC	Broad	3	Access	3 (1.8%)	3 (10.7%)	1 (25%)	----	7 (3.4%)
AZI	Broad	3	Watch	39 (22.8%)	4 (14.3%)	1 (25%)	1 (50%)	45 (21.9%)
CFX	Broad	3	Watch	4 (2.3%)	2 (7.1%)	----	----	6 (2.9%)
CHL	Broad	2	Access	----	----	----	1 (50%)	1 (0.5%)
CTX	Broad	1	Access	10 (5.8%)	4 (14.3%)	---	----	14 (6.8%)
ERY	Broad	2	Watch	2 (1.2%)	----	----	----	2 (1.0%)
MET	Broad	1	Access	2 (1.2%)	1 (3.6%)	----	----	3 (1.5%)
PcV	Narrow	1	Access	23 (13.4%)	5 (17.9%)	1 (25%)	----	29 (14.1%)

AMX: amoxicillin; AMC: amoxicillin-clavulanic acid; AZI: azithromycin; CFX: cefixime; CHL: chloramphenicol; CTX: cotrimoxazole; ERY: erythromycin; MET: metronidazole; PcV: phenoxymethylpenicillin.

3.4 Complication rates

We attempted to follow participants in both arms for 15 days following their initial clinic visit, with reassessments scheduled for days 5, 10, and 15 to assess for any complications (Figure 10). When comparing study groups, the rate of complications was higher in the control group (6.6%) compared to the intervention group (2.9%), representing a 3.7% reduction in complications seen ($p = 0.096$). Patients managed with the CDSA (intervention group) had a 56% lower likelihood of developing a complication as compared to the control group (RR = 0.44; 95% CI: 0.16–1.20), though this was not statistically significant. The most frequently observed complications were pneumonia (intervention arm 80% vs. control arm 23%) and pharyngotonsillitis (control arm only 46.2%).



Test for effect: $X^2 = 2.77$ ($p = 0.096$)
Not significant at $p < 0.05$

Complication	Intervention	Control	Total	p-value
Asthma	--	2 (15.4%)	2 (11.1%)	0.176
Pneumonia	4 (80.0%)	3 (23%)	7 (38.9%)	0.610
Bronchitis	--	1 (7.7%)	1 (5.6%)	0.340
Sinusitis	1 (20.0%)	1 (7.7%)	2 (11.1%)	0.946
Pharyngotonsillitis	--	6 (46.2%)	6 (33.3%)	**0.019**

Figure 10. Comparison of the complication rates between the intervention and control groups. A reduced complication rate is observed in the intervention group. Pearson's chi-square test was used to test the significance of the reduction ($p = 0.096$). Although the reduction was insignificant, the RR was less than 1, meaning that the intervention reduced the risk of developing a complication.

3.5 Recovery time

Table 13 shows the cumulative data stratified by study group and over 20 days. Complete recovery was seen in most participants (78%) within five days of their initial visit, regardless of study group, with a mean time to complete recovery of 6.3 ± 2.7 days. No significant differences ($p = 0.378$) were observed between the intervention and control groups regarding time to recovery within five days. Figure 11 shows the cumulative probability of patients recovering by study group. The control group seems to recover slightly faster than the intervention group. Still, this difference is not clinically significant, as regardless of the study groups, all participants fully recovered in about 2 weeks of symptom onset or treatment.

Table 13. Time to complete recovery between the two treatment groups.

Recovery time	Intervention n (%) *	Control n (%) *	Total n (%) *	*p-value*
Day 5	134 (77%)	158 (80%)	291 (78%)	0.378
Day 10	162 (93%)	195 (99%)	357 (96%)	0.010
Day 15	172 (99%)	197 (100%)	369 (99%)	0.488
Day 20	174 (100%)	197 (100%)	371 (100%)	---
Mean ± SD	6.5 ± 3.2	6.0 ± 2.2	6.3 ± 2.7	

* Accumulated frequency

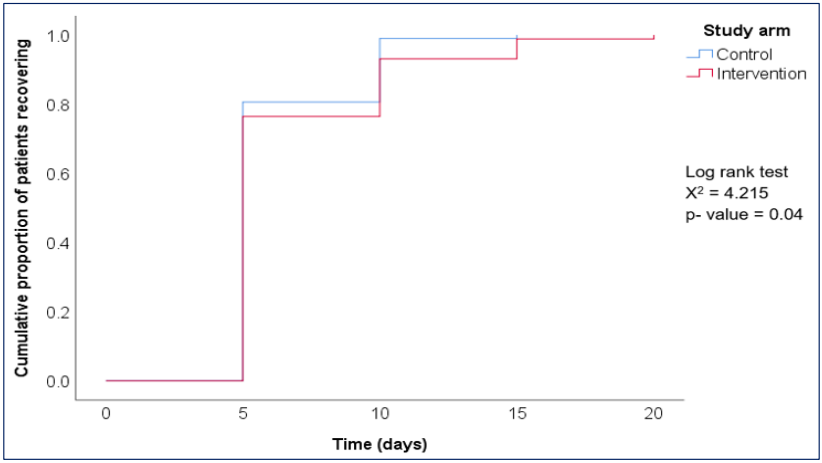


Figure 11. Cumulative probability of patients recovering stratified by control and intervention groups. Irrespective of study arms, all participants are fully recovered in about 2 weeks of symptom onset. Log-rank test was used to test for equality of recovery distributions between the two curves (i.e., intervention and control). Statistically significant differences were observed around days 10 and 15 of follow-up visits, favoring control, but with no clinical significance.

4. STUDY 4 (Paper V)

4.1 Study participants

A total of 34 clinicians, including clinical technicians (n=30, 88.2%), nurses (n=3, 8.8%), and physicians (n=1, 3%), provided care to a total of 379 HIV-infected patients with URTI symptoms. The majority of clinicians were females (82.4%), young (79.4%), with a mean age of 30.5 ± 8.5 years. Additionally, the majority had 10 years or less of work experience (73.5%).

Among HIV-infected patients recruited, the majority were adults, with a mean age of 44 ± 12.3 years and a predominance of females (75.5%). Over half of the participants (57%) were single, and slightly more than half reported a secondary or technical (53.5%) level of education (Table 14). Most presented with common cold and flu-like symptoms with no fever (84.4%). Around two-thirds (65.8%) received care in the city of Maputo.

Table 14. Patient and clinician characteristics

Characteristic		Intervention	Control	Total	p-value
Patient sex	Male	44 (24.2%)	49 (24.9%)	93 (24.5%)	0.875
	Female	138 (75.8%)	148 (75.1%)	286 (75.5%)	
Patient age range	Mean ± SD	45 ± 11.5	43 ± 12.9	44 ± 12.3	0.051
	18 – 35 years	35 (19.2%)	60 (30.5%)	95 (25.1%)	
	36 – 45 years	65 (35.7%)	51 (25.9%)	116 (30.6%)	
	46 – 59 years	62 (34.1%)	65 (32.9%)	127 (33.5%)	
	≥ 60 years	20 (11.0%)	21 (10.7%)	41 (10.8%)	
Patient marital status	Married	67 (36.8%)	70 (35.5%)	137 (36.6%)	0.276
	Divorced	6 (3.3%)	4 (2.0%)	10 (2.7%)	
	Single	106 (58.2%)	113 (57.4%)	219 (57.0%)	
	Widower	3 (1.6%)	10 (5.1%)	13 (3.7%)	
Patient's level of education	Illiterate	6 (3.4%)	14 (7.6%)	20 (5.5%)	<0.001
	Primary	78 (44.1%)	47 (25.5%)	125 (34.6%)	
	Secondary/Technical	88 (49.7%)	105 (57.1%)	193 (53.5%)	
	Higher	5 (2.8%)	18 (9.8%)	23 (6.4%)	
Signs and Symptoms	Fever low-grade	11 (6.6%)	19 (29.7%)	30 (13%)	<0.001
	Fever high grade	3 (1.8%)	3 (4.7%)	6 (2.6%)	
	No fever	153 (91.6%)	42 (65.6%)	195 (84.4%)	
	Rhinorrhoea	113 (62.1%)	113 (57.4%)	226 (59.6%)	0.349
	Sore throat	80 (44%)	106 (53.8%)	186 (49.1%)	0.055
	Cough < 10 days	139 (76.4%)	145 (73.6%)	284 (74.9%)	0.534
	Cough > 10 days	11 (6%)	12 (6.1%)	23 (6.1%)	0.985
	Nasal congestion < 10 days	89 (48.9%)	115 (58.4%)	204 (53.8%)	0.065
	Nasal congestion > 10 days	5 (2.7%)	5 (2.5%)	10 (2.6%)	0.899
	Chills	66 (36.3%)	67 (34%)	133 (35.1%)	0.646
	Runny nose	61 (33.5%)	45 (22.8%)	106 (28%)	0.021
	Headache	114 (62.6%)	117 (57.9%)	227 (60.2%)	0.329
Place of patient care	Maputo	112 (64.0%)	136 (67.3%)	248 (65.8%)	0.497
	Matola	63 (36.0%)	66 (32.7%)	129 (34.2%)	
Clinician sex	Male	4 (28.6%)	2 (10%)	6 (17.6%)	0.162
	Female	10 (71.4%)	18 (90%)	28 (82.4%)	
Clinician age range	Mean ± SD	30.6 ± 6.3	30.4 ± 9.8	30.5 ± 8.5	0.192
	18 – 35 years	10 (71.4%)	17 (85%)	27 (79.4%)	
	36 – 45 years	4 (28.6%)	1 (5%)	5 (14.7%)	
	46 – 59 years	---	2 (10%)	2 (5.9%)	
Clinician category	Nurse	---	3 (15%)	3 (8.8%)	0.760
	Clinical technician	13 (92.9%)	17 (85%)	30 (88.2%)	
	Physician	1 (7.1%)	---	1 (3%)	
Clinician's years of experience	Mean ± SD	5.6 ± 4.7	6.6 ± 8.5	6.2 ± 7.2	0.677
	≤ 10 years	10 (71.4%)	15 (75%)	25 (73.5%)	
	11 – 20 years	4 (28.6%)	3 (15%)	7 (20.6%)	
	≥ 21 years	---	2 (10%)	2 (5.9%)	

4.2 Pre-implementation

Based on insights garnered from the pre-implementation phase of the study, we modified our implementation strategy to involve healthcare facility leadership in coordinating and monitoring, as well as supervising the process on-site and reminding clinicians to utilize all available tools provided.

4.3 Adaptation and implementation

During the adaptation period, health providers were trained in the use of the CDSA and data collection tools. Afterward, they familiarized themselves with the intervention tools and implementation protocol to achieve the desired level of readiness for the start of the intervention. After a two-month adaptation period, we felt that all the health facilities and intervention agents had achieved the desired level of readiness. Then, a four-month implementation period followed, in which an implementation audit and continuous feedback were conducted to guarantee and monitor adherence to the implementation protocol.

4.4 Post-implementation

Reach

Reach was assessed at the individual (i.e., patient) level. A total of 387 HIV-infected patients deemed eligible were approached, and 379 (97.9%) agreed and were successfully recruited. Eight patients (2.1%) were excluded due to either refusal of consent or because they had a confirmed lower respiratory tract infection. Among the recruited patients, 182 (48%) were assigned to the intervention group, while 197 (52%) were assigned to the control group. The recruitment rate was high in both arms, 98.4% (182/185) in the intervention group and 97.5% (197/202) in the control group (Table 15). The overall attrition rate was less than 5%, indicating a low bias and no cause for concern.

Table 15. Implementation outcomes according to the RE-AIM dimensions

RE-AIM	Indicator	Level	Group	N (%) or results
Reach	Patients recruited with URTI symptoms	Patients	Intervention	182/185 (98.4%) patients
			Control	197/202 (97.5%) patients
			Total	379/387 (97.9%) patients
	Attrition rate	Patients	Intervention	8/182 (4.4%) patients
			Control	0 patients
			Total	8/387 (2.1%) patients
	Patients recruited and completed at least one follow-up visit	Patients	Intervention	174/182 (95.6%) patients
			Control	197/197 (100%) patients
			Total	371/379 (97.9%) patients
Effectiveness	Patients who received antibiotic prescriptions	Patients	Intervention	42/182 (23.1%) patients
			Control	111/197 (56.3%) patients
			Total	153/379 (40.4%) patients
	Patients with complications (complication rate)	Patients	Intervention	5/174 (2.9%) patients
			Control	13/197 (6.6%) patients
			Total	18/371 (4.9%) patients
	Patients recovered within 5 days	Patients	Intervention	133/174 (76.4%) patients
			Control	158/197 (80.2%) patients
			Total	291/371 (78.4%) patients
	Patients recovered within 10 days	Patients	Intervention	162/174 (93.1%) patients
			Control	195/197 (98.9%) patients
			Total	357/371 (96.2%) patients
	Patients recovered within 15 days	Patients	Intervention	172/174 (98.8%) patients
			Control	197/197 (100%) patients
			Total	369/371 (99.5%) patients
Adoption	Intervention sites that successfully implemented the strategy	Healthcare facility	Intervention sites	3/3 (100%) sites
	Clinicians who adopted the de-implementation strategy	Healthcare providers	Intervention	14/14 (100%) clinicians
Implementation	Clinicians who effectively followed the implementation protocol	Healthcare providers	Intervention	14/14 (100%) clinicians
			Control	20/20 (100%) clinicians
			Total	34/34 (100%) clinicians
Maintenance	Not assessed			

Effectiveness

Among HIV-infected patients seen for URTI in the outpatient setting, the antibiotic prescribing rate was 23.1% (42/182) in the intervention group and 56.3% (111/197) in the control (Table 15). The overall rate (combining both groups) was 40.4% (153/379). The intervention resulted in a 33.2% reduction in antibiotics compared to the control group. Individuals in the intervention group were less likely to receive an antibiotic prescription than those in the control group (RR = 0.41, 95% CI: 0.31 – 0.55).

Adoption

We evaluated the intervention adoption dimension to measure which sites and intervention agents (i.e., clinicians) adopted the de-implementation strategy of unnecessary antibiotics. Our direct observation found that the three sites (100%) and all intervention agents (100%) assigned to the intervention group showed commitment to promoting the de-implementation of unnecessary antibiotics (Table 2). Sixteen clinicians participated in the intervention group, comprising four doctors (25%) and 12 clinical officers (75%).

Implementation

Fidelity

The implementation protocol was delivered as intended. Overall, 100% (36/36) of clinicians in both groups adhered strictly to the implementation protocol, observing all stages of the implementation process. In both arms, patients were visited four times (on days 0, 5, 10, and 15). An additional follow-up visit was required in a few cases. Clinicians duly filled out the data collection forms and case record notebooks. Within 15 days of a follow-up visit, 100% (197/197) of patients in the control arm had recovered completely from their symptoms, and 99% (172/174) in the intervention arm. Only 1% (2/174) in the intervention arm required more than 15 days (i.e., 20 days) to completely recover.

Health providers' satisfaction

In total, 21 health providers from the intervention sites participated in the FGDs. This included 12 clinicians who were involved in providing direct patient care to HIV-infected adults, three pharmacists, two laboratory technicians, and one public health officer. The pharmacists, laboratory technicians, and the public health officer were additionally included to provide their opinions and experiences with how the intervention impacted their sectors of the healthcare facility (Table 16). The majority were female (81%), young with an age range of 18 – 35 years (66.7%), and had a mean age of 31 ± 6 years. They had less than 10 years of service (76.2%) and were primarily clinical technicians (57.1%). Almost all participants were either satisfied or very satisfied with the intervention (i.e., whole CDSA, diagnosis procedure, and patient reference). Then, to explore the health providers' opinion regarding the implementation process, six major themes were extracted from the FGDs: (1) CDSA effectiveness, (2) changing attitudes and prescribing practices,

(3) maintenance and dissemination of the use of the CDSA, (4) barriers to implementing the intervention, (5) enablers in implementing the intervention, and (6) reduction in requests for laboratory tests and antibiotics.

Table 16. Degree of satisfaction of the FGD participants

Feature	Total n (%)	Satisfaction with the whole CDSA		Satisfaction with the diagnosis procedure in the CDSA		Satisfaction with patient reference in the CDSA	
		Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)
Sex							
Female	4 (19%)	4 (19%)	--	4 (19%)	--	4 (20%)	--
Male	17 (81%)	17 (81%)	--	17 (81%)	--	16 (80%)	1 (100%)
Age							
Mean ± SD	31 ± 6.0						
18 – 35 years	14 (66.7%)	14 (67%)	--	14 (67%)	--	13 (65%)	1 (100%)
36 – 45 years	7 (33.3%)	7 (33%)	--	7 (33%)	--	7 (35%)	--
Length of service							
Mean ± SD	6 ± 4.9						
≤ 2 years	6 (28.6%)	6 (28.6%)	--	6 (28.6%)	--	5 (25%)	1 (100%)
3 – 10 years	10 (47.6%)	10 (47.6%)	--	10 (47.6%)	--	10 (50%)	--
11 – 20 years	5 (23.8%)	5 (23.8%)	--	5 (23.8%)	--	5 (25%)	--
Job Category							
Clinical Technician	12 (57.1%)	12 (57.1%)	--	12 (57.1%)	--	11 (55%)	1 (100%)
General Physician	3 (14.3%)	3 (14.3%)	--	3 (14.3%)	--	3 (15%)	--
Pharmacist	3 (14.3%)	3 (14.3%)	--	3 (14.3%)	--	3 (15%)	--
Laboratory technician	2 (9.5%)	2 (9.5%)	--	2 (9.5%)	--	2 (10%)	--
Public health officer	1 (4.8%)	1 (4.8%)	--	1 (4.8%)	--	1 (5%)	--
Focus group							
1º de Maio	9 (42.9%)	9 (42.9%)	--	9 (42.9%)	--	9 (45%)	--
Bagamoyo	7 (33.3%)	7 (33.3%)	--	7 (33.3%)	--	6 (30%)	1 (100%)
Matola 2	5 (23.8%)	5 (23.8%)	--	5 (23.8%)	--	5 (25%)	--

Yes satisfaction (very satisfied or satisfied); No satisfaction (neutral, dissatisfied, very dissatisfied).

CDSA effectiveness: Participants were asked about the effectiveness of the CDSA in improving symptoms without the use of an antibiotic. Respondents stated that most patients improved after the first intervention, even without antibiotic prescription. They received positive feedback from patients, indicating that they were feeling better, even without antibiotic use. When questioned about its effectiveness in reducing overprescription and adverse reactions, they stated that the CDSA decreased the irrational use of antibiotics and helped prevent adverse events. Some said that the CDSA helped them avoid prescribing many medications for the same patient and reduce excessive prescriptions.

> *"There was a decrease in the excessive use of antibiotics compared to the period before and after the introduction of the algorithm. The algorithm helped us think logically, and we prescribed fewer medications for the same patient. Treatment is mild, and adverse reactions are rare. In most cases, we did not prescribe antibiotics and treated the patients symptomatically by giving them analgesics and decongestants/antihistamines."* (FGD 3)

Changing attitudes and prescribing practices: Participants realized that the CDSA has guided them in diagnosing and treating URTI symptoms appropriately. Clinicians were able to change their prescribing behavior in treating URTIs. They explained that, previous to our CDSA-based intervention, antibiotics were widely prescribed to relieve any URTI symptoms. Following this intervention, clinicians began to prescribe antibiotics less frequently and to avoid unnecessary antibiotic prescriptions.

> *"Truly, working with the algorithm helped us a lot. Before, every flu case was given antibiotics. I was able to assess when I should and should not give antibiotics"*. (FGD 1)

Maintenance and dissemination of the CDSA: Participants recognized the value of continuing to use the CDSA, as it enhances their practices and makes their work easier. They agreed that the tool should be used as standard guidance in the Mozambican National Health Service (NHS) in the management of URTIs in primary care settings for both HIV-infected and non-infected patients.

> *"The algorithm should be considered as standard and be used in other healthcare facilities, especially primary care. It should be recommended for use because it helps reduce the excessive prescription of antibiotics for URTIs. In addition to HIV-infected patients, it can also be used for HIV-uninfected patients. It should be used for all patients regardless of their HIV test status."* (FGD 1)

Barriers to implementing the intervention: FGD participants described several challenges in putting the intervention into practice. A common difficulty was managing patient expectations, as some patients anticipated receiving an antibiotic prescription—most often cotrimoxazole—which

they believed would relieve their symptoms. Obtaining informed consent also posed challenges for patients who could not read or write, requiring the involvement of a witness to sign on their behalf. Limited availability of decongestants, such as nasal drops, in the NHS led clinicians to prescribe chlorpheniramine instead, which itself was sometimes out of stock. Follow-up by phone created further complications: when patients did not have a personal telephone, contact numbers of relatives or friends were requested, raising concerns from the patient that their HIV status might be disclosed. In such cases, some patients refused to participate and were excluded from the study. Finally, FGD participants noted that at the start, unfamiliarity with the CDSA and a shortage of thermometers for all the consultation rooms further hindered the smooth implementation of the intervention.

> *"Decongestant drugs, such as nasal drops in the National Health System, are unavailable. So, we prescribed chlorpheniramine to perform this function, and sometimes it was not available in the facility. For patients who had no personal contact number, we asked for the confidant's contact details. Some of these patients thought that we were exposing their HIV status."* (FGD 2)

Enablers in implementing the intervention: We asked the participants what enabled the implementation of the intervention. Some stated that they adopted a practice of motivating patients to participate by informing them that, in cases of persistent or worsening symptoms, they could return to the healthcare facility and speak directly to the clinician who treated them, without needing to make an appointment, wait in line, or even make a phone call.

Others stated that the presence of an on-site intervention coordinator facilitated monitoring of the implementation process by reminding the clinicians to adhere strictly to the intervention protocol. Some participants agreed that what enabled the follow-up of some patients who were inaccessible or unreachable by phone calls is the availability of a database of HIV-infected patients undergoing antiretroviral therapy (ART), where there are alternative contact numbers.

> *"The patient did not have to wait in line and was told to speak directly to me, which motivated them to participate. I provided my telephone number so that the patient could call me if their symptoms worsened. The algorithm itself facilitated the*

implementation. In the beginning, the doctor, our supervisor, and coordinator reminded us to use the algorithm and not to prescribe antibiotics for URTI according to the algorithm." (FGD 1)

Reduction in requests: We asked the participants about their perspectives on reducing requests for antibiotics and laboratory tests from the pharmacy and laboratory standpoints. They declared that a reduction in requests for unnecessary laboratory tests was observed during the implementation period. Previously, in any case of URTI, some clinicians were ordering a tuberculosis (TB) test. During the intervention period, no shortage of reagents and antibiotics was observed.

During the intervention, we did not have any stockouts. There was a reduction in antibiotic use, and we had a good stock of antibiotics due to the use of the algorithm by clinicians. There was a reduction in orders for unnecessary laboratory tests. Any URTI patient was requested to undergo a TB test. With the study, there was a reduction in orders, and no shortage of reagents was observed during the intervention period." (FGD 1)

CHAPTER 5

DISCUSSION

DISCUSSION

In this thesis, we evaluated the effectiveness and implementation of a CDSA to de-prescribe unnecessary antibiotics among HIV-infected adults with URTI symptoms. First, we described antibiotic prescribing for ambulatory HIV-infected patients regardless of their condition and age. Then, we developed a strategy to de-prescribe unnecessary antibiotics for URTIs among HIV-infected adults. Afterward, we explored the real context of the selected sites before the roll-out of our intervention strategy. Ultimately, we evaluated the intervention outcomes (i.e., the effectiveness of the CDSA) and the implementation outcomes (i.e., the success of the process of delivering that intervention).

Our findings indicated that:

a) Antibiotics are commonly overprescribed to adult HIV-infected patients to treat RTIs in Maputo and Matola cities.
b) The lack of decision support tools and limited laboratory diagnostic support justified the roll-out of our CDSA to manage URTIs.
c) HCP enthusiasm and willingness to adhere to a new intervention that would support their decision to prescribe antibiotics for URTIs supported their intervention readiness.
d) The intervention outcomes showed the effectiveness of our CDSA in reducing antibiotic prescribing for URTIs and reducing the incidence of new symptoms or complications.
e) The implementation outcomes were relatively high, showing that our intervention strategy was delivered with high fidelity.

1. Antibiotic prescribing for HIV-infected patients in outpatient care in Mozambique

We report a considerable use of antibiotics for HIV-infected patients, 65.9% of all prescriptions. This rate is high compared to the WHO reference of 20% – 26.8% (Isa et al., 2008). The study recruited only HIV-infected patients. This group is more prone to develop opportunistic infections that can be treated or controlled by antibiotics, and this may have influenced the high rate of prescription. The rate is also higher compared to studies reported in Brazil (12.5% – 56%), Norway (27%), and Nigeria (43.3%) (Colombo et al., 2004; Abrantes et al., 2007; Gjelstad et al., 2009; Tamuno, 2011). Other studies in different countries also reported higher rates, such as Brazil (66%),

Tanzania (84.9%), and Thailand (81.0%) (Paganotti et al., 2013; Gwimile et al., 2012; Issarachaikul et al., 2013). But none of these studies had HIV-infected patients as the study population. These divergences may reflect the antibiotic use in different settings, as well as a different behavioral pattern of prescribers in those countries.

Among several factors that could influence antibiotic prescribing, only the diagnosis had a statistically significant association ($p < 0.0001$). Respiratory tract illnesses were the diagnosis where more antibiotics were prescribed (36.8%), followed by genitourinary (19.4%) and gastrointestinal tract diseases (18.4%). Respiratory and gastrointestinal tract infections are common in these patients, and they are the most susceptible to empirical use of antibiotics, especially in low-income countries where there is a limited laboratory diagnostic support (Crum-Cianflone, 2010; Lubega et al., 2023). The most common classes of antibiotics used in these cases are penicillin and sulfonamide (Kumar et al., 2003; Van Hecke et al., 2019). With advances in ART, HIV-infected individuals become well controlled, and the risk of infection is reduced substantially and, in most cases, is similar to HIV-non-infected individuals (Tseng et al., 2014). There is a perception that these advances in ART are not accompanied by changes in attitudes and prescribing practices, and persist in the high empirical use of antibiotics.

The higher rate of antibiotic prescribing for respiratory tract illnesses, observed in this study, is consistent with what was reported in other countries (Falcão et al., 2003; Tamuno, 2011). There is evidence of inappropriate use of antibiotics for the treatment of RTIs, especially URTIs (i.e., sinusitis, influenza, and common cold) (Sumaila & Tabong, 2018; Wong et al., 2020). Most RTIs are of viral origin, and the use of antibiotics is not indicated, being restricted to patients with a confirmed diagnosis or high suspicion of a bacterial infection and when prophylaxis is strongly recommended if the consequences of infection can be severe (Wong et al., 2020). However, the data reported here were collected in the winter season, where there is an increase in cases of URTIs, which may have contributed to increased rates of antibiotic prescribing.

Unexpectedly, some patients whose diagnosis was related to non-infectious diseases of the cardiovascular system and nervous system were ineligible for antibiotics but received an antibiotic prescription.

For the treatment of infections, penicillin and sulfonamide were the most commonly prescribed classes of antibiotics. Several studies report higher consumption of penicillin in primary healthcare facilities and hospitals (Tamuno, 2011; Paganotti et al., 2013; Marchete et al., 2011). The predominance of penicillin use aligns with practice in other countries (Tamuno, 2011; Van Hecke et al., 2019). In this study, more than half of the

penicillin was used for the treatment of RTIs. Amoxicillin and a combination of amoxicillin and clavulanic acid were the most prescribed within the class of penicillin. According to Paganotti et al. (2013), amoxicillin is the antibiotic of the first choice against the main bacterial agents that cause RTIs. Some studies indicate that amoxicillin is the most prescribed antibiotic to treat bacterial infections in vulnerable groups, such as children and patients with weakened immunity, either in primary care or in hospital emergency care (Tamuno, 2011; Paganotti et al., 2013). Overuse of penicillin may result in bacterial resistance, as observed in a study conducted in Cambodia, where 96.2% of HIV-infected patients had resistance to amoxicillin (Phe et al., 2013). In Mozambique, resistance to penicillin has been reported in 44% of the strains causing pneumococcal pneumonia in patients, irrespective of their HIV condition (Bos et al., 2014).

High consumption of penicillin has been observed in primary healthcare facilities (Sulis et al., 2020; Mujaini et al., 2024; Faiela et al., 2025). Penicillin is a preferred class of antibiotics in most infections, except for urinary tract infections (UTIs), because of its inadequate pharmacokinetic characteristics (Flórez et al., 1992). For UTIs, quinolones are most suitable (Flórez et al., 1992). Quinolones are not the first line of treatment for UTIs in Mozambique, but given their pharmacological characteristics, their use is beginning to be high, which may compromise the potential of this group of drugs and the emergence of resistance (Thompson et al., 2024). Therefore, more than half of the prescribed quinolones in this study were used to treat genitourinary tract infections, although the literature also describes their successful therapeutic use for RTIs (Blasi et al., 2003; Aldred et al., 2014). This study shows that in addition to genitourinary infections, quinolones were also used to treat RTIs and gastrointestinal tract infections.

Most of the sulfonamides were prescribed for the treatment of RTIs and gastrointestinal tract infections, as well as for the prophylaxis of infections, mainly in undiagnosed patients. Cotrimoxazole is indicated as an alternative to ß-lactam allergic patients in UTIs and RTIs. It is also the first choice for the treatment and prophylaxis of P. carinii pneumonia in patients with a weakened immune system (Flórez et al., 1992). The predominant use of sulfonamides in this study may be related to the fact that it is part of the WHO recommendations for the reduction of morbidity and mortality by opportunistic diseases associated with HIV or AIDS. The WHO recommends prescribing cotrimoxazole prophylactically for HIV-infected patients with symptomatic illness (WHO stage II, III, or IV) in resource-limited settings, such as the lack of laboratories for CD4 cell counting and viral load measurement (Zachariah et al., 2007). All healthcare facilities included in this study were not equipped to perform CD4 cell counting and viral load

measurement. Therefore, in this situation is expected a high prescription rate of cotrimoxazole for prophylaxis purposes to all patients in these stages (II, III, or IV) of the disease. We found that more than half of the prescribed cotrimoxazole was for patients in stages II, III, or IV. The reduction of morbidity and mortality because of opportunistic diseases in HIV-infected patients taking co-trimoxazole has been reported (Zachariah et al., 2007; Huang et al., 2011). However, the problem is the excessive and inappropriate use, which contributes to increased bacterial resistance (Ahmed et al., 2024; Aslam et al., 2024).

There is evidence in Mozambique of high levels of cotrimoxazole resistance related to the past inappropriate use of sulfonamides for the treatment of malaria (sulfadoxine/ pyrimethamine) and prophylaxis against P. carinii pneumonia in HIV-infected patients (Ibarz-Pavón et al., 2011).

2. Health facilities' readiness for implementing a strategy to reduce unnecessary antibiotics for URTIs among ambulatory HIV-infected adults in Mozambique

After exploring antibiotic prescribing to HIV-infected patients and finding that they are commonly prescribed to adult patients for treatment of RTIs, we aimed to explore the state of readiness of healthcare facilities for implementing a new intervention consisting of a CDSA for rational antibiotic use in treating URTIs. Based on our analysis, we have identified several strengths that we felt would support the successful implementation of our intervention package, as well as several gaps in current capacity, which we felt justified the roll-out of our proposed intervention.

We observed an overwhelming interest and enthusiasm among HCPs to contribute to the implementation of a new tool to support them in managing URTIs and thus support intervention readiness. They believed that the tool would make their work simpler and possibly help reduce antibiotic prescriptions because there is no specific guideline to broadly manage URTIs. Although interest and enthusiasm were high, we found some gaps in the current context of the health facilities. We observed a lack of current guideline possession and use, and limited laboratory capacity to support decisions around antibiotic prescribing. The lack of possession and use of guidelines is linked to the lack of specific guidelines to support clinicians in managing URTIs. Those that exist are not helpful for the treatment of a URTI (MISAU, 2023). In general, URTIs are more common than lower respiratory tract infections and are associated with inappropriate antibiotic use, as most of

them are viral in origin, and antibiotics are not recommended (Abuelgasim et al., 2021; Sur & Plesa, 2022). These gaps justify the introduction of our CDSA to promote the de-implementation of unnecessary antibiotic prescribing in treating URTIs among HIV-infected patients.

Furthermore, we observed that due to the limited laboratory capacity and a delay in reporting laboratory results when available, most clinicians (90.6%) relied on clinical diagnosis (i.e., signs and symptoms) alone to decide whether to treat URTI with antibiotics. The delay in reporting laboratory results leads to empirical treatment of infections in primary healthcare settings (Shiferaw & Yismaw, 2019). Therefore, we assume that introducing a CDSA will help clinicians make timely, rational decisions even when laboratory tests are not available and accessible.

The overprescribing of antibiotics (65%) observed in this study, compared to the WHO recommendation (20%-26.8 %), could be linked to the absence of guidance tools (i.e., a CDSA for rational antibiotic use), and thus, clinicians tend to prescribe antibiotics in a variety of situations (Isa et al., 2008; Desalegn et al., 2013; Xu et al., 2023). Compared to other studies conducted in Mozambique, this rate (65%) is lower than the 97.6% reported by Monteiro et al. (2017) and 97.5% by Xavier et al. (2022) in pediatric patients and similar to 65.9% reported by Faiela & Sevene (2022) in HIV-infected patients. These high rates reported in the country suggest an excessive use of antibiotics.

The excessive use of antibiotics due to the lack of support tools contributes to losing their effectiveness against bacteria, threatening the emergence of bacterial mutations and resistance (Battah, 2021). This problem calls for the health system to adopt strategies to de-implement unnecessary antibiotic use. Strategies may include CDSAs and on-site antibiotic stewardship initiatives (Schwartz et al., 2020; Dunsmore et al., 2023). Integrating antibiotic stewardship initiatives into a CDSA may minimize misdiagnosis in situations of limited laboratory capacity, ensure the use of the right medication, and drive effective results with significant reductions in antibiotic use (Glasziou et al., 2022). The existence of a pharmacist who manages the use of antibiotics and the strong relationships and intercommunication among clinicians, pharmacists, and laboratory technicians observed in this study are facts that we believe constitute opportunities for antibiotic stewardship initiatives. Pharmacists are aware of the list of essential medicines and use it to update clinicians on available medicines, which reinforces the existence of opportunities for antibiotic stewardship initiatives.

Similarities and differences across sites in implementation readiness were reported indeed. Based on our findings, we modified our implementation strategy to involve health facility leadership in coordinating and monitoring

or supervising the process on-site and in reminding prescribers to use all available tools, thereby increasing engagement in the intervention. Our findings highlight the need to conduct training before the launch of the intervention to standardize the implementation process and perform prescription audits and feedback during the implementation. The literature has shown that prescription audits and feedback enabled primary care clinicians to prescribe antibiotics appropriately and effectively reduced their antibiotic prescription rates (Jyoti et al., 2013; Yang et al., 2023). Therefore, implementing our CDSA along with integrating supervision of HCPs and prescription audits, and feedback will allow us to monitor antibiotic prescribing during the implementation process and then contribute to the success of our intervention.

The study allowed us to assess the existence of antibiotics that could be useful if a patient needed to use them during implementation. The existence of antibiotics and good prescribing practices observed in this study gave researchers confidence in implementing the intervention.

3. Effectiveness of a CDSA on reducing unnecessary antibiotic prescriptions for URTIs among ambulatory HIV-infected adults in Mozambique

We demonstrated the effectiveness of a CDSA-based intervention in reducing antibiotic prescribing for URTIs among HIV-infected adults in the primary healthcare settings. Clinician use of the CDSA tool - coupled with targeted education, prescription audits, and feedback - was associated with a 33.2% reduction in antibiotic use compared to the control arm. This reduction was more than double the anticipated effect size of 15% specified in our implementation protocol (Faiela et al., 2024).

Participants in the intervention arm were significantly less likely to receive an antibiotic prescription than those in the control arm (RR = 0.41; 95% CI: 0.31–0.55). This reduction is attributed to clinicians' commitment to de-implementing unnecessary antibiotic prescribing practices. Notably, the antibiotic prescribing rate in the intervention arm (23.1%) fell within the WHO-recommended reference range of 20 – 26.8%, underscoring the value of using the CDSA to guide rational antibiotic use within this population (Isa et al., 2008; Desalegn et al., 2013; Xu et al., 2023).

In contrast, the control arm had a higher antibiotic prescribing rate (56.3%), exceeding WHO recommendations, though still lower than the baseline level (65%). This reduction from baseline may be partially due to clinicians' exposure during the pre-implementation phase, where they became aware of the study's aims and may have modified their prescribing behavior

accordingly. Additionally, the difference in data collection methods—retrospective for baseline and prospective for the implementation phase—could have influenced clinician behavior. Participants in prospective studies often modify their actions due to the perception of being observed, a known phenomenon that can lead to improved prescribing practices (Mangione-Smith et al., 2002). Our findings align with a study from Tanzania that reported a 26% antibiotic use rate in the CDSA group versus a 70% rate in the control group (Rambaud-Althaus et al., 2017).

Overall, the combined antibiotic prescribing rate in our study (40.4%) was lower than rates reported in other studies in Mozambique—97.6% by Monteiro et al. (2017); 97.5% by Xavier et al. (2022) among pediatric patients; and 65.9% by Faiela & Sevene (2022) among HIV-infected adults. It was also lower than rates reported in neighboring countries—84.9% in Tanzania and 70.6% in Botswana (Gwimile et al., 2012; Anand et al., 2019). However, our findings are consistent with reports from South Africa (37.7%) and Kenya (46.7%) (Dlamini et al., 2019; Maina et al., 2020). The reduced rate observed in this study is attributed to the CDSA, which helped clinicians manage URTIs with a rational clinical decision, including de-implementing unnecessary antibiotics and only prescribing them if a bacterial infection was suspected. In addition to the CDSA, we felt that the presence of an on-site coordinator who monitored and supervised the study's implementation process, reminding clinicians (in the intervention arm) to adhere to the CDSA and conducting prescription audits with feedback to the clinicians, contributed to this reduction.

When antibiotics were prescribed, amoxicillin (48%) and phenoxymethylpenicillin (14%) were the most commonly used, consistent with first-line recommendations for bacterial URTIs like tonsillitis and pharyngitis (Alvear et al., 2022; Monaghan et al., 2022). However, the use of azithromycin (22%) was unexpectedly high, given that it is typically reserved for patients with penicillin allergies. This trend is concerning due to its higher cost and the potential for fostering antimicrobial resistance (WHO, 2023). Although azithromycin was widely used during the COVID-19 pandemic, there is no evidence to support its use for viral URTIs (Ayerbe et al., 2021).

Despite established guidelines advising against routine antibiotic use for URTIs, some clinicians prescribe them to prevent complications (Chan et al., 2019). However, our findings showed no increased risk of complications or increased incidence of new symptoms in the intervention arm. There was a non-significant 3.7% reduction in complication rates ($p = 0.096$) compared to the control arm. Pneumonia (38.9%) and pharyngotonsillitis (33.3%) were the most common complications.

Patient recovery within five days was slightly higher in the control arm, where over half received antibiotics. However, more than three-quarters of patients in the intervention arm also recovered within five days, despite lower antibiotic use, highlighting one measure of the intervention's effectiveness. Since bacterial URTIs may take several days to resolve, many patients in the control group likely received unnecessary antibiotics (Reveiz & Cardona, 2015).

Most patients presented with mild symptoms, such as the common cold and flu-like illness. Empiric antibiotic therapy should be reserved for patients with suspected bacterial infection (i.e., high-grade fever, purulent nasal discharge, difficulty swallowing, or persistent worsening symptoms), particularly when the risk of complications is high (Hickner et al., 2001; Harris et al., 2016). Broader implementation of this CDSA-based intervention may further reduce unnecessary antibiotic use, helping mitigate stockouts, reduce treatment costs, and slow the development of antimicrobial resistance (Schwartz et al., 2020).

Comparison of antibiotic prescribing patterns among studies 1, 2, and 3

The overall antibiotic prescribing rate in study 3 (40.4%) was relatively lower than the rates we reported in study 1 (65.9%) and study 2 (65%), reinforcing the utility of our intervention in reducing antibiotic use in primary healthcare settings. The rate in studies 1 and 2 was almost the same and relatively higher, underscoring the effect of the absence of an intervention.

Among the three studies, amoxicillin was among the most prescribed antibiotics. This finding suggests that amoxicillin was commonly used in the study area because it is an effective, affordable, and relatively safe antibiotic for treating many common bacterial infections, particularly those of the respiratory tract (Sharland et al., 2024). Clinicians tend to prescribe more amoxicillin to treat Streptococcus bacterial infections, such as strep throat, because it can destroy bacteria at the root of infections while reducing symptoms, including a sore throat with fever (Kong, 2022). Likewise, azithromycin was among the most prescribed antibiotics in studies 2 and 3. It is widely used given that it is the most cost-effective option with lower direct and indirect costs compared to alternative treatments. The shorter treatment duration of azithromycin, typically 3-5 days, promotes treatment adherence and enhances patient compliance (Bharathi et al., 2024). However, its high use is a concern because of potential contribution to increasing resistance of bacteria to azithromycin, making it less effective and potentially diverting resources from more appropriate treatments (Tsai et al., 2021).

4. Implementation outcomes of the de-implementation strategy of unnecessary antibiotics for URTIs among ambulatory HIV-infected adults in Mozambique

We evaluated a de-implementation strategy of unnecessary antibiotic prescriptions among HIV-infected adults with URTIs using the RE-AIM framework. The implementation outcomes (i.e., reach, effectiveness, adoption, and implementation) were relatively high, indicating that the intervention strategy was delivered with high fidelity.

We observed a high patient participation rate, indicating a high proportion of HIV-infected adult patients reached by the intervention among those approached. An increased participation rate in randomized controlled trials can be achieved when participants perceive that they will receive better care and extra attention (Naidoo et al., 2020). Therefore, the relatively high participation rate observed in this study may be attributed to the clinicians, who provided better information about the study, including the risks and benefits of participating, building trust, and establishing a collaborative relationship. Furthermore, the connection between the clinician and the patient, as well as the facilitation of rapid contact during the follow-up visit, which would not have occurred in other circumstances, enabled greater patient participation in the process of implementing the planned intervention.

We report a productive deployment of our strategy in the intervention group, translated by both facilities and health providers into de-implementing unnecessary antibiotic prescriptions for HIV-infected patients with URTIs. As a result of the adoption of the de-implementation strategy, the intervention was effective in reducing the antibiotic prescribing rate by approximately one-third (33.2%) compared to the control. This decrease in the antibiotic prescribing rate is supported by health providers' opinions regarding the implementation of the intervention. They reported that the intervention enabled them to change their attitudes and prescribing practices, resulting in a reduction of unnecessary prescription of antibiotics.

The antibiotic prescribing rate in the intervention group (23.1%) aligns with the WHO reference of 20 – 26.8% (Isa et al., 2008; Desalegn et al., 2013). In our control sites, in the absence of the intervention, the antibiotic prescribing rate (56.3%) was nearly double the WHO reference. These findings reveal the strong effect of our intervention in reducing antibiotic prescriptions. Our findings align with those reported in Tanzania, where the intervention resulted in a significant reduction in antibiotic use (26%) compared to the control (70%) (Rambaud-Althaus et al., 2017).

Although some barriers were observed during the implementation process, all of them were effectively overcome, allowing the success of our intervention. The success reported in this study is partly due to the high fidelity of the intervention during implementation (Sekhon et al., 2017; Trutschel et al., 2023).

HCPs were satisfied with the implementation of the CDSA, and we felt that it would drive them to continue using the CDSA and promote a reduction in unnecessary antibiotic prescriptions for URTIs. The continued use of the CDSA, coupled with health providers' satisfaction, will reflect on the sustainability of the intervention, improving health outcomes in the mid and long term, thus contributing to the combat of unnecessary antibiotic use. However, HCPs' ownership of the intervention is crucial for maintaining the use of the CDSA even after the trial period (Iwelunmor et al., 2016). An unexpected benefit of implementing our intervention was a simultaneous reduction in requests for unnecessary laboratory tests. This demonstrates the utility of our CDSA in contributing to the attitudes and behavior change in regards to antibiotic prescribing.

CHAPTER 6

CONCLUSION

6.1 CONCLUSION

1. Findings from study 1 indicated that the prescription of antibiotics for HIV-infected patients in the study sites was high and influenced by patient clinical conditions. Antibiotics were prescribed either for treatment or prophylaxis of infections, and in some cases, associations of different classes were used. Penicillin and sulfonamide were the most prescribed classes of antibiotics for the treatment of infections. Most of these antibiotics were indicated to treat respiratory tract infections.
2. The baseline assessment indicated that a lack of existing decision-support tools and limitations in laboratory diagnostic support justified the introduction of our adapted CDSA for rational antibiotic prescribing. Furthermore, our pre-implementation evaluation generated important information about HCP enthusiasm and willingness to implement the new CDSA, supporting intervention readiness. Further, we identified modifiable gaps in existing capacity that have led to a revision of our implementation strategy. Our findings highlighted that our CDSA should be implemented along with the supervision of HCPs and antibiotic prescription audits, and feedback. HCPs should be trained before the intervention launch to standardize the implementation process.
3. The intervention (CDSA coupled with education and audits with feedback) effectively reduced antibiotic usage. Furthermore, when decisions were made to withhold antibiotics for URTI, this approach did not increase the incidence of new symptoms or complications.
4. This study revealed an effective and successful implementation of our intervention in the primary healthcare setting. The intervention was effective in de-implementing unnecessary antibiotic prescriptions for URTIs. The reach, adoption, and implementation outcomes were relatively high.

6.2 RECOMMENDATIONS

The findings represented in this thesis express the efforts to provide support to clinicians for rational antibiotic use in managing URTIs in primary healthcare settings, where limited laboratory support is a serious problem. These efforts will contribute to combating AMR in the medium to long term. Targeted specific recommendations are below:

Healthcare facilities and healthcare providers

- Healthcare providers should be encouraged to consistently apply delayed prescribing for patients with non-serious URTIs. Facilities that were part of the intervention group should be supported to sustain the use of the Clinical Decision Support Algorithm (CDSA).

Patients

- Strengthen patient education among HIV-infected individuals with URTI symptoms to increase awareness of the risks of inappropriate antibiotic use. Patients with mild symptoms lasting fewer than 10 days should be encouraged to delay antibiotic use and take them only if symptoms worsen.

Researchers

1. Advocacy for this CDSA should be maintained with the Ministry of Health to implement it in a larger number of sites. This will allow many healthcare facilities and providers to be involved in reducing unnecessary antibiotic use in treating URTIs.
2. Researchers should also conduct an economic and cost-effectiveness analysis of this intervention compared to usual care to support evidence-based policy and investment decisions. This analysis will help identify efficient resource allocation, guiding policy decisions in sectors like healthcare, where benefits are difficult to monetize, and promoting better outcomes by directing interventions with the lowest cost for a given benefit.
3. This research project was conducted in urban and peri-urban areas of Maputo and Matola cities, involving only six primary healthcare facilities, where clinicians tend to be better informed about AMR. Therefore, future research projects using this intervention should

expand to new areas across Mozambique to determine if these findings are consistent elsewhere. Simultaneously, the mid and long-term sustainability of this intervention should be evaluated.

4. Besides, primary healthcare settings, new studies can be developed using our approach in other settings, including in secondary and tertiary levels of the health system, and contribute to necessary changes in attitudes and prescribing behavior for more appropriate and evidence-based antibiotic prescription.
5. Researchers should integrate antibiotic use studies with AMR surveillance data to establish links between prescribing behaviors and resistance patterns in a particular study area.

Decision makers (Ministry of Health, Provincial and District Health Services, Municipalities)

- The findings presented in this thesis can be used by decision makers to implement interventions to enhance awareness among clinicians for the rational use of antibiotics in treating URTIs, clinical education, and surveillance of antibiotic use in primary healthcare settings.

CHAPTER 7

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ANNEXES

Printed copies of articles published or under review in scientific journals as part of this Doctoral thesis

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AOSIS

Page 1 of 7 Original Research

Antibiotic prescription for HIV-positive patients in primary health care in Mozambique: A cross-sectional study

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Background: Antibiotic overuse is a major public health challenge worldwide and it can result in the emergence and spread of drug resistance. In Mozambique, there are limited data related to primary care physicians' antibiotic prescription patterns. The aim of this study was to assess the antibiotic prescription patterns for HIV- positive patients in primary health care.

Methods: A prospective cross-sectional quantitative study was conducted in eight primary health care units in Southern Mozambique. The study was based on recording outpatient prescriptions using a structured questionnaire. Three hundred and sixty-nine prescriptions and clinical records of HIV-positive patients from 31 prescribers were assessed. A total of eight general practitioners, 13 medical technicians and 10 nurses participated.

Results: Antibiotics were used in 65.9% of prescriptions, with an average of 0.9 antibiotics per prescription. Of a total of 334 prescribed antibiotics, 69.8% were for the treatment of infections and 30.2% for prophylaxis. Penicillin (29.2%), sulphonamides (19.7%), and quinolones (16.3%) were the most prescribed classes of antibiotics for treatment. For prophylaxis, only sulphonamides (93.1%) and macrolides (6.9%) were prescribed. The diagnosis was the only variable that had a significant association with antibiotic prescription ($p < 0.001$). Most of penicillins (68.0%) and sulphonamides (21.4%) were prescribed to treat infections related to the respiratory tract.

Conclusion: The prescription of antibiotics was high and influenced by patient clinical conditions. Antibiotics were prescribed either for treatment or prophylaxis of infections, mostly to treat respiratory tract infections. Prescribers should be encouraged to adopt a rational use of antibiotics to reduce unnecessary prescriptions.

Keywords: prescription; antibiotics; HIV; primary health care; drug resistance; drug interactions.

Introduction

Antibiotics are often prescribed for HIV-positive patients to prevent or treat opportunistic and associated infections. They are sometimes administered in combination with other medications, such as antiretrovirals (ARVs), antivirals, antifungals, antiparasitics, and antidiarrheals.[1] Simultaneous administration of antibiotics with other medicinal products may result in synergistic or antagonistic drug interactions.[2] Seden et al. reported an 18.7% prevalence of drug-drug interaction among patients on ARV drugs in Kampala, and the most common interactions were with antibiotics (4.8%).[3] Schlaeppi et al. found a high prevalence (33.0%) of potential drug-drug interaction in patients on ARVs in Tanzania being more prevalent with antimicrobial drugs.[4] The potential interaction between clarithromycin and clindamycin with ARVs (nevirapine, efavirenz and ritonavir, saquinavir; respectively) are also described.[4]

Drug interaction may decrease the effectiveness of one drug, contributing to therapeutic failure, but may also cause an increased pharmacological effect leading to the emergence of adverse drug reactions (ADRs). Patients with low CD4 levels are more prone to adverse effects and toxicity resulting from drug therapy,[5] which may accelerate disease progression and lead to patient death.[6]

Antibiotics are a class of drugs most prescribed and stand out for the higher incidence of adverse reactions.[7] However, these reactions could be avoided through rational drug use strategies. As a result of overuse and misuse of antibiotics, there is an increasing development of antibiotic resistance by many bacteria worldwide.[8,9,10] The emergence of resistant strains has been attributed,

among other reasons, to the inappropriate use of antibiotics, in conditions that antibiotic therapy is not indicated, especially in viral infections such as influenza and common cold, that can be resolved without treatment.[11]

In Mozambique, there are limited data on physician antibiotic prescription patterns. Most of the available studies focus on antimicrobial drug resistance.[12,13,14,15,16] Therefore, this study was conducted to assess the antibiotic prescription patterns for HIV-positive patients attending primary healthcare in Maputo and Matola cities.

Methods

Study design

A cross-sectional descriptive study was conducted with prospective data collection from the prescriptions and records of HIV-positive patients from March 2013 to September 2013.

Study site and population

The study was conducted in urban and peri-urban areas of Maputo and Matola cities, located in Southern Mozambique covering an area of 300 km^2 (in Maputo) and 367 km^2 (in Matola). In 2013, there were in total 35 primary level health facilities (HFs) in both the cities. Primary health care is the first level of healthcare and is characterised by a set of health actions, at the individual and collective level, which covers health promotion and protection, disease prevention, diagnosis, treatment, rehabilitation, harm reduction, and health maintenance. We selected in total eight primary care HFs according to established criteria, which included the existence of prescribers in the screening and consultation rooms, attendance of more than 600 HIV patients per month, and a pharmacy dispensing medication to HIV patients. All selected HFs had antiretroviral therapy (ART) service, patient counselling service, and voluntary testing service, and appropriate follow-up.

We only targeted HIV-positive patients because HIV weakens the immune system, resulting in opportunistic infections that may require antibiotic use.[1] With advances in antiretroviral therapy (ART), HIV-positive individuals become well controlled, and the risk of infection reduce substantially and, in most cases, is similar to HIV-negative individuals.[17] There is a perception that these advances in ART are not accompanied by changes in prescription patterns for this specific group and persist in the high empirical use of antibiotics. Furthermore, there are several strategies directed to this group and we thought targeting HIV-positive patients would add information to the existing strategies towards the use of antibiotics.

The primary care for HIV-positive people in the study area is provided by general practitioners, medical technicians, and nurses. All HIV-positive patients of all ages who presented consecutively at HF medical visit with a complaint were included in the study, based on the following inclusion criteria: (1) HIV-positive patient in follow-up or diagnosed on the same day of consultation, (2) absence of severe pathology that would interfere with the ability to consent and (3) accepting freely to sign the consent.

According to the World Health Organization (WHO), a statistically viable antibiotic prescribing analysis requires a minimum of 100 prescriptions.[18] Thus, a total of 369 HIV-positive patient records, with and without antibiotic prescription were enrolled for further analysis.

Data collection

Data collection was based on self-completion of a questionnaire by the prescribers. The questionnaire was structured with questions related to prescriber identification, patient socio-demographic data, signs and symptoms, laboratory tests, diagnosis, and drug prescription. The questionnaires were placed in the screening and consultation rooms of the HF so that the prescriber prospectively filled out whenever he or she treated an HIV-positive patient after the patient gave free informed consent. For cases requiring additional tests, the prescriber withheld the questionnaire to complete with the results of the tests requested. The researchers were responsible for training the prescribers to fill out the questionnaires, monitor the filling, collecting the questionnaires, clean up the data (completeness, incongruous data, unreadable data), and data entry in the database created on the Statistical Package for Social Sciences (SPSS) version 20.

Data analysis

Data were analysed using SPSS version 20. Data analysis was performed descriptively by drawing up frequency tables. The descriptive analysis was based on the characterisation of the pattern of antibiotic prescription in general, by socio-demographic and clinical features.

Univariate analysis was performed for the following variables: antibiotic prescription, antibiotic class, prescriber gender, patient age, category and time of service. For the age variable, the measures of central tendency and dispersion were also calculated. For bivariate analysis, the Pearson's chi-squared test with a 95% confidence interval was used to verify if there was an association between patient characteristics (socio-demographic and clinical) and an antibiotic prescription, and $p \leq 0.05$ were considered statistically significant. For variables (age and clinical diagnosis) where expected frequencies below five were found, Fisher's exact test[19] was used.

Data definitions

Drugs were classified according to the Mozambique National Medicines Formulary (Formulário Nacional de Medicamentos [FNM]) classification following the WHO recommended classification (Anatomical Therapeutic Chemical Classification). Non-FNM drugs were classified as extra-formulary. And the diagnoses or indications for antibiotic use were classified according to the International Classification of Diseases (ICD10).

TABLE 1: Prescribers' demographic characteristics.

Characteristics	*N*	%
Sex		
Male	14	45.2
Female	17	54.8
Age (years)		
20–35	14	45.1
36–49	10	32.3
50–65	7	22.6
Category		
General practitioner	8	25.8
Medical technician	13	41.9
Nurse	10	32.3
Service time (years)		
0–10	14	46.6
> 10	17	53.4
Total	**31**	**100.0**

To calculate the frequency of antibiotic prescriptions, the proportion of medical visits in which at least one antibiotic was prescribed was considered.[11] For the variable, the class of antibiotics, the classification according to the pharmacological group (Penicillins, aminoglycosides, macrolides, quinolones, sulphonamides, tetracyclines and other antibiotics) was considered.

For the ART variable, two categories were defined: ART Yes and ART No. All patients who were receiving ARV drugs and those who started ART on the day of the medical visit were included in the category of ART Yes. Those patients who were not yet eligible to start ART were included in the category of ART No.

With an antibiotic prescription, all patients who received a prescription with at least one antibiotic for either therapeutic or prophylactic purposes were considered. No prescription antibiotics, for patients who received a prescription for drugs that did not belong to the antibiotic group.

Ethical considerations

The study was approved by the Mozambique's National Bioethics Committee for Health with reference number 258/CNBS/12. All methods were carried out by relevant guidelines and regulations. Informed consent was obtained from all participating prescribers and HIV-positive patients.

Patient and public involvement

This research was performed without patient involvement. Patients were not invited to design or comment on this study and were not consulted to develop outcomes or analyse results. Patients were not invited to contribute to the writing of this manuscript.

Results

Participants' characteristics

Data were collected from 31 prescribers who recorded prescription information on 369 medical visits of HIV-positive patients. Most of the prescribers were women (54.8%), aged 20–35 years (45.1%), medical technicians (41.9%), and with more than 10 years of service time (53.4%) (Table 1).

For the attendees, the majority were women (63.7%), aged between 25 years and 49 years (74%) with a mean (standard deviation [s.d.]) age of 37 (11.7) years and on ART (71.3%) (Table 2).

Frequency of antibiotics prescription

Antibiotics were prescribed in 65.9% (n = 243) of medical visits (Table 2). Most antibiotics were prescribed to female patients (62.9%), adults 25–49 years old (76.3%), HIV diseases stages I and II (66.9%), on ART (68.6%). Children (0–14 years) and the elderly (65+ years) received antibiotics less frequently (1.6% and 0.8%, respectively) compared with young and adults (15–64 years). Prescribers' category (p = 0.374) and length of service (p = 0.200) did not significantly influence the prescription of antibiotics (Table 2).

Number of antibiotics prescribed in each prescription

Among those patient visits with antibiotics prescribed, 48.2% received one antibiotic, 12.0% received two different kinds of antibiotics, 3.3% received three different kinds of antibiotics and 2.4% received four different kinds of antibiotics (Figure 1). Overall, the antibiotic combinations were 17.6%. In the antibiotic combinations, 69.4% were from two different classes, 24.2% of three classes, and 6.4% of four different classes (Table 3). The association between penicillin and sulphonamide was the most frequent with 29.2%, followed by macrolide associated with quinolone and metronidazole (12.3%).

Antibiotics choice for prescription

Antibiotics were prescribed in a total of 334 patients, of which 233 (69.8%) were for treatment and 101 (30.2%) for prophylaxis of infections (Table 4). For treatment, penicillin was the most commonly prescribed class of antibiotics with a frequency of 29.2%, followed by sulphonamides (19.7%) and quinolones (16.3%). In contrast, aminoglycosides and tetracyclines were the least prescribed antibiotics with a frequency of 4.3% and 2.6%, respectively. For prophylaxis, only sulphonamides and macrolides were prescribed, with the first-class being prescribed more frequently (93.1%). Of all prescribed sulphonamides (n = 139), 67.1% were used for prophylaxis of infections.

We assessed the existence of an association between antibiotic prescription and patient socio-demographic and clinical characteristics (Table 2). The diagnosis was the only variable that had a significant association ($p < 0.0001$).

Most of the penicillin (68.0%) prescribed were used to treat respiratory tract infections (Table 5).

Amoxicillin and a combination of amoxicillin and clavulanic acid were the most prescribed penicillin (62.3%), followed by

TABLE 2: Antibiotic prescribing by patient characteristics.

Characteristics	Antibiotic prescribing				Total		*p*
	Yes		No				
	n	%	*n*	%	*N*	%	
Sex							
Male	91	37.1	43	34.7	134	36.3	0.642
Female	154	62.9	81	65.3	235	63.7	
Age (years)							
0–14	4	1.6	6	4.8	10	2.7	0.063
15–24	22	9.0	8	6.5	30	8.1	
25–39	124	50.6	63	50.8	187	50.7	
40–49	63	25.7	23	18.5	86	23.3	
50–64	30	12.2	19	15.3	49	13.3	
65+	2	0.8	5	4.0	7	1.9	
ART							
Yes	168	68.6	95	76.6	263	71.3	0.107
No	77	31.4	29	23.4	106	28.7	
HIV stage							
Stage I (*n* = 124)	88	35.9	36	29.0	124	33.6	0.445
Stage II (*n* = 124)	76	31.0	48	38.7	124	33.6	
Stage III (*n* = 104)	70	28.6	34	27.4	104	28.2	
Stage IV (*n* = 17)	11	4.5	6	4.8	17	4.6	
Diagnosis							
Cardiovascular system (I)	3	1.2	22	17.4	25	6.8	< 0.0001
Infectious and parasitic disease (A)	2	0.8	3	2.4	5	1.4	
Genitourinary tract (N)	39	16.0	3	2.4	42	11.4	
Bone-muscular system and connective tissue (M)	6	2.5	4	3.2	10	2.7	
Skin and sub cutis tissue (L)	22	9.1	29	23.0	51	13.8	
Respiratory tract (J)	74	30.5	7	5.6	81	21.8	
General symptoms (R)	16	6.6	23	18.3	39	10.6	
Gastrointestinal tract (K)	37	15.2	23	18.3	60	16.3	
Nervous system (G)	2	0.8	12	9.5	14	3.8	
No information	42	17.3	0	0.0	42	11.4	
Prescriber Category							
General practitioner	53	22.0	34	27.0	87	23.6	0.374
Medical technician	107	44.0	58	46.0	165	44.7	
Nurse	83	34.0	34	27.0	117	31.7	
Service time (years)							
0–10	119	49.0	53	41.9	172	46.6	0.200
> 10	124	51.0	73	58.1	197	53.4	
Total	**243**	**100.0**	**126**	**100.0**	**369**	**100.0**	

ART, antiretroviral therapy.

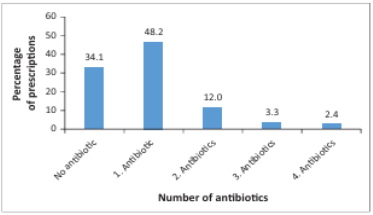

FIGURE 1: Number of antibiotics prescribed in each prescription.

phenoxymethyl penicillin (21.7%) and benzyl penicillin (10.1%). Aminoglycosides were specially prescribed to treat genitourinary tract infections (66.6%), with kanamycin being the most prescribed aminoglycoside (85.7%). Macrolides were mainly used to treat infections of the genitourinary tract (44.8%), skin and subcutaneous tissue (26.3%), and respiratory tract (21.1%), with erythromycin (57.9%) being the most commonly prescribed macrolide. Tetracyclines were used to treat genitourinary (50.0%) and respiratory (40.0%) infections, with doxycycline being the most commonly prescribed tetracycline (70.0%).

Discussion

The study found a considerable use of antibiotics for HIV-positive patients. They were prescribed in 65.9% of all prescriptions with an average of 0.9 antibiotics per prescription. This frequency is high compared to the WHO reference of 20% – 26.8%.[19] The study recruited only HIV-positive patients. This group is more prone to develop opportunistic infections that can be treated or controlled by antibiotics and it may have influenced the high rate of prescription. The rate is also higher compared to studies reported in Nigeria[20] (43.3%), Brazil (12.5%[21] – 56.0%[22]), and

Norway[23] (27.0%). Other studies in different countries also reported higher rates such as Brazil[24] (66.0%), Tanzania[25] (84.9%), and Thailand[26] (81.0%). But none of these studies had HIV-positive patients as the study population. These divergences may reflect the antibiotic use in different settings, as well as a different behavioural pattern of prescribers in those countries.

Among several factors that could influence antibiotic prescribing, only the diagnosis had a statistically significant association ($p < 0.0001$). Respiratory tract diseases were the diagnosis where more antibiotics were prescribed (36.8%), followed by genitourinary tract diseases (19.4%) and gastrointestinal tract (18.4%). Respiratory and gastrointestinal tract infections are common in these patients, and they are the most susceptible to empirical use of antibiotics, especially in low-income countries where access to diagnostic exams is scarce. The most common antibiotics used in these cases are penicillin and sulphonamides.[27,28,29] With advances in ART, HIV-positive individuals become well controlled, and the risk of infection reduce substantially and, in most cases, is similar to HIV-negative individuals.[18] There is a perception that these advances in ART are not accompanied by changes in prescription patterns for this specific group and persist in the high empirical use of antibiotics.

The higher prevalence of antibiotic prescriptions for respiratory tract diseases, observed in this study, is consistent with what was reported in other countries.[20,30] There is evidence of irrational use of antibiotics for the treatment of respiratory system diseases,[11,20,21,22] especially upper respiratory tract diseases (sinusitis, influenza, and simple cold).[31,32,33] Most respiratory infections are of viral aetiology,[33,34,35] and the use of antibiotics is not indicated, being restricted to patients with a confirmed diagnosis of a bacterial infection or with high suspicion and when prophylaxis is strongly recommended[36] when the consequences of infection can be severe. However, this study was conducted in winter, where there is an increase in cases of upper respiratory tract infections, which may have contributed to increased rates of antibiotic prescribing.

Some patients who were not eligible for antibiotic therapy received a prescription for this class of drugs. Therefore, antibiotics were not expected to be prescribed to individuals whose diagnoses were related to non-infectious diseases of the cardiovascular system and nervous system.

For the treatment of infections, penicillin and sulphonamides were more commonly prescribed. Several studies report higher consumption of penicillins in primary healthcare units[11,18,20,24,] and hospitals.[37] The predominance of penicillin

TABLE 3: Association of classes of antibiotics.

Number of classes of antibiotics	Association of antibiotics	*n*	%	Total	
				N	%
2	Penicillin + Sulphonamide	19	29.2	43	69.4
	Penicillin + Tetracycline†	3	4.6		
	Penicillin + Macrolide	2	3.1		
	Aminoglycoside + Macrolide	1	1.5		
	Aminoglycoside + Metronidazole	1	1.5		
	Aminoglycoside + Tetracycline	1	1.5		
	Macrolide + Quinolone	1	1.5		
	Macrolide + Sulphonamide	5	7.7		
	Macrolide + Metronidazole	1	1.5		
	Quinolone + Metronidazole	1	1.5		
	Quinolone + Sulphonamide	2	3.1		
	Sulphonamide + Metronidazole	6	9.2		
3	Penicillin + Tetracycline + Sulphonamide†	1	1.5	15	24.2
	Penicillin + Sulphonamide + Quinolone	1	1.5		
	Penicillin + Aminoglycoside + Chloramphenicol	1	1.5		
	Aminoglycoside + Tetracycline + Metronidazole	2	3.1		
	Macrolide + Quinolone + Metronidazole	8	12.3		
	Macrolide + Quinolone + Sulphonamide	2	3.1		
4	Aminoglycoside + Tetracycline + Metronidazole + Sulphonamide†	1	1.5	4	6.4
	Macrolide + Quinolone + Sulphonamide + Metronidazole†	3	4.6		

†, Associations not recommended because of increased risk of adverse reactions: Sulphonamide + Metronidazole and Penicillins + Tetracyclines.

TABLE 4: The choice for prescribing a class of antibiotic.

Antibiotic class	Treatment		Prophylaxis		Total	
	n	%	*n*	%	*n*	%
Penicillin	68	29.2	0	0.0	68	18.4
Aminoglycoside	6	2.6	0	0.0	6	1.8
Macrolide	31	13.3	8	6.9	39	14.3
Quinolone	38	16.3	0	0.0	38	14.4
Sulphonamide	46	19.7	93	93.1	139	37.9
Tetracycline	10	4.3	0	0.0	10	3.0
Others	34	14.6	0	0.0	34	10.2
Total	**233**	**100.0**	**101**	**100.0**	**334**	**100.0**

TABLE 5: Antibiotic prescribing following diagnosis.

Diagnosis (ICD10)	Penicillins		Aminoglycosides		Macrolides		Tetracyclines		Quinolones		Sulphonamides		Other antibiotics	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Cardiovascular system (I)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	3	2.1	0	0.0
Infectious and parasitic diseases (A)	1	1.5	0	0.0	1	2.6	0	0.0	0	0.0	0	0.0	0	0.0
Genitourinary tract (N)	8	11.6	4	66.6	17	44.8	5	50.0	24	64.1	10	7.1	17	50.0
Musculoskeletal system and connective tissue (M)	0	0.0	0	0.0	1	2.6	0	0.0	1	2.6	4	2.8	0	0.0
Skin and subcutaneous tissue (L)	4	5.8	0	0.0	10	26.3	0	0.0	0	0.0	14	10.6	0	0.0
Respiratory tract (J)	46	68	1	16.7	8	21.1	4	40.0	6	15.4	30	21.4	1	3.0
General symptoms (R)	6	8.7	0	0.0	0	0.0	0	0.0	0	0.0	11	7.8	0	0.0
Gastrointestinal tract (K)	2	2.9	0	0.0	1	2.6	1	10.0	7	17.9	25	17.7	15	44.0
Nervous system (G)	1	1.5	1	16.7	0	0.0	0	0.0	0	0.0	1	0.7	1	3.0
Unknown	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	42	29.8	0	0.0

ICD, International Classification of Diseases.

use aligns with practice in other countries.[20,27] In this study, more than half of the penicillins were used for the treatment of respiratory tract infections. Amoxicillin and a combination of amoxicillin and clavulanic acid were the most prescribed penicillin. According to Paganotti,[24] amoxicillin is the antibiotic of the first choice against the main bacterial agents that cause respiratory infections. Some studies indicate that amoxicillin is the most prescribed antibiotic to treat bacterial infections in vulnerable groups, such as children and patients with compromised immunity, either in primary care or in emergency services.[22,24] Overuse of penicillin may result in bacterial resistance,[18] as observed in a study conducted in Cambodia, where 96.2% of HIV-positive patients had resistance to amoxicillin.[38] In Mozambique, resistance to penicillin has been reported in 44% of the strains causing pneumococcal pneumonia in patients, irrespective of their HIV status.[39]

High consumption of penicillin has been observed in health units providing primary health care. Penicillins are preferred drugs in almost all infections, except for urinary tract infections, because of their inadequate pharmacokinetic characteristics, being quinolones, antibiotics most suitable for this condition. Quinolones are not the first line of treatment for urinary tract infections in Mozambique, but given their pharmacological characteristics,[40] their use is beginning to be high, which may compromise the potential of this group of drugs and the emergence of resistance.[41] Therefore, more than half of the prescribed quinolones in this study were used to treat genitourinary tract infections, although the literature also describes their successful therapeutic use for respiratory tract infections.[41,42,43] This study shows that in addition to genitourinary infections, quinolones were also used to treat gastrointestinal and respiratory infections.

Most of the sulphonamides were prescribed for the treatment of respiratory and gastrointestinal infections as well as for the prophylaxis of infections mainly in undiagnosed patients. Cotrimoxazole is indicated as an alternative to ß-lactam allergic patients in the urogenital tract and respiratory tract infections. It is also the first choice for the treatment and prophylaxis of *P. carinii* pneumonia in patients with immunosuppression.[40] The predominant use of sulphonamides in this study may be related to the fact that it is part of the WHO recommendations for the reduction of morbidity and mortality by opportunistic diseases associated with HIV or AIDS. The WHO recommends prescribing cotrimoxazole prophylactically to all HIV-positive patients in stages 2, 3, and 4 in resource-limited settings, such as the lack of laboratories for CD4 cell counting and viral load measurement.[44] Nearly all health units included in this study lack these facilities. Therefore, in this setting, it is recommended to prescribe cotrimoxazole to all patients in these stages of the disease. We found that more than half of the prescribed cotrimoxazole was for patients in stages 2–4. The reduction of morbidity and mortality because of opportunistic diseases in HIV-positive patients taking co-trimoxazole has been reported.[36,44] However, the problem is inappropriate use, which contributes to increased bacterial resistance.[9]

Studies in Mozambique reported high levels of co-trimoxazole resistance related to the past inappropriate use of sulphonamides for the treatment of malaria (sulfadoxine/pyrimethamine) and prophylaxis against *P. carinii* pneumonia in HIV-positive patients.[14,16]

The study relied on prescriber self-reported practices. Therefore, there may have been biases towards prescribing behaviours and Hawthorne effect because of prescribers' awareness of being observed. The study was conducted in a primary healthcare setting where access to accurate diagnosis was limited because of lack of laboratory support. We did not measure antibiotic use and prescription audit to determine the appropriate use of antibiotics. Despite these limitations, our study provides a good insight into the antibiotic prescription patterns for HIV-positive patients in primary health care in Mozambique. Data from this study can be used to enhance medical education, antibiotic surveillance, and prescribing patterns in our settings.

Conclusion

The prescription of antibiotics for HIV-positive patients in the study area was high and influenced by patient clinical conditions. Antibiotics were prescribed either for treatment or prophylaxis of infections and in some cases, associations of different classes were used. Penicillin and sulphonamide were the most prescribed antibiotics for the treatment of infections. Most of these antibiotics were indicated to treat respiratory tract infections. We recommend a more detailed study to measure the appropriate use of antibiotics. Actions need to be taken to encourage healthcare professionals to adopt a rational use of antibiotics, to reduce unnecessary prescriptions, especially in primary care units attended by HIV-positive patients.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contribution

C.F. and E.S. designed the study, collected and analysed the data and wrote the article. C.F. prepared the figure and tables and E.S. reviewed them. Both authors reviewed the article.

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Data availability

The authors confirm that the data supporting the findings of this study are available within the article.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated institutions of the authors.

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Implementation Science

STUDY PROTOCOL

Open Access

De-implementation strategy to reduce unnecessary antibiotic prescriptions for ambulatory HIV-infected patients with upper respiratory tract infections in Mozambique: a study protocol of a cluster randomized controlled trial

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Abstract

Background Antibiotics are globally overprescribed for the treatment of upper respiratory tract infections (URTI), especially in persons living with HIV. However, most URTIs are caused by viruses, and antibiotics are not indicated. De-implementation is perceived as an important area of research that can lead to reductions in unnecessary, wasteful, or harmful practices, such as excessive or inappropriate antibiotic use for URTI, through the employment of evidence-based interventions to reduce these practices. Research into strategies that lead to successful de-implementation of unnecessary antibiotic prescriptions within the primary health care setting is limited in Mozambique. In this study, we propose a protocol designed to evaluate the use of a clinical decision support algorithm (CDSA) for promoting the de-implementation of unnecessary antibiotic prescriptions for URTI among ambulatory HIV-infected adult patients in primary healthcare settings.

Methods This study is a multicenter, two-arm, cluster randomized controlled trial, involving six primary health care facilities in Maputo and Matola municipalities in Mozambique, guided by an innovative implementation science framework, the Dynamic Adaption Process. In total, 380 HIV-infected patients with URTI symptoms will be enrolled, with 190 patients assigned to both the intervention and control arms. For intervention sites, the CDSAs will be posted on either the exam room wall or on the clinician´s exam room desk for ease of reference during clinical visits. Our sample size is powered to detect a reduction in antibiotic use by 15%. We will evaluate the effectiveness and implementation outcomes and examine the effect of multi-level (sites and patients) factors in promoting the de-implementation of unnecessary antibiotic prescriptions. The effectiveness and implementation of our antibiotic de-implementation strategy are the primary outcomes, whereas the clinical endpoints are the secondary outcomes.

Discussion This research will provide evidence on the effectiveness of the use of the CDSA in promoting the de-implementation of unnecessary antibiotic prescribing in treating acute URTI, among ambulatory HIV-infected

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patients. Findings will bring evidence for the need to scale up strategies for the de-implementation of unnecessary antibiotic prescription practices in additional healthcare sites within the country.

Trial registration ISRCTN, ISRCTN88272350. Registered 16 May 2024, https://www.isrctn.com/ISRCTN88272350

Keywords Antimicrobial stewardship, Acute respiratory infections, Protocol, Implementation science, De-implementation, Clinical decision support tool, HIV, Mozambique

Contribution to the literature

- Antibiotic use for acute upper respiratory tract infections is usually unnecessary, as most infections are viral and self-limited. Interventions that promote the de-implementation of this practice will contribute in turn to combat the global threat of antimicrobial resistance.
- This multicenter cluster randomized controlled trial assesses if a multiprong de-implementation strategy anchored on a clinical decision support algorithm will promote practice change and thus reduce unnecessary antibiotic prescriptions.
- De-implementation has been understudied in primary healthcare settings in low- and middle-income countries. This study will add to the evidence base around how to de-implement unnecessary antibiotic use in a primary healthcare setting.

Background

Upper respiratory tract infections (URTIs) are common in adults worldwide [1]. These infections are typically diagnosed clinically based on predominant signs and symptoms and then classified according to their anatomical location such as nasopharyngitis, pharyngitis, tonsillitis, or otitis media [2]. Approximately 90% of all URTIs are of viral etiology and the use of antibiotics may not be indicated [3]. Despite this, as much as 50% to 70% of patients with URTI end up being prescribed antibiotics [4]. Excessive or inappropriate antibiotic use for URTIs is considered a low-value and unnecessary practice and thus needs to be de-implemented [5]. De-implementation is perceived as an important area of research that can lead to reductions in unnecessary, wasteful, or harmful practices [6].

Strategies to promote the de-implementation of unnecessary and wasteful antibiotic use should focus not only on appropriate use but also on the sustainability of behavioral change for both clinicians and patients [7]. Improving antibiotic prescribing requires complementary strategies which include changing clinician behavior and educating patients and families about the role of antibiotics in medical care and their well-being. Commitment to these strategies by clinicians and other relevant health workers may optimize antibiotic prescribing and patient safety. Several studies have recommended appointing a clinical "champion" to promote appropriate antibiotic prescribing [7, 8]. Clinicians who have demonstrated ownership of the process are more likely to be committed to the appropriate use of antibiotics [7].

In high-income countries, several strategies are being employed to promote the de-implementation of unnecessary antibiotic use in patients with URTI across a variety of different clinical settings. These strategies include 1) the use of clinical decision support algorithms (CDSA) by antibiotic prescribers; 2) employment of rapid diagnostic testing or a biomarker to try and reduce uncertainty in diagnosis in real-time, and thus the need for empiric antibiotics; 3) education of healthcare providers, including feedback and auditing concerning their prescribing practices; 4) establishing institutional antibiotic stewardship programs; and 5) creation of, and then deployment of essential medicines policies [9–19].

CDSAs are effective among several strategies to promote the de-implementation of inappropriate prescribing, mainly when combined with the education of health workers [20]. CDSAs have been used in both printed form and within electronic prescribing systems. CDSAs developed for the management of respiratory tract infections have shown significant implementation effectiveness [7]. A considerable number of these tools have been integrated into electronic prescribing platforms and have been associated with reduced inappropriate antibiotic prescribing [7, 11, 21]. In situations in which an electronic platform may not be available, such as in many low- and middle-income countries (LMIC) there is evidence documenting the successful implementation of CDSA in printed form. Rambaud-Althaus et al. evaluated the effect of either a print version of a CDSA or a smartphone-based electronic version and compared it with a control group in a primary healthcare setting. The authors found a significant reduction in antibiotic use in both the printed paper (26%) and electronic CDSA arms (25%), as compared to the control arm (70%) [11].

In persons living with HIV (PLHIV), URTIs are the main reason for an antibiotic being prescribed, especially in those patients with a low viral load [3, 22]. With advances in antiretroviral therapy (ART), the risk of URTIs in PLHIV has reduced over time and is now similar to HIV-uninfected individuals [23]. One exception to

this is the HIV-infected patients who quit taking their ART, increasing their vulnerability and risk of getting an infection [24].

In Mozambique, the approach for treating URTIs among HIV-infected patients in the outpatient setting is predominantly empirical and often results in the prescription of antibiotics despite strong etiologic evidence of a bacterial infection. Our previous work found a high frequency of antibiotic prescriptions being given to HIV-infected patients (65.9%) in the outpatient settings, mostly for respiratory tract infections, and recommended the development of strategies to promote the reduction of unnecessary antibiotic use in this population [25]. At the time, it was felt that one potential solution to this problem would be the utilization of a CDSA that could help clinicians differentiate when a patient with acute respiratory symptoms needs antibiotics versus those who do not, thus ideally reducing the number of unnecessary antibiotics being prescribed [6, 26]. In this research, we hypothesize that the CDSA, when added to the usual or routine care, is effective as part of a de-implementation strategy in reducing unnecessary antibiotic prescriptions.

Interventions that promote the de-implementation of unnecessary, wasteful, or harmful practices may improve the quality of patient care and reduce the empirical use of antibiotics [6]. Considering that PLHIV are subject to taking medications their entire life, reducing the use of antibiotics, will contribute to reducing the number of medications these patients are exposed to taking and therefore reducing the likelihood of drug interactions and adverse reactions [27].

We summarize below our protocol for this de-implementation study, describing the conceptual frameworks that have guided its development, the different phases that will be employed throughout its implementation, and the measures we propose for evaluating its implementation and effectiveness.

Methods/Design

Aims and objectives

The overall aim of this study is to evaluate the implementation and effectiveness of a de-implementation strategy for reducing the unnecessary use of antibiotics for the treatment of acute URTIs in HIV-infected adult patients that are being managed in select ambulatory primary healthcare clinics (PHC) in Mozambique. The focus of this evaluation is a multifaceted de-implementation strategy that includes a combination of interventions including health worker education, audit and feedback, organizational adjustments, and the introduction of a CDSA for decision-making around antibiotic use. We subsequently evaluate its implementation and effectiveness as a function of the RE-AIM conceptual framework. The reporting of this protocol adheres to the SPIRIT checklist [28].

Study setting

This study will be implemented within outpatient primary healthcare clinics in Maputo (the nation's capital city) and Matola (a city approximately 30 min outside Maputo which is the capital of Maputo Province) municipalities in southern Mozambique. Both municipalities are subdivided into 10 administrative units, hereafter referred to as clusters, containing a total of 31 eligible primary healthcare facilities. All healthcare facilities providing primary care to HIV-infected patients within the study area will be eligible and enlisted for the randomization process.

Study design and conceptual frameworks

We propose a multicenter two-arm cluster randomized controlled trial that will employ a mixed-methods approach. This study will be guided by two conceptual frameworks, the Dynamic Adaptation Process (DAP) and the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework, and will be carried out in three phases (Fig. 1). The DAP framework was developed to provide the structure for an iterative process to guide, monitor, and evaluate the introduction of a new intervention into practice. DAP is a framework that allows changes to be made according to the real context by the possibility of tailoring the elements of the intervention based on data obtained during the pre-implementation and the adaptation. DAP engages stakeholders at all levels to develop robust implementation strategies and will guide the work of phases one, two, and three in our study [29]. *Phase one* (pre-implementation) will consist of a formative baseline evaluation of the current situation for antibiotic prescribing for URTI in the outpatient setting among PLHIV and occur over three months. It will consist of interviews with identified health workers to understand the current antibiotic prescribing practices for URTI among HIV-infected ambulatory patients, as well as perceived facilitators and barriers to the roll-out of our de-implementation strategy. A document review will be performed to identify the existence of national guidelines or normative documents driving antibiotic prescribing for URTI. Phase one will also include documentation of current laboratory diagnostic capacity for URTI and a situational assessment of the availability of medicines to treat URTI. *Phase two* (adaptation and implementation) consists of our de-implementation strategy roll-out and will occur over six months. Based on information learned in phase one, we will

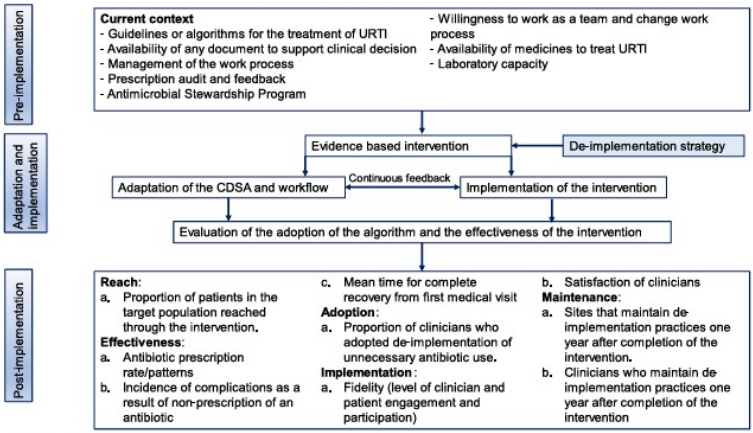

Fig. 1 The framework of the dynamic adaptation process of the intervention

make workflow adjustments to address realities on the ground. The CDSA will be rolled out within a two-arm cluster randomized control trial design in which our primary outcome measure will be the clinical decision to use antibiotics or not. Intervention elements and study tools will be adapted before the intervention is implemented. Throughout this phase, an implementation audit and continuous feedback will be conducted to guarantee and monitor adherence to the intervention protocol. *Phase three* (post-implementation) will consist of a three-month post-implementation phase in which we will analyze implementation outcomes and processes as a function of the RE-AIM conceptual framework, in real-time. *Reach* will be assessed in terms of patient recruitment, refusal, and attrition. *Effectiveness* will be analyzed by comparing antibiotic use rates and patient-related clinical outcomes between the intervention and control arms. For *adoption*, clinicians who adopted the practice of de-implementation of unnecessary antibiotic use will be assessed using prescriptions and clinical records. For *implementation*, the fidelity and satisfaction of clinicians regarding the intervention will be assessed. For *maintenance*, sites and clinicians that maintain de-implementation practices and use of the CDSA will be assessed one year after completion of the intervention.

Randomization within the two-arm cluster randomized trial and characteristics of the study participants

To mitigate contamination threat to internal validity among participating facilities, randomization and allocation will be primarily among the 10 administrative units (primary clusters). Primary clusters are considered municipal districts (Maputo) or administrative posts (Matola). Randomization will be performed before the initiation of our pre-implementation phase. Initially, randomization will be undertaken through the generation of a sequence of random numbers corresponding to each primary cluster. A total of six primary clusters will be randomly assigned to either the intervention or control arms (three each). Afterwards, in each selected primary cluster only one primary healthcare facility (secondary cluster) will be randomly selected to participate in the study. All participants in the same facility will be assigned to the same treatment, either intervention or control. A statistician will generate the allocation sequence and assign participating healthcare facilities to intervention or control groups.

During phase one (pre-implementation), we will enroll 42 health workers as part of our formative baseline

assessment. Eligible health workers will include clinicians, laboratory technicians, pharmacists, and health managers at each of our six study facilities. During phase two (adaptation and implementation), all clinicians at each site working with adult HIV-infected patients aged 18 years and older will be enrolled in the study. Eligible health workers are nurses, clinical officers (called *Técnicos de Medicina* in Portuguese), and physicians. Health workers attending to pediatric patients and those not engaged in the HIV outpatient clinic will be excluded from the study. One identified person (health worker or manager) from each cluster facility will function as a local coordinator, responsible for coordinating activities on site and being the contact between healthcare providers participating in the intervention and the research team. A sample of 380 HIV-infected patients with URTI will be enrolled and assigned to each study arm in a 1-to-1 ratio (190 for each arm) (Fig. 2). To achieve adequate participant enrollment, all clinicians who examine HIV-infected patients in the screening and outpatient consultation rooms at each selected health facility will be requested to identify potential participants among their patients, and the study team will invite them to participate in the study.

For phase three (post-implementation), we will re-interview all clinicians from each of the intervention sites concerning aspects of the intervention implementation and satisfaction.

Intervention and control

Eligible patients allocated to intervention will be managed using the CDSA. Eligible patients are adult HIV-infected with respiratory symptoms (nasal secretions or runny nose, congestion, sore throat, coughing, sneezing, chills, smell and taste disorders, with or without a fever)

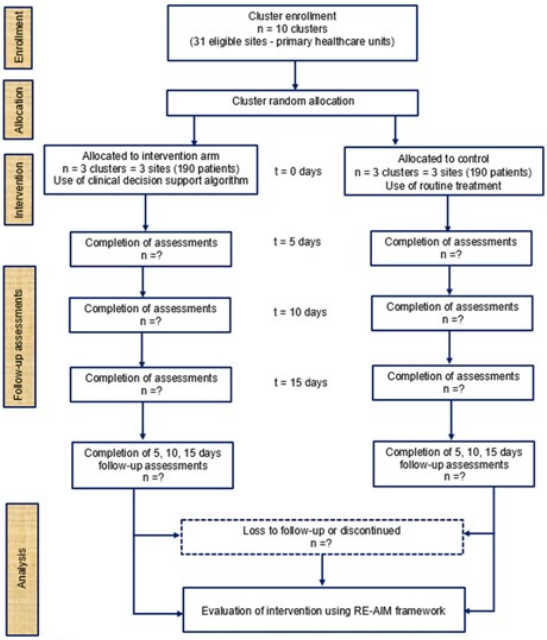

Fig. 2 Study flow diagram: enrollment, intervention, and assessments

[30]. Adult HIV-infected patients without URTI symptoms, those with fever ≥ 39°C, severe mental illness, or advanced HIV status will be excluded from the study. All PLHIV with URTI symptoms lasting less than 10 days will not receive an antibiotic unless there is an additional symptom suggesting a suspect of bacterial infection. Otherwise, bacterial infection will be suspected in the following situations: (i) higher-grade fever than normally observed with the common cold, with the presence of yellow or greenish nasal discharge, pain/difficulty swallowing, or an intense sore throat; (ii) URTI symptoms lasting longer than 10 days; (iii) URTI symptoms continuing to get worse rather than improve over several days (5 days after the first visit) [31].

Decongestants and/or antihistamines may be used to relieve symptoms of cough, congestion, and runny nose at the clinician's discretion [32]. Those with an increase in symptoms after five days, or a persistence of symptoms after 10 days, without systemic symptoms, will be treated with topical nasal steroids. If improvement of symptoms is observed after five days of treatment with nasal steroids, patients will continue with treatment for seven to fourteen days. Without improvement, consider 5 days of treatment with antibiotics. If improvement, patients should continue with treatment for seven to fourteen days. If symptoms get worse after 5 days of antibiotics, patients will be referred to an ear-nose-throat specialist (ENT). On the other hand, those with systemic symptoms without complications will follow five days of treatment with antibiotics, nasal decongestants, and topical nasal steroids (Fig. 3). Those with complications (acute otitis media, sinusitis, bronchitis, and pneumonia) will be given five days of treatment with antibiotics. Then, without improvement after 5 days of antibiotics, patients will be referred to an ear-nose-throat specialist. The promotion of de-implementation of unnecessary antibiotic use for HIV-infected patients with URTI symptoms lasting less than 10 days will be the core strategy of using the CDSA in the experiment arm.

Patients allocated to control will follow usual or routine treatment and will be used as a comparator group. The control arm will allow a fair comparison of the effectiveness of the intervention. No specific intervention will be assigned to the control arm except for follow-up. The clinicians will decide to prescribe medication during each medical visit as they are used to do. For both arms, patients will be enrolled for the first time (t0 = 0 days) and monitored three times (t1 = 5 days, t2 = 10 days, t3 = 15 days) after the initial medical visit to see improvement of symptoms through a phone call, and if necessary, will be asked to visit the healthcare facility for a follow-up clinical examination in person (Fig. 2). If the patient fails to answer the calls at t1, t2, or t3, a home visit on the following day will be made for a follow-up procedure. Participation will be discontinued if the patient's HIV clinical condition worsens as a result or not of the intervention and appropriate care and treatment will be provided including hospitalization if required.

De-implementation strategy

The process to tailor the de-implementation of unnecessary antibiotic prescriptions will combine multifaceted interventions which include health worker education, organizational adjustments, audit and feedback, and roll-out of the CDSA (Table 1). We will start the intervention period by holding an educational meeting with clinicians

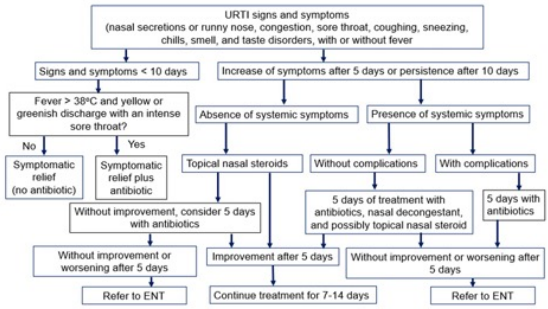

Fig. 3 Clinical decision support algorithm

Table 1 Summary of de-implementation strategy

Item	Description
Education	Educate clinicians in using the CDSA highlighting the de-implementation of unnecessary antibiotic prescriptions to treat URTI
Organizational adjustments	We will adjust the workflow based on the local setting to fit the intervention
Audit and feedback	Some prescriptions will be audited in the clinical sessions and feedback will be given. Once in two weeks, the principal investigator will meet the local coordinator or champion to monitor and evaluate the records and feedback will be given to improve the implementation of the intervention
Roll-out the CDSA	A4 poster with the algorithm to support clinical decisions will be posted on the wall of the consultation room or placed on the table

from the three intervention sites about the de-implementation of unnecessary antibiotic prescriptions to treat URTI as indicated in the CDSA. During the meeting, we will explain to the prescribers how to use the CDSA. In this meeting, we will distribute the CDSA to each participant. In addition, CDSAs will be posted on either the exam room wall or on the clinician´s exam room desk for ease of reference during clinical visits. Further, based on the results of our baseline assessment about potential barriers and facilitators to the use of our CDSA, we will work with the facility to make any organizational adjustments that may be necessary to address potential barriers. In each participating facility, we will identify one local coordinator who will function as a local champion for this intervention, be responsible for the enrollment of participants and obtaining informed consent from potential trial participants or surrogates, and serve as the study focal point for coordination with the study researchers. Finally, throughout the implementation phase, the study researchers will conduct a prescription audit and feedback on 50% of the antibiotic prescriptions that were made during this period. They will then meet with intervention site clinicians, every other week, to review the audit findings and provide feedback as to maximizing the use of the CDSA.

Data collection and measures

Phase one (Pre-implementation)

Data for the study will be drawn from multiple sources. For phase one, we will collect qualitative data about the current context of both intervention and control sites regarding the treatment of URTI among outpatient HIV-infected patients. We will conduct in-depth interviews among relevant healthcare workers which will include clinicians, pharmacists, and laboratory technicians using interview forms to guide and collect data. Interviews will include a combination of close-ended and open-ended questionnaires to explore current antibiotics prescribing practices for URTI, current workflow of patients through the facility, management of work processes, existence of current practices and normative documents in performing prescription audits and feedback, existence of any initiatives for implementing an antimicrobial stewardship program (ASP), willingness to work as a team to change work processes, availability of medicines to treat URTI, and current laboratory capacity for diagnosing the etiology or a URTI.

Phase two (adaptation and implementation) and phase three (post-implementation)

Throughout phases two and three we will collect both quantitative and qualitative data. For each HIV-infected patient determined to be eligible for this study, we will collect information related to their socio-demographics, current symptoms, and management decisions related to antibiotics. If antibiotics are prescribed, we will collect data on the type of antibiotic, and expected length of treatment. Antibiotic prescriptions data will be collected from both pharmacy and medical records. To assess whether a clinician has adopted the de-implementation of unnecessary antibiotic use, the duration of symptoms and prescriptions will be reviewed in the clinical records. This will be measured as the proportion of clinicians who adopted the de-implementation of unnecessary antibiotic use practices among those who participated in the study. The "Reach" outcome will be measured as the proportion of patients in the target population reached by the intervention (in terms of # patients recruited, # patients refused and # patients recruited and dropped out during the intervention). This data will be collected from the study data record form.

Qualitative data will be collected to measure the satisfaction of health workers regarding the implementation of the intervention including information related to adoption and acceptability of the intervention. This data will be collected through in-depth interviews with intervention site clinicians, using an interview guide and will be audio recorded. The interview guide will contain open-ended questions related to the adoption, fidelity,

and acceptability of the intervention. An additional survey will be used to assess the degree of clinicians' satisfaction. Maintenance will be measured as both the number of sites and clinicians that maintain the use of the de-implementation strategy one year after completion of the intervention implementation. This data will be collected from prescriptions and clinical records.

Secondary outcomes consist of the incidence of complications as a result of non-prescription of an antibiotic and the mean time for complete recovery from the first medical visit. This information will be collected from the study data record form. The incidence of complications will be measured as the proportion of complications arising from non-prescription of an antibiotic among patients who did not receive antibiotics. The mean time for complete recovery will be measured as the average time that the patients took to recover completely from their symptoms.

Data management and statistical analysis

We will design our study forms in REDCap (Research Electronic Data Capture), a secure web data capture tool developed by Vanderbilt University that offers a range of functions to collect, store, and analyze basic data from the desired population. Forms will be stored and de-identified in REDCap with access to all study researchers and the REDCap data manager of the Faculty of Medicine of Eduardo Mondlane University. The forms will be exported to SPSS (Statistical Package for Social Sciences) version 25 for statistical analysis.

Quantitative data analysis

Descriptive and inferential statistical analysis deemed relevant based on collected data will be performed. The descriptive analysis will be based on the elaboration of absolute and relative frequency tables and charts. To explore the factors associated with antibiotic prescribing and the need for antibiotic prescribing, multivariate logistic regression analysis will be performed. The dependent variables to be considered separately will be the prescription of antibiotics and the need for the antibiotic. Each dependent variable will be crossed with the possible factors (independent variables). ANOVA will be used to test differences among sites within the same group for both intervention and control sites with a significance level of 5%.

To compare the effect of the intervention between the intervention and control sites, Pearson's chi-square test will be used, with a significance level of 5%. To verify the magnitude of the effect of the intervention, the relative risk (RR) will be calculated and to estimate the effectiveness of the intervention, the effectiveness ratio (1 − RR) will be determined. For inferential analysis, the 95% confidence interval will be calculated for the RR parameter.

For power calculation, we have set alpha equal to 0.05 and 80% power to detect differences in proportion greater than or equal to 0.15. In other words, if we get a reduction of 15% of the overall antibiotic rate in the intervention sites compared to control sites, we could detect a significant change in proportion. We assumed a coefficient of variation equal to 0.2 for this estimate.

Quantitatively, satisfaction will be measured as the degree of satisfaction of the prescribing clinicians at the intervention study sites using the CDSA. To identify the factors that influence their degree of satisfaction using the CDSA, a multivariate logistic regression analysis will be performed. For the dependent variable, the satisfaction of clinicians, the 5-point Likert scale will be reduced to a binary category of dissatisfied (very dissatisfied, dissatisfied, neutral) and satisfied (very satisfied, satisfied). Potential factors that influence satisfaction to be considered are sex, age, length of time in current position, and the professional category of the health worker.

Qualitative data analysis

Qualitative data will be coded and analyzed using qualitative analytic software (*NVivo version 12*). Audio recordings will be transcribed and coded using constructs consistent with our study aims and relevant implementation outcomes (adoption, acceptability) which will be outlined in a codebook with definitions. After encoding the constructs, a directed content analysis approach with allowance for the emergence of new themes will be used. After the qualitative analysis, we will perform a quantitative analysis of the contents or themes using a frequency table to be created in the Excel program.

Trial status

The trial commenced recruitment in June 2024, and all the sites have already started enrollment.

Dissemination plans

The results of this study will be discussed with all health professionals who participated in it, with the relevant stakeholders at the provincial level, and with the Ministry of Health. Reports and scientific publications will be used to disseminate the results to the broader scientific community. Results will be disseminated regardless of the magnitude or direction of the effects.

Discussion

This study will evaluate the effectiveness and implementation of a CDSA in promoting the de-implementation of unnecessary and wasteful antibiotic prescriptions in treating acute URTI among an HIV-infected adult

population in an ambulatory clinic setting. Most acute URTIs have a viral etiology and antibiotic use for these conditions is perceived as unnecessary and inappropriate [1]. The de-implementation of unnecessary antibiotic use will result in a reduction of antibiotic prescription rates and in turn, contribute to combat antibiotic resistance. Inappropriate and unnecessary antibiotic use for acute URTI is among the main contributors to the development of antibiotic resistance [22, 23]. Considering that HIV-infected patients take medicines their entire lives, the reduction of antibiotic use will reduce the number of medicines prescribed to them, thus reducing the chance of potential interactions and adverse reactions [33].

Evidence suggests that the use of a CDSA can improve management and reduce antibiotic prescription rates. Tabatabaei et al., evaluated the feasibility of a new CDSA in reducing rates of misdiagnosis and inappropriate use of antibiotics for the treatment of acute respiratory tract infections (ARTI) in pediatric patients [34]. The study concluded that the use of the new CDSA was feasible and could help to reduce diagnostic errors and the frequency of antibiotic prescriptions in pediatric patients with ARTI. Shao et al., in a quasi-experimental study in primary health care, evaluated a CDSA to improve antibiotic use in the integrated management of childhood illness [9]. The study observed a statistically significant improvement in adherence to CDSA use between the control group and the intervention group. The study concluded that using the new CDSA improved clinical outcomes and reduced antibiotic prescribing by 80%. However, the CDSAs used in these two studies are differentiated and different from the CDSA proposed here. The studies described above were carried out in primary healthcare facilities and among pediatric patients. This study will be carried out in primary healthcare settings, but in adult and HIV-infected patients.

The randomized design employed in this study will strengthen our results and help to create a fair comparison across the intervention and control arms. Additionally, the study will be targeting a relatively simple and short-term intervention. Short-term and simple interventions are generally viewed as easier to de-implement than more complex interventions [6].

Findings from this study could be scaled up to additional primary health care settings expanding de-implementation practices. To our knowledge, this will be the first study in Mozambique targeting the de-implementation of unnecessary antibiotic use practices in treating acute URTIs among an ambulatory HIV-infected population. It will contribute to the literature on de-implementation science by determining whether the use of CDSA is an effective strategy for promoting the de-implementation of unnecessary and wasteful antibiotic prescriptions to HIV-infected patients.

Abbreviations

ART	Antiretroviral therapy
ARTI	Acute respiratory tract infection
ASP	Antimicrobial Stewardship program
CDSA	Clinical Decision Support algorithm
CNBS	National Bioethics Committee for Health (*Comité Nacional de Bioética para Saúde*)
DAP	Dynamic Adaptation Process
ENT	Ear, Nose, and Throat Specialist
HIV	Human immunodeficiency virus
PHC	Primary healthcare
PLHIV	People living with HIV
RE-AIM	Reach, effectiveness, adoption, implementation, and maintenance framework
URTI	Upper respiratory tract infections

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13012-024-01382-8.

Supplementary Material 1.

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Not applicable.

Authors' contributions
All authors made substantial contributions to the concept and design of the study. CF drafted the manuscript. CF, TM, and MS made substantial revisions. ES commented on the entire manuscript and critically revised the manuscript with input from all co-authors. The authors read and approved the final version of the document.

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Availability of data and materials
The protocol and all data generated will be available from the corresponding authors upon request and will be deposited at the Faculty of Medicine, Eduardo Mondlane University data repository.

Declarations

Ethics approval and consent to participate
Ethics approval for this study was obtained from the Mozambican National Bioethics Committee for Health (Comité Nacional de Bioética para Saúde, CNBS). CNBS approved the protocol on 14 August 2023 (register number 52/CNBS/2023, see supplementary material). Any protocol modifications will be submitted for approval by the CNBS and will be communicated to relevant parties. Participants will be enrolled in the study after providing informed consent. The intervention is implemented pragmatically based on health services' real, local context. Suppose any adverse events occur with the patient during the intervention. In that case, they will be dealt with within the local health system, including referral to secondary or tertiary level health facilities if required. However, the interventions are deemed a negligible risk, and therefore, no compensation plan was put in place.

Consent for publication
Not applicable.

Competing interests
Not applicable.

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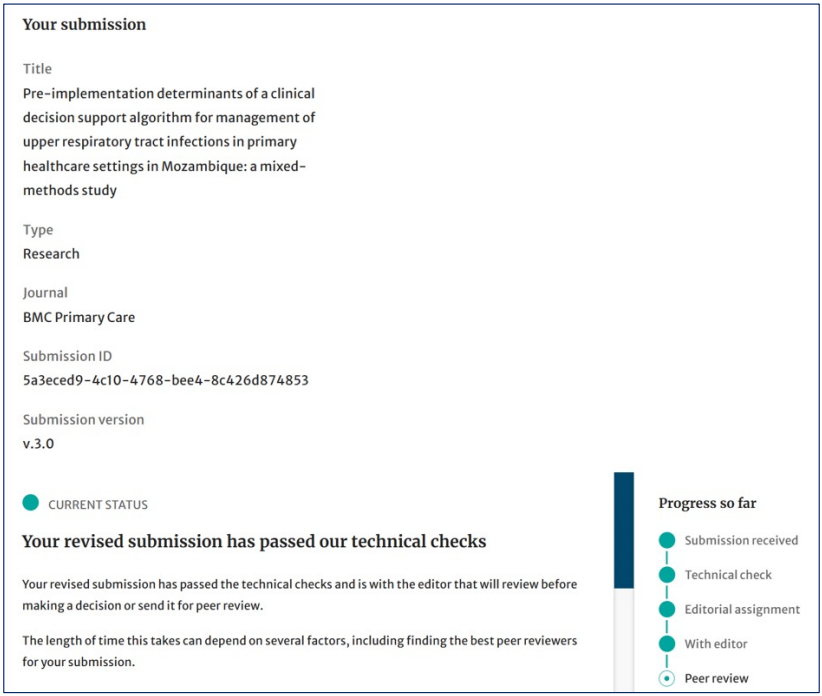

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Pre-implementation determinants of a clinical decision support algorithm for management of upper respiratory tract infections in primary healthcare settings in Mozambique: a mixed-methods study

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Abstract

Background: Upper respiratory tract infections (URTIs) are illnesses caused by acute viral or bacterial infections of the nose, sinuses, pharynx, and larynx. These are among the main reasons for antibiotic prescribing among ambulatory HIV-infected patients, despite strong evidence that most URTIs have a viral etiology. This study aims to explore the systemic, organizational, and healthcare provider determinants of the successful implementation of an adapted clinical decision support algorithm (CDSA) to de-implement unnecessary antibiotic prescriptions in treating URTIs.

Methods: We conducted a convergent parallel mixed-methods study, combining qualitative and quantitative data in six primary health facilities in Mozambique from October to December 2023. Semi-structured in-depth interviews were used to collect qualitative data. A data extraction form was used to collect quantitative data on past prescriptions from pharmacies. Directed content analysis was used for qualitative data, and descriptive statistics for quantitative data analysis.

Results: Thirty-nine healthcare providers (HCPs) were interviewed, including 27 clinicians, six laboratory technicians, and six pharmacists. Less than 50% of clinicians reported access to or use of clinical guidelines/algorithms for respiratory illness management, and all study facilities reported limited capacity for performing diagnostic tests and/or ancillary laboratory tests to aid evidence-based clinician antibiotic prescribing in managing URTI among ambulatory adults living with HIV. Most respondents (92.6%) reported using clinical diagnosis alone to guide antibiotic choice. Pharmacy records showed a roughly threefold higher frequency of antibiotic prescribing

(65%) at our study facilities compared to WHO recommendations (20-26.8%). In contrast, HCP respondents overwhelmingly described enthusiasm and willingness to utilize a new CDSA intervention. They described strong relationships and intercommunication among clinicians, pharmacists, and laboratory technicians.

Conclusion: The lack of existing decision-support tools, the limitations of laboratory diagnostic support, and the routine prescribing practices are negative determinants that foster the introduction of our CDSA. On the other hand, HCP enthusiasm and willingness to use a new CDSA, and the effective interaction among HCPs are positive determinants that will enable the implementation of our intervention. For better results, the CDSA should be implemented alongside continued supportive supervision of HCPs, and antibiotic prescription audits and feedback.

Clinical trial number: not applicable

Keywords: Pre-implementation, implementation process, readiness, antibiotics, respiratory tract infections, Mozambique

Introduction

Upper respiratory tract infections (URTIs) are illnesses caused by acute viral or bacterial infections of the nose, sinuses, pharynx, and larynx [1,2]. Approximately 90% of URTIs are of viral origin, short, mild, self-limiting, and generally resolve without further complications, so antibiotic prescribing may not be required [3]. Despite this, as many as over two-thirds of patients with URTI end up being prescribed antibiotics [4]. Excessive or inappropriate antibiotic prescribing for URTIs is considered an unwarranted and unnecessary practice and contributes to the emerging global threat of antimicrobial resistance (AMR) [5].

AMR is rapidly increasing among bacteria that commonly cause URTIs, and its emergence makes future infections more difficult to treat [4,6]. Combating AMR requires that antibiotics be used appropriately and that patients receive medications appropriate to their clinical needs [7]. People living with HIV (PLHIV) have more frequent hospital admissions, clinic visits, and antibiotic treatment courses compared to individuals without HIV infection, putting them at increased risk of acquiring an infection with resistant bacteria [8].

According to Olaru et al. (2021), PLWH have a 2.12 (95%CI 1.36–3.30) higher odds for colonization and 1.90 (95%CI 1.45–2.48) higher odds for infection with methicillin-resistant *S. aureus*, a 2.28 (95%CI 1.75–2.97) higher odds of infection with *S. pneumoniae* with decreased penicillin susceptibility, and a 1.59 (95%CI 0.83-3.05) higher odds of resistance to third-generation cephalosporins in *E. coli* and Klebsiella pneumoniae [8].

Opportunistic infections, typically respiratory, are the main reason for antibiotic prescribing in PLHIV, who are on antiretrovirals (ARVs) for life. Avoiding unnecessary antibiotic prescriptions will reduce the likelihood of drug interactions and adverse events [9,10]. In addition, antibiotic prescriptions are more frequent among PLWH even before HIV diagnosis [8]. On the other hand, ARV-antibiotic interactions are widespread, impacting nearly half of HIV patients and often requiring dose adjustments, with consequences ranging from reduced ARV effectiveness to increased toxicity [11,12].

As for many other diseases, countries produce guidelines to support healthcare providers' decision-making. In Mozambique, only three documents exist, such as guidelines/algorithms that are designed to orient clinicians on the management of respiratory illnesses generally, or of opportunistic respiratory infections among adult HIV-infected patients more specifically. These include: 1) a guideline that includes two algorithms for the management of acute and chronic lower respiratory tract infections in HIV-infected adults and adolescents [13], 2) a guideline that is specific to the management of pulmonary tuberculosis (TB), latent TB, and multidrug-resistant TB [14], and 3) a document with flowcharts and protocols for managing suspected COVID-19 patients at differing points within the health facility, which were created for use during the height of the COVID-19 pandemic [15]. None of these documents provides specific guidance for the management of URTI symptoms.

Several evidence-based interventions to reduce antibiotic use have been assessed in different contexts [16,17,18,19,20]. Among those interventions, clinical decision support algorithms (CDSAs) have effectively promoted the de-implementation of inappropriate prescribing practices [19,20]. Based on this finding, we adapted a CDSA from Bird et al. (2013) to implement and evaluate its effectiveness in reducing antibiotic use [21,22]. This CDSA is structured to promote the de-prescription or delay of antibiotic prescriptions for patients with URTI symptoms lasting less than 10 days. An exception will apply to patients presenting with symptoms suggestive of a bacterial infection, such as a high-grade fever, yellow or greenish discharge, and an intense sore throat [23]. The CDSA may be used in settings with limited laboratory capacity, including in remote areas without access to rapid diagnostic tests, to optimize antibiotic prescribing based on signs and symptoms.

However, before launching any new intervention, it is recommended to conduct a pre-implementation evaluation to identify issues that may positively or negatively influence its successful implementation [24,25]. Without this pre-evaluation, intervention studies may fail to translate into meaningful patient care or public health outcomes [24,26].

Eventual success may depend, in part, on the implementation processes during the earliest phases, i.e., pre-implementation [25]. For example, in one study, sites with higher implementation process fidelity earlier on were more likely to reach the point of delivering services due to increased engagement in pre-implementation activities, particularly those related to readiness, which predicted the sustainability of program implementation [24]. Furthermore, in another study, among sites that encountered implementation challenges, most were discontinued during the pre-implementation phase due to the implementing team's lack of competence and inability to sustain the intervention after the start-up period [27]. These findings support the notion that conducting a pre-implementation evaluation may lay the groundwork for later intervention success [24].

A pre-implementation evaluation that elucidates the actual context and conditions of a participating site regarding the proposed intervention will inform which areas need improvement before the intervention's launch [26].

The Dynamic Adaptation Process (DAP) framework was developed to provide a structure for an iterative process that guides, monitors, and evaluates the introduction of a new intervention into practice. DAP allows changes by tailoring the intervention elements to the real context. It

comprises four phases: exploration (pre-implementation), preparation, implementation, and sustainment [28].

In this study, we used the DAP framework to describe a pre-implementation evaluation conducted to gather information about the current context of healthcare facilities. This information will then inform each facility's readiness for implementing a new CDSA to de-implement unnecessary antibiotics in treating URTIs among HIV-infected ambulatory adults in Mozambique. This study aims to explore and understand the systemic, organizational, and healthcare providers' potential determinants of implementing a new CDSA.

Methods

Study design

This analysis represents baseline (phase one) data collection of a larger multi-phase implementation science study. Our protocol has been published elsewhere [21]. For this analysis, we employed a convergent parallel mixed-methods study that combined qualitative and quantitative approaches. For the qualitative portion, we used a systematic methodological orientation and deductive theoretical approach. For the quantitative portion, we used a cross-sectional design. We integrated both qualitative and quantitative approaches to contextualize our findings, adding richer detail to the conclusions [29].

The research was guided by the exploration phase of the DAP framework, which assesses three levels: (1) system-level assessment, (2) organizational-level assessment, and (3) healthcare providers' assessment.

Study setting and population

The study was conducted in the primary healthcare facilities of Maputo and Matola, cities in Mozambique. Maputo is the nation's capital city, and Matola is the capital of Maputo Province, located around 20 km outside the city of Maputo. Maputo occupies an area of 346 km^2 with a population of 1,130,319 inhabitants and a population density of 3,768 inhabitants/km^2. Matola occupies an area of 375 km^2 with a population of 1,245,799 inhabitants and a population density of 3,322 inhabitants/km^2. The prevalence of HIV is 16.9% for Maputo City and 22.9% for Maputo Province, which includes the city of Matola.

The primary healthcare facilities within this catchment area offer free or almost free outpatient services for all ages, including HIV care and treatment clinics; family planning; maternal and child health services; youth and adolescent care; health counseling and screening; and a pediatric immunization program. None of these facilities offer inpatient services; thus, if required, patients are referred to a nearby referral hospital with inpatient capacity.

To be included in this study, the healthcare facility should offer primary care to HIV-infected patients. All the primary healthcare facilities in this catchment area were eligible for this study, and are urban and semi-urban government facilities.

For site selection, we used cluster sampling. The healthcare facilities were divided into clusters (administrative units). Randomization was performed in two stages. In the first stage, 10 administrative units in both cities, comprising 31 primary healthcare facilities, were randomized.

A random sequence was generated on the computer, and six administrative units were selected. In the second stage, among the six selected administrative units, a sequence of healthcare facilities was generated for each unit, and only one was randomly selected from that sequence. Due to resource constraints, only six healthcare facilities were selected. To prevent contamination between facilities, only one healthcare facility was selected per administrative unit. A statistician generated the allocation sequence.

Purposive sampling was used to select the participants who met the inclusion criteria. The study participants included clinicians, pharmacists, and laboratory technicians who met the following inclusion criteria: 1) Providers of primary healthcare to HIV-infected patients, 2) Dispensers of prescribed medications for HIV-infected patients, and 3) Laboratory technicians who perform laboratory tests in the healthcare facility participating in the study. HCPs who refused to cooperate or provided off-topic responses for over 50% of the interview were excluded.

At each site, participants included clinicians, one pharmacist, one laboratory technician, and a clinical director. Clinicians were general physicians, nurses, and clinical technicians (*técnicos de medicina*), a cadre responsible for providing direct patient care for the most common diseases in places without physicians. They have a medium level of education and undergo two to three years of training in their area of interest. The number of clinicians at each site was determined by data saturation, which was achieved when no new themes emerged from additional interviews.

Data collection

In-depth interviews with healthcare providers

We conducted face-to-face in-depth interviews with identified HCPs, guided by one of three interview scripts, one designed for clinicians, one for pharmacists, and one for laboratory technicians (Supplementary file 1). Interviews took place between October and December 2023 and lasted approximately 15-20 minutes each. Informed consent was provided before the conduct of any interviews.

The data collection tools included a combination of closed-ended and open-ended questions designed to explore: 1) systemic determinants of a new intervention consisting of CDSA (availability of any normative documents for the management of respiratory illness); 2) organizational determinants (willingness to work as a team and change work process; identification of a champion; implementation climate; implementation readiness; laboratory capacity to support clinical decision making); and 3) healthcare providers' determinants (practices toward management of URTIs) (Supplementary file 2).

Although the tools included some closed-ended questions, each was chosen to ensure key topics were addressed. The interviewer could probe further if needed. The tools were pre-tested with a group of providers not assigned to the study sites to verify their reliability and validity using the content-related method.

To assess participants' willingness to work as a team to change work processes, we asked about their perceptions of interactions/communications between clinicians and pharmacists within a given facility. We classified the interaction as an “effective interaction” if the HCP stated they felt

they could ask their counterpart for help and if they felt there was strong cooperation amongst colleagues in cases of clinical doubt.

The interviews were conducted in Portuguese (Mozambique's national language), individually, in a private room, on a day convenient for each participant. Two researchers were involved: one conducted the interview, and the other took notes on the responses. The interviews were audio-recorded. Two researchers transcribed all audio files.

Past pharmacy prescription reviews

To assess indicators of prescription quality and to describe antibiotic prescription patterns, quantitative data were collected from copies of past medical prescriptions stored at the healthcare facility's pharmacy. According to the World Health Organization (WHO), a statistically valid analysis of antibiotic prescribing requires a minimum of 100 prescriptions [30]. Therefore, one hundred prescriptions were randomly selected at each site for review, half from summer (September to December 2023) and the other half from winter (May to August 2023). For prescription selection, a stratified random sampling method was employed. Prescriptions were divided into subgroups by the date they were issued. Then, at each subgroup, a simple random sampling was used to select 10 prescriptions.

The tools for abstracting antibiotic data were adopted from the WHO tools [30]. We assessed the overall compliance of facilities with the World Health Organization's (WHO) reference indicators for quality prescriptions: average number of medicines per prescription, antibiotic prescription rate, prescriptions with an injectable antibiotic, prescriptions with medications prescribed by generic name, and prescriptions with medicines listed in the National Medicines Formulary (NMF). We considered facilities in good compliance if the indicator was within the WHO reference range or if the rate exceeded 90%. We described antibiotics by their type and class, spectrum of action, and prescription level.

Five antibiotic prescription levels (Levels 0-4) based on the Mozambican NMF were assessed. Level 0 prescriptions are those that can be prescribed or dispensed by the lowest-licensed healthcare provider. Each increase in level represents a medication that requires a higher cadre of health professionals to be involved in its prescribing, with Level 3, for example, requiring a general medical physician to prescribe, and Level 4 requiring a physician specialist [31].

Data management and statistical analysis

Interview forms were designed and stored in REDCap (Research Data Capture) version 10.6.12, a secure electronic data capture tool accessible through a computer or tablet, and stored on a server at the Faculty of Medicine at the University Eduardo Mondlane (UEM). All forms were de-identified, and access was limited to the study researchers only. In addition, we stored our literature search results on normative documents and the de-identified past prescription reviews within our project-specific REDCap database. Generated transcripts in Word were exported to and stored in REDCap.

For statistical analysis, data were exported to SPSS version 25. Descriptive statistics were used to characterize the sample, with absolute and relative frequencies for categorical variables and means and standard deviations for numerical variables. Transcripts were generated in Word and exported to an EXCEL matrix for coding and analysis. Qualitative analysis was performed

manually following a combination of content and thematic analysis. Deductive content analysis was employed for thematic analysis. We used content analysis because it can determine themes or concepts within the data, allowing researchers to quantify their occurrence [32,33]. Content analysis was initiated by organizing and categorizing the content based on pre-defined themes (the same ones that guided the collection process), and ultimately quantified.

Results

Characteristics of healthcare providers

We interviewed 39 HCPs out of 41 approached (two did not consent), including 27 clinicians, six laboratory technicians, and six pharmacists (Table 1). Across all health worker cadres included, the majority of participants were female (74.4%, 29/39) and young, aged 18 to 35 years (71.8%, 28/39), with a mean age of 32 years (Standard Deviation ± 4.5). For clinicians (18/27) and pharmacists (4/6), roughly 66% of each group had been in their positions for more than 2 years. In contrast, for laboratory technicians, the opposite was seen, with roughly 66% (4/6) having been in their positions for 2 years or less. Of the clinicians interviewed, 81.5% (22/27) were clinical technicians (*técnicos de medicina*). Most clinicians (74.1%, 20/27) worked in the HIV care and treatment sector.

Table 1. Characteristics of healthcare providers

General antibiotic prescribing practices

In our review of pharmacy prescriptions to assess quality indicators, we found an antibiotic prescribing rate of 65%. Less than half (49.3%) of prescriptions had one antibiotic prescribed, 6.2% had two antibiotics, and 9.3% had three antibiotics prescribed (Figure 1). Roughly 65% of prescriptions had the prescriber's name documented. Nearly 100% of prescriptions had the date, dosage, patient's name, and duration of treatment documented. Further, we observed good compliance with the core WHO indicators for prescriptions with generic names (99.3%) and with medicines listed in the NMF (100%). In contrast, the antibiotic prescribing frequency of 65% is roughly three times the WHO recommendation, and the average number of medications per prescription of 2.5 is greater than the WHO recommendation of between 1.6-1.8 medications (Table 2). We also observed good compliance with additional prescribing quality indicators for all except prescriptions with documentation of the prescriber's name (65%).

Figure 1. Number of antibiotics per prescription

Table 2. Quality prescription indicators

Across the prescriptions we reviewed (regardless of disease condition), we found that 16 different antibiotics were among those most prescribed, of which 12 were broad-spectrum. Amoxicillin (30.5%), metronidazole (18.7%), azithromycin (13.7%), and ciprofloxacin (12.5%) were the most frequently prescribed (Table 3). Of the antibiotics prescribed, five were level 1 antibiotics (can be prescribed by a clinical agent/nurse), five were level 2 (prescribed by a clinical technician), and six were level 3 (prescribed by a general practitioner).

Table 3. Antibiotic prescribing patterns

Theme 1: Systemic determinants

Availability of any normative documents for the management of RTI

We asked the clinicians about their practices toward the management of acute respiratory tract infections, and less than half (44.4%, 12/27) stated having access to or utilizing any normative document (guideline/algorithm), either in paper or electronic format. The only document remotely useful that clinicians mentioned having access to was a guideline that includes two different algorithms for the management of acute and chronic opportunistic respiratory tract infections in HIV-infected adults and adolescents. However, only 48.1% (13/27) of respondent clinicians used that guideline (Table 4).

> *"For respiratory opportunistic infections, I follow the algorithm for the management of acute or chronic respiratory infections found in HIV Care Guidelines for Adults, Adolescents, Pregnant Women, Breastfeeding Women, and Children." (IDI, Clinician 1/Male)*

Table 4. Results of the interview with healthcare providers

Theme 2: Healthcare providers' determinants

- ***Practices toward the management of URTIs***

We asked clinicians about their decision-making process for treating URTI symptoms with antibiotics. Most (92.6%, 25/27) stated that they used clinical signs and symptoms as the sole determinant for deciding whether to treat with antibiotics. In comparison, 7.4% (2/27) reported using a combination of clinical diagnosis and laboratory test results.

> *"To decide what to prescribe for URTI, I only use clinical diagnosis." (IDI, Clinician 3/Female)*
>
> *"To decide what to prescribe for URTI, I use clinical diagnosis and laboratory results if I have already ordered them." (IDI, Clinician 10/Female)*

Theme 3: Organizational determinants

- ***Willingness to work as a team and change the work process***

We asked clinicians about their interactions with colleagues when they had uncertainties about their treatment decisions. One hundred percent (100%, 27/27) of clinicians stated that they effectively interact with their colleagues, both among other prescribers and with pharmacists and laboratory technicians.

> *"When a colleague comes to me with a question related to a prescription or diagnosis, I explain and discuss the matter with the colleague until we find a decision that benefits the patient." (IDI, Clinician 19/Female)*

Clinician's knowledge about the availability of medicines at any given moment, and thus which options are available to them for prescribing, depends on the state of communications between clinicians and pharmacists within a given facility. We asked the pharmacists about their interactions with clinicians, and all (100%, 6/6) stated that they interact effectively with clinicians and that when they have doubts about a prescription, they ask the prescribing clinician for clarification.

> *"If we receive an unclear prescription, we interact with the clinician who prescribed it to ask for clarification or discuss the issue". (IDI, Pharmacist 3/Male)*

In addition, pharmacists were questioned about the existence of an essential medicines list and the importance they attach to it. All of them (100%, 6/6) said that they have the list and use it to update clinicians on the medicines available in the pharmacy and to guide them in deciding what

to prescribe. They also stated that they use the list to manage medicine stocks. All pharmacists questioned stated that when they receive a prescription for an antibiotic not available at the health facility, they advise the patient to obtain it from private pharmacies.

"We use the list of essential medicines to inform clinicians about the stock of medicines and what they can prescribe". (IDI, Pharmacist 4/Female)

"If we receive a prescription for a medicine out of stock, we send the patient to get it in private Pharmacies". (IDI, Pharmacist 2/Female)

- ***Identification of a champion***

Among clinicians, we asked clinical managers how they would identify a clinician to coordinate activities and advocate for the intervention. They said that a clinician would be nominated for the role.

"We will nominate someone who may coordinate the activities on-site and get in touch with the researchers. Such one will also update the facility leadership about the process of implementation and supervise its proper implementation". (IDI, Clinician 5 /Female)

- ***Implementation climate***

Clinicians were asked about introducing a new tool to help them make clinical decisions when managing URTIs. All of them (100%, 27/27) stated that they were available and eager to contribute to the upcoming intervention.

"Any complementary tool that would support us in managing URTIs is welcome. I am personally available to contribute to such an intervention." (IDI, Clinician 25/Female)

- ***Implementation readiness***

We asked clinicians whether they were prepared for the workflow change during intervention implementation, and all stated that they were ready to make any necessary adjustments to ensure the intervention's success.

"Given that the intervention is to improve antibiotic prescribing in treating URTIs, I think that we are all prepared for any changes if necessary." (IDI, Clinician 19/Female)

- ***Laboratory capacity to support clinical decision-making***

When examining the patient, the clinician may request laboratory tests to support clinical decisions on what to prescribe. We asked laboratory technicians about laboratory capacity to support clinicians. The majority (83.3%, 5/6) of laboratory technicians stated that their laboratory could perform a complete blood count (CBC) test. However, none could reportedly perform a blood culture and antibiotic sensitivity testing, and only 16.7% (1/6) could perform a C-reactive protein (CRP) test (Table 4).

Those unable to perform the tests on-site may send samples to another reference laboratory; however, the turnaround time for a CBC can range from 2 to 18 days, and for blood culture and antibiotic sensitivity testing, it can range from 21 to 60 days. If the clinician requires a chest X-ray, 83.3% (5/6) of participating healthcare facilities will refer the patient to another facility, with a reported turnaround time of between 1-7 days.

"We can perform a blood count test (...). However, we cannot perform a C-reactive protein test. For this test, we refer the patient to the Mozambican National Institute of Health. The patient may come back with the results after two weeks (...). We also do not perform a culture and antibiotic sensitivity test. For this one, we send samples to Maputo Central Hospital, and the patient gets the result roughly after 30 days (...). It is not frequent to ask for a chest X-ray test. When it is needed, we send the patient to get it at Machava General

Hospital or Matola Provincial Hospital, and after one day, the patient can come back with the report." (IDI, Laboratory technician 5/Male)

Discussion

This study aimed to explore the systemic, organizational, and healthcare providers' determinants of implementing a new intervention consisting of a CDSA for de-implementing unnecessary antibiotic prescribing in treating URTIs among ambulatory HIV-infected adults. Based on our analysis, we have identified several strengths that we believe will support the successful implementation of our intervention package, as well as several gaps in current capacity that we believe justify the roll-out of our proposed intervention.

We observed overwhelming interest and enthusiasm among HCPs in contributing to implementing a new tool to support them in managing URTIs and thus enhancing intervention readiness. They believed the tool would simplify their work and possibly help reduce antibiotic prescriptions, as there is no specific guideline for managing URTIs.

The unavailability of specific guidelines to broadly manage URTIs is a systemic determinant that fosters the rollout of our intervention. As a result, clinicians tend to prescribe antibiotics empirically based on experience and guesswork due to uncertainty [34]. In this study, we observed an overprescribing of antibiotics (65%) compared with the WHO recommendation (20%-26.8 %) [35]. Among other factors, the high rate of antibiotic prescribing may be linked to the absence of guidance tools (i.e., a CDSA for rational antibiotic use). Our goal is to introduce a CDSA that will reduce antibiotic overprescribing by at least 15% [21]. The use of the CDSA for managing URTIs in patients living with HIV will reduce the high rates of unnecessary antibiotic prescriptions and the likelihood of antibiotic-ARV drug interactions [11,12].

Compared to other studies conducted in Mozambique, the rate of 65% is lower than the 97.6% reported by Monteiro et al. (2017) and 97.5% by Xavier et al. (2022) in pediatric patients and similar to 65.9% reported by Faiela & Sevene (2022) in HIV-infected patients [36,37,38]. These high rates reported in the country suggest excessive antibiotic use. Compared with regional studies, the rate is also higher compared to 37.7% reported in South Africa and 46.7% in Kenya [39,40]. Other regional studies also reported high rates, such as 84.9% in Tanzania, 80.6% in Nigeria, and 70.6% in Botswana [41,42,43].

Due to limited laboratory capacity and delays in reporting laboratory results (when available), clinicians reported relying on clinical diagnosis (i.e., signs and symptoms) alone to decide whether to treat URTI with antibiotics. In the context of limited laboratory capacity, a CDSA may support clinicians in decision-making regarding antibiotic prescription. The habit of prescribing based on experience and guesswork, using only signs and symptoms as observed in this study, may hinder the implementation, because clinicians may forget to use the CDSA and continue using the routine practice. To minimize this effect, a *champion* will be appointed at each study site to advocate for the intervention, oversee implementation, and conduct prescription audits with feedback.

The literature has shown that prescription audits and feedback enabled primary care clinicians to prescribe antibiotics appropriately and effectively reduced their antibiotic prescription rates [44,45,46]. Therefore, implementing our CDSA, integrating supervision of HCPs, conducting prescription audits, and providing feedback will allow us to monitor antibiotic prescribing during

implementation and contribute to the success of our intervention. In addition, we assume that introducing our CDSA will help clinicians make timely, rational decisions even when laboratory tests are unavailable or inaccessible.

The excessive use of antibiotics due to the lack of support tools contributes to the loss of their effectiveness against bacteria, threatening the emergence of bacterial mutations and resistance [47]. This problem calls for the health system to adopt strategies to de-implement unnecessary antibiotic use. Strategies may include CDSAs and on-site antibiotic stewardship initiatives [6,20]. Integrating antibiotic stewardship initiatives into a CDSA may minimize misdiagnosis in settings with limited laboratory capacity, ensure appropriate antibiotic use, and drive better outcomes, with significant reductions in antibiotic use [48]. The presence of a pharmacist who manages antibiotic use, and the strong relationships and intercommunication among clinicians, pharmacists, and laboratory technicians observed in this study, we believe, constitute opportunities for antibiotic stewardship initiatives.

Similarities and differences across sites in implementation readiness were reported indeed. Our findings highlight the need to conduct training before the intervention's launch to standardize implementation.

Our study had some limitations. As we aimed to explore general site contexts that could impact the implementation of our intervention, the study lacks focus on patients with HIV. Due to limited resources, the assessment was done in only six health facilities. Prescription data were collected retrospectively from copies kept in the pharmacy, which may have introduced information bias. We were unable to ascertain the type of infection being treated from prescription records stored at the pharmacy. However, we assume that these limitations did not significantly influence our results, as the study provides valuable insight into the contexts of health facilities that enable the successful implementation of the intervention.

Conclusions

A broader range of determinants may influence the implementation of our adapted CDSA. The lack of existing decision-support tools, the limitations in laboratory diagnostic support, and the routine prescribing practice are negative determinants that foster the introduction of our CDSA. On the other hand, HCP enthusiasm and willingness to use a new CDSA, and the effective interaction among HCPs are positive determinants that will enable the implementation of our intervention. For better results, the CDSA should be implemented alongside continued supportive supervision of HCPs and antibiotic prescription audits and feedback. HCPs should be trained before the intervention launch to standardize the implementation.

Abbreviations

AMR	Antimicrobial resistance
ARVs	Antiretrovirals
CBC	Complete blood count
CDSA	Clinical Decision Support algorithm
CI	Confidence interval
COVID-19	Coronavirus disease-19
CRP	C- reactive protein test

DAP	Dynamic adaptation process
HCP	Healthcare provider
HIV	Human immunodeficiency virus
IDI	In-depth interview
NMF	National Medicines Formulary
PLHIV	People living with HIV
REDCap	Research Electronic Data Capture
RTI	Respiratory tract infection
SD	Standard deviation
SPSS	Statistical Package for Social Sciences
TB	Tuberculosis
URTI	Upper respiratory tract infection
WHO	World Health Organization

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Authors contributions

All authors made substantial contributions to the study's concept and design. CF was involved in data collection and analysis and drafted the manuscript. ES supervised the data collection and analysis, commented on the entire manuscript, and critically revised it. TM and MS made substantial revisions. All authors read and approved the final version of the manuscript.

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Availability of data and materials

All data generated will be available from the corresponding authors upon reasonable request and will be deposited at the Faculty of Medicine, University Eduardo Mondlane data repository.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Mozambican National Bioethics Committee for Health (*Comité Nacional de Bioética para Saúde*, CNBS) on 14 August 2023 (register number 52/CNBS/2023). This study was conducted under the Declaration of Helsinki. Participants were enrolled in the study after providing informed consent. All participants were informed about the purpose of the study, participation was voluntary, and all responses were anonymous.

Consent for publication

Not applicable.

Competing interests

Not applicable

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Table 1. Characteristics of healthcare providers

Feature	Clinician n = 27	Pharmacist n = 6	Laboratory Technician n = 6	Total N = 39
Sex				
Female	21 (77.8%)	4 (66.7%)	4 (66.7%)	29 (74.4%)
Male	6 (22.2%)	2 (33.3%)	2 (33.3%)	10 (25.6%)
Age Mean ± SD				32 ± 4.5
18 – 35 years	21 (77.8%)	2 (33.3%)	5 (83.3%)	28 (71.8%)
36 – 45 years	5 (18.5%)	4 (66.7%)	1 (16.7%)	10 (25.6%)
46 – 60 years	1 (3.7%)	--	--	1 (2.6%)
Length of service				
≤ 2 years	9 (33.4%)	2 (33.3%)	4 (66.7%)	15 (38.5%)
3 – 10 years	13 (48.1%)	4 (66.7%)	1 (16.7%)	18 (46.1%)
11 – 20 years	4 (14.8%)	--	1 (16.7%)	5 (12.8%)
21 – 30 years	1 (3.7%)	--	--	1 (2.6%)
Job Category				
Clinical Assistant	1 (3.7%)	--	--	1 (2.6%)
Clinical Technician	22 (81.5%)	--	--	22 (56.4%)
General Physician	4 (14.8%)	--	--	4 (10.2%)
Pharmacist	--	1 (16.7%)	--	1 (2.6%)
Pharmacist Technician	--	5 (83.3%)	--	5 (12.8%)
Laboratory Technician	--	--	6 (100%)	6 (15.4%)
Facility Work Sector				
HIV care and treatment	20 (74.1%)	--	--	20 (51.3%)
General outpatient consultation	2 (7.4%)	--	--	2 (5.1%)
Triage Services	5 (18.5%)	--	--	5 (12.8%)
Pharmacy	--	6 (100%)	--	6 (15.4%)
Laboratory	--	--	6 (100%)	6 (15.4%)

Table 2. Quality prescription indicators

Prescription quality indicators	Total	WHO reference
WHO core quality indicators		
Average number of medicines per prescription	2.5	1.6 – 1.8
Antibiotic prescription rate	65%	20 – 26.8%
Prescriptions with an injectable antibiotic	--	13.4 – 24.1%
Prescriptions with medicines prescribed by generic name	99.3%	100%
Prescriptions with medicines listed in the National Medicines Formulary	100%	100%
Additional quality indicators		
Average number of antibiotics per prescription	1.0	--
Prescriptions with the documented patient's name	99.8%	--
Prescriptions with the documented prescriber's name	65.5%	--
Prescriptions with documentation of the date	100%	--
Prescriptions with documentation of the dosage	100%	--
Prescriptions with documentation of the duration of the treatment	100%	--

658 **Table 3**. Antibiotic prescribing patterns

Antibiotic name	Class	Spectrum of action	Prescription level	Summer n (%)	Winter n (%)	Total n (%)
Nalidixic acid	Quinolones	Narrow	2	2 (0.8)	2 (0.7)	4 (0.8)
Amoxicillin	Penicillin	Broad	1	101 (38.3)	62 (23.0)	163 (30.5)
Amoxicillin-clavulanic acid	Beta-lactamase inhibitor	Broad	3	2 (0.8)	1 (0.4)	3 (0.6)
Azithromycin	Macrolides	Broad	3	26 (9.8)	47 (17.4)	73 (13.7)
Benzathine-benzylpenicillin	Penicillin	Narrow	1	9 (3.4)	3 (1.1)	12 (2.2)
Cefixime	Third-generation-cephalosporins	Broad	3	1 (0.4)	1 (0.4)	2 (0.4)
Ciprofloxacin	Fluoroquinolones	Broad	3	31 (11.7)	36 (13.3)	67 (12.5)
Chloramphenicol	Amphenicols	Broad	2	2 (0.8)	0 (0)	2 (0.4)
Cotrimoxazole	Sulfonamide-trimethoprim combinations	Broad	1	17 (6.4)	21 (7.8)	38 (7.1)
Doxycycline	Tetracyclines	Broad	2	1 (0.4)	5 (1.8)	6 (1.1)
Erythromycin	Macrolides	Broad	2	9 (3.4)	13 (4.8)	22 (4.1)
Gentamicin	Aminoglycosides	Broad	3	6 (2.2)	0 (0)	6 (1.1)
Kanamycin	Aminoglycosides	Narrow	3	0 (0)	1 (0.4)	1 (0.2)
Metronidazole	Imidazoles	Broad	1	45 (17.0)	55 (20.4)	100 (18.7)
Phenoxymethylpenicillin	Penicillin	Narrow	1	11 (4.2)	21 (7.8)	32 (6.0)
Tetracycline	Tetracyclines	Broad	2	1 (0.4)	2 (0.7)	3 (0.6)
Total				264 (100)	270 (100)	534 (100)

Table 4. Results of the interview with healthcare providers

Category	Content	Yes n (%)	No n (%)	Turnaround time
Clinician perspective	Use of guidelines or algorithms for treating respiratory illness (n=27)	13 (48.1)	14 (51.9)	--
	Possession of a normative document (guideline or algorithm) for treating respiratory illness (n=27)	12 (44.4)	15 (55.6)	--
	Willingness to adhere to an intervention that would support clinical decisions in managing URTIs (n=27)	27 (100)	--	--
	Effective interaction between colleagues (n=27)	27 (100)	--	--
Pharmacist perspective	Effective interaction with clinicians (n = 6)	6 (100)	--	
Laboratory capacity from the perspective of laboratory technicians	HIV test (n=6)	6 (100)	--	--
	CD4 (n=6)	4 (67.3)	2 (33.3)	2-18 days
	Viral load (n=6)	--	6 (100)	8-28 days
	Blood count (n=6)	5 (83.3)	1 (16.7)	2-18 days
	C-reactive protein (n=6)	1 (16.7)	5 (83.3)	8-14 days
	Culture and antibiotic sensitivity test (n=6)	--	6 (100)	21-60 days
	Gram stain test (n=6)	1 (16.7)	5 (83.3)	7 days
	X-ray (n=6)	1 (16.7)	5 (83.3)	3-7 days

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Effectiveness of a clinical decision support algorithm (CDSA) on reducing unnecessary antibiotic prescriptions for upper respiratory tract infections among ambulatory HIV-infected adults in Mozambique: a cluster randomized controlled trial

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Abstract

Background: Antibiotics are widely overprescribed to treat upper respiratory tract infections (URTIs), even though viruses cause most URTIs. We evaluated the effectiveness of a clinical decision support algorithm (CDSA)- based intervention in reducing antibiotic prescriptions among ambulatory HIV-infected adult patients with acute URTI symptoms.

Methods: Between June and September 2024, we conducted a multicenter, two-arm parallel, cluster-randomized controlled trial in six primary healthcare facilities in Mozambique. The intervention included applying the CDSA, educating and supervising clinicians, and conducting prescription audits. We used Pearson's chi-square test and relative risk to assess the effectiveness of the intervention in reducing antibiotic prescribing.

Results: Three hundred seventy-nine (97.9%) HIV-infected adult patients with URTI symptoms were recruited, 182 (48%) in the intervention arm and 197 (52%) in the control. Most were females (75.5%) and single (57%). Most appeared with common cold and flu-like symptoms. Participants in the intervention arm were less likely to receive an antibiotic prescription (RR 0.41, 95% CI: 0.31 - 0.55) and develop a complication (RR 0.44, 95% CI: 0.16 - 1.20) than those not exposed. The antibiotic prescribing rate was 23.1% for the intervention and 56.3% for the control. The intervention was associated with a significant reduction in antibiotic prescribing by 33.2% ($p < 0.001$) and a non-significant decrease in incidence of complications by 3.7% ($p = 0.096$). In both arms, most patients (78%) recovered completely within five days. Amoxicillin (47.8%), azithromycin (21.9%), and phenoxymethylpenicillin (14.1%) were the most prescribed antibiotics.

Conclusions: Our CDSA, coupled with education and audits with feedback, effectively reduced antibiotic usage. Furthermore, withholding antibiotics for URTIs did not increase the incidence

of complications. The intervention worked in our six sites, but larger studies must be performed with our CDSA across Mozambique to see if these findings also hold up elsewhere.

Trial registration: ISRCTN, ISRCTN88272350. Registered 16 May 2024, https://www.isrctn.com/ISRCTN88272350

Keywords: Antibiotics, Clinical decision support algorithm, Implementation Science, Upper respiratory tract infections, HIV, Mozambique

Background

Despite extensive research over the years, the overuse and inappropriate prescribing of antibiotics for upper respiratory tract infections (URTIs) remains widespread [1]. Approximately 90% of URTIs are viral in origin, self-limiting, and typically resolve without complications, making antibiotic treatment unnecessary and not recommended [2,3]. Prescribing antibiotics in such cases is considered both wasteful and unwarranted [4]. Moreover, the misuse of antibiotics for URTIs can contribute to the development and spread of antibiotic-resistant organisms, ultimately making future infections more difficult to treat [5].

Opportunistic infections are the primary reason for prescribing antibiotics in adult HIV-infected patients, who require lifelong antiretroviral therapy (ART). Avoiding unnecessary antibiotic use in these patients can help minimize the risk of drug interactions and ultimately, adverse events [6, 7]. Furthermore, immunocompromised patients are at higher risk of adverse outcomes from unnecessary antibiotic use, including *Clostridioides difficile* infection [8].

Many studies have evaluated the use of clinical decision support algorithms (CDSA) to reduce antibiotic prescribing for URTIs in the context of primary care, with mixed results. Using a cluster randomized controlled trial design, two studies tried to evaluate the implementation of a particular CDSA in reducing or improving antibiotic prescribing for URTIs, but found no significant differences between the intervention and control arms [1,9]. Others, using a pre- and post-intervention and a randomized controlled trial design, tried to do the same (i.e., evaluating the implementation of a CDSA in decreasing or improving antibiotic prescribing), but found a significant difference favoring the intervention. May et al. (2021) reported a 12.6% decrease in inappropriate antibiotic prescriptions from the pre- to post-intervention period, while Rambaud-Athaus et al. (2017) found a drop in the antibiotic prescription rate from 70% in the control to 26% and 25%, respectively, for a CDSA in paper format or electronic format [10,11].

In Mozambique, the management of URTIs among HIV-infected patients in primary healthcare settings is predominantly empirical and often ends up with a prescription of antibiotics. In our previous work examining the types of prescriptions given to HIV-infected patients seen in an outpatient setting, roughly two-thirds (65.9%) of the patients received a prescription for antibiotics, most of them for respiratory tract infections [12]. Recommendations that came out of this work included developing strategies to promote the reduction of unnecessary antibiotic use in this population. Furthermore, these results informed the development of a larger multi-phase implementation science study protocol aimed at determining the effectiveness of a CDSA-based intervention in reducing unnecessary antibiotic prescriptions for URTIs among ambulatory HIV-infected adults. In this trial, we hypothesized that the CDSA, when introduced into routine outpatient care, would effectively reduce unnecessary antibiotic prescriptions by at least 15% [13].

Methods

This analysis represents phase two data collection of our larger multi-phase implementation science study. Our study protocol has been published elsewhere [13]. The trial was registered on isrctn.com (ISRCTN88272350), a publicly accessible clinical trial registry recognized by the World

Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE). The study adheres to CONSORT 2025 guidelines.

Study design

We conducted a multicenter two-arm parallel cluster randomized control trial design in which our primary outcome measure was the clinical decision to use antibiotics or not. Intervention elements included health worker education and supervision, prescription audit and feedback, organizational adjustments, and the introduction of a CDSA for decision-making around antibiotic use among ambulatory HIV-infected patients presenting with a URTI. The study tools were adapted before the intervention was implemented. An implementation audit and continuous feedback were performed to guarantee and monitor adherence to the intervention protocol.

Study setting

This study was conducted within outpatient primary healthcare facilities in Maputo and Matola cities in Mozambique. Maputo is the nation's capital, and Matola is the capital of Maputo Province, located around 20 km outside Maputo city. These primary healthcare facilities offer outpatient care for all ages, including HIV care and treatment clinics, family planning, maternal and child health services, youth and adolescent care, health counseling and screening, and an immunization program. All primary healthcare facilities within the study area were eligible for inclusion and considered for randomization. Six of the thirty-one eligible facilities in the catchment area were randomly selected for this study - four from Maputo and two from Matola.

Randomization

Randomization and allocation were conducted at the level of 10 administrative units, referred to as primary clusters - municipal districts in Maputo and administrative posts in Matola. A random sequence was generated through the computer to assign six of these primary clusters equally to either the intervention or control arms (three each). Within each selected primary cluster, one primary healthcare facility (secondary cluster) was then randomly chosen to participate in the study. All participants within a given facility received the same group assignment. Due to resource constraints, only six primary clusters were included, and to prevent contamination between facilities, only one health facility was selected per cluster. The allocation sequence was generated by a statistician, who also assigned the selected facilities to either the intervention or control arm.

Intervention and control

Eligible participants were adult HIV-infected individuals who presented to the outpatient clinics with symptoms of an acute URTI, such as nasal discharge or congestion, sore throat, cough, sneezing, chills, or disturbances in smell and taste, with or without fever. Patients were excluded if they exhibited symptoms of lower respiratory tract infection (i.e., severe cough, chest pain, tightness, or difficulty breathing), had a fever of ≥39ºC, severe mental illness (i.e., self-harm, suicidal thoughts, hallucinations, delusions, or disorganized thinking), or advanced HIV disease, or had self-medicated with any medicine.

Eligible patients allocated to the intervention arm were managed using the CDSA **(Supplementary File 1)**. Per the CDSA, patients were not to receive antibiotics if their URTI symptoms lasted less than 10 days, unless there was an additional symptom suggesting a suspicion of bacterial infection. Bacterial infection was suspected in the following situations: (i) higher-grade fever than usually observed with the common cold, with the presence of yellow or greenish nasal discharge, pain or difficulty swallowing, or an intense sore throat; (ii) URTI symptoms lasting longer than 10 days; (iii) URTI symptoms continuing to get worse rather than improve over several days (5 days after the first visit). For recording body temperatures at the intervention sites, we distributed at least one infrared thermometer that could be used by all participants in a designated room.

Twice per month, the study coordinator at each intervention site would review all antibiotic prescriptions provided to participants in the prior two weeks. Clinicians were provided feedback on the use of the CDSA in all cases where the CDSA was not followed and where no clinically appropriate justification was provided.

In the control sites, clinicians were instructed to continue managing patients according to their usual practices. Twice per month, antibiotic prescribing data from these clinicians were recorded, but no feedback was shared with them during the study period.

For both arms, patients were enrolled in the study at the time they presented to the clinic with URTI symptoms (t0 = day 0). They were then subsequently monitored through a phone call at three different time points after the initial medical visit to ascertain improvement of symptoms (t1 = day 5, t2 = day 10, and t3 = day 15). Participants were instructed that they could visit the healthcare facility for a follow-up clinical examination in person, at any time, if necessary.

Data collection and measures

We used a structured questionnaire to collect patient-related sociodemographic and clinical information. We also utilized a case record notebook where additional information had been registered. The on-site coordinator was responsible for collecting data in synchrony with the clinicians. Twice per month, data quality checks were performed by the study PI for completeness, accuracy, consistency, validity, and uniqueness.

The effectiveness of the CDSA was analyzed by comparing antibiotic prescribing rates, incidence of complications, and mean time for complete recovery between the intervention and control arms. Our primary outcome was the antibiotic prescribing rate. Secondary outcomes consisted of the incidence of complications and the time for complete recovery from the first medical visit were the secondary outcomes. Complications were defined as worsening of symptoms that were deemed to result from not receiving antibiotics, such as sinusitis, pharyngotonsillitis, pneumonia, bronchitis, and asthma. These were documented for the first time at one of the follow-up visits. The antibiotic prescribing rate was calculated as the number of patients who received at least one antibiotic prescription on Day 0, among all participants enrolled. Antibiotics were classified according to the spectrum of action, prescription level according to the national medicine formulary (level 1, can be prescribed by a clinical agent/nurse; level 2, prescribed by a clinical technician; level 3, prescribed by a general practitioner; and level 4, prescribed by a medical specialist), and WHO AWaRe 2023 classification. We included the AWaRe classification to check for a prescribing trend of antibiotics with a safety profile regarding adverse effects and the potential risk of resistance development. According to the AWaRe classification, antibiotics are classified as Access, Watch, and Reserve, taking into account the impact of different antibiotics on antimicrobial resistance [14]. The incidence of complications was measured as the proportion of complications among patients who were recruited and completed at least one follow-up visit. The mean time to complete recovery was calculated as the average time the patients took to recover completely from their symptoms.

Data management, statistical analysis, and power calculation

Data collection forms and other patient registries were created in both paper and electronic format in REDCap (Research Electronic Data Capture) [15]. Study clinicians filled out the data collection forms during the initial visit, while the on-site study coordinator completed the forms during follow-up visits. These were then submitted to the study PI, who input data from the forms into the REDCap system. Data were then exported to SPSS (Statistical Package for Social Sciences) version 25 for statistical analysis [15,16].

Descriptive and analytical statistics were used to analyze the data. Descriptive analysis involved constructing tables of absolute and relative frequencies. Analytical statistic was used for bivariate

analysis. Pearson's chi-square test was employed to compare outcomes between intervention and control sites, using a 5% significance level. The same test was used to assess baseline comparability between the two arms and to evaluate differences in recovery time rates. To quantify the intervention's impact, relative risk (RR) was calculated, along with the effectiveness ratio (1 – RR), and 95% confidence intervals were reported for RR.

Sample sizes were selected based on power calculations to detect a minimum difference of 15% in antibiotic prescribing rates between the two arms, with 80% power and type I error set at 5%. Thus, our calculations resulted in a sample size of 345 participants to be assigned to either the intervention or control arms in a 1-to-1 ratio (i.e., 50% for the intervention and 50% for the control). Allowing for an attrition rate of 10%, we aimed to recruit a total of 380 (190 for each arm) HIV-infected patients with URTIs to account for refusals, loss to follow-up, or loss of patient information.

Results

Participants

Among 387 patients approached, 379 (97.9%) were successfully recruited into the study. Two patients (0.5%) were excluded from enrollment due to their refusal to provide consent, and 6 (1.6%) were excluded as they were subsequently determined to have a lower respiratory tract infection. Of the patients recruited, 182 (48%) were allocated to the intervention arm and 197 (52%) to the control arm. Of these, 174 (95.6%) patients in the intervention arm and 197 (100%) patients in the control arm participated in at least one follow-up visit **(Figure 1).**

Figure 1. Study flow diagram: enrollment, intervention, and assessments

A total of 34 clinicians, including clinical technicians (n=30, 88.2%), nurses (n=3, 8.8%), and general practitioners (n=1, 3%), provided care to a total of 379 HIV-infected patients with URTI symptoms. The majority of clinicians were females (82.4%) and young (79.4%), with 10 years or less of work experience (73.5%). Regarding clinician characteristics (sex, p=0.162; age, p=0.192; category, p=0.760; work experience, p=0.677), no statistically significant differences were observed between the intervention and control arms **(Table 1)**.

The study participants (i.e., patients) were adults aged 18 years or older, with a mean age of 44 years (SD = 12.3), and a majority were female (75.5%). Over half of the participants (57%) were single and had a secondary level of education or higher (59.9%) **(Table 1)**. The majority of participants presented to clinic with common cold and flu-like symptoms, with no fever (84.4%) or only a low-grade fever (13%), a cough lasting less than 10 days (74.9%), headache (60.2%), rhinorrhea (59.6%), nasal congestion lasting less than 10 days (53.8%), and sore throat (49.1%). Of our enrolled participants, roughly two-thirds (65.8%) were enrolled at clinics in the city of Maputo.

When comparing characteristics of the study participants in the intervention arm versus the control arm, we found no major differences except for a statistically significantly higher proportion of control participants with a secondary education or higher (66.9% vs. 52.5%, p<0.001). Additionally, a higher proportion of participants in the control arm presented with a low-grade fever (29.7% vs 6.6%) or a high-grade fever (4.7% vs. 1.8%) (p<0.001) as compared to those in the intervention arm. As part of the study, each intervention site received at least one thermometer for use during the study. As such, a much larger proportion of participants in the intervention arm had their body temperature recorded than in the control arm (91.7% vs. 32.4%).

Table 1. Sociodemographic and clinical characteristics of the study participants

Antibiotic prescribing rates

Overall, 40.4% of ambulatory HIV-infected patients presenting with a URTI were prescribed an antibiotic. When comparing study arms, antibiotic prescribing was higher in the control group (56.3%) compared to the intervention group (23.1%), representing a 33.2% reduction in antibiotic prescribing ($p < 0.001$) **(Figure 2)**. Patients managed with the CDSA (intervention arm) had a 59% lower likelihood of antibiotic prescription compared to the control group (RR = 0.41; 95% CI: 0.31–0.55).

Figure 2. Comparison of antibiotic prescribing rates between intervention and control arms.

Antibiotic prescribing pattern

In a review of medications prescribed throughout the study, we found that nine types of antibiotics were among those most prescribed, of which eight were broad-spectrum. Amoxicillin (47.8%), azithromycin (21.9%), and phenoxymethylpenicillin (14.1%) were the most prescribed. Six of the nine antibiotics are classified as "*access*" antibiotics and three as "*watch*" antibiotics according to the AWaRe classification. Among the most prescribed antibiotics, amoxicillin and phenoxymethylpenicillin are classified as "*access*" and azithromycin as "*watch*" **(Table 3)**. Regarding the prescription level according to the national medicine formulary, four were level 1 antibiotics, two were level 2, and three were level 3.

Table 3. Antibiotic prescribing pattern

Incidence of complications

We attempted to follow participants in both arms for 15 days following their initial clinic visit, with reassessments scheduled for days 5, 10, and 15 to assess for any complications **(Figure 3).** When comparing study arms, the rate of complications was higher in the control group (6.6%) compared to the intervention group (2.9%), representing a 3.7% reduction in complications seen ($p = 0.096$) **(Figure 3)**. Patients managed with the CDSA (intervention arm) had a 56% lower likelihood of developing a complication as compared to the control group (RR = 0.44; 95% CI: 0.16–1.20), though this was not statistically significant. The most frequently observed complications were pneumonia (intervention arm 80% vs. control arm 23%) and pharyngotonsillitis (control arm only 46.2%).

Figure 3. Comparison of the incidence of complications between the intervention and control arms

Time to complete recovery from the first medical visit

Table 4 shows the cumulative data stratified by study group and over 20 days. Complete recovery was seen in most participants (78%) within five days of their initial visit, regardless of study arm, with a mean time to complete recovery of 6.3 days (SD = 2.7)**.** No significant differences ($p = 0.378$) were observed between the intervention and control arms regarding time to recovery within five days. **Figure 4** shows the cumulative probability of patients recovering by study arm. The control arm seems to recover slightly faster than the intervention group. Still, this difference is not clinically significant, as regardless of the study arms, all participants fully recovered in about 2 weeks of symptom onset or treatment.

Table 4. Time to complete recovery per group of participants

Figure 4. Cumulative probability of patients recovering stratified by control and intervention arms

Discussion

This trial demonstrated the effectiveness of a CDSA-based intervention in reducing antibiotic prescribing for URTIs among HIV-infected adults in the primary healthcare settings. Clinician use

of the CDSA tool - coupled with targeted education, prescription audits, and feedback - was associated with a 33.2% reduction in antibiotic use compared to the control arm. This reduction was more than double the anticipated effect size of 15% specified in our implementation protocol [13].

Participants in the intervention arm were significantly less likely to receive an antibiotic prescription than those in the control arm (RR = 0.41; 95% CI: 0.31–0.55). This reduction is attributed to clinicians' commitment to de-implementing unnecessary antibiotic prescribing practices. Notably, the antibiotic prescribing rate in the intervention arm (23.1%) fell within the WHO-recommended reference range of 20 – 26.8%, underscoring the value of using the CDSA to guide rational antibiotic use within this population [17,18]. Conversely, the control arm had a higher antibiotic prescribing rate (56.3%), exceeding WHO recommendations. Our findings align with a study from Tanzania that reported a 26% antibiotic use rate in the CDSA group versus a 70% rate in the control group [11].

Overall, the combined antibiotic prescribing rate in our study (40.4%) was lower than rates reported in other studies in Mozambique—97.6% by Monteiro et al. (2017); 97.5% by Xavier et al. (2022) among pediatric patients; and 65.9% by Faiela & Sevene (2022) among HIV-infected adults. It was also lower than rates reported in neighboring countries—84.9% in Tanzania and 70.6% in Botswana [12,19,20,21,22]. However, our findings are consistent with reports from South Africa (37.7%) and Kenya (46.7%) [23,24]. The reduced rate observed in this study is attributed to the CDSA, which helped clinicians manage URTIs with a rational clinical decision, including de-implementing unnecessary antibiotics and only prescribing them if a bacterial infection was suspected. In addition to the CDSA, we feel the presence of an on-site coordinator who monitored and supervised the study's implementation process, reminding clinicians (in the intervention arm) to adhere to the CDSA and conducting prescription audits with feedback to the clinicians, contributed to this reduction.

When antibiotics were prescribed, amoxicillin (48%) and phenoxymethylpenicillin (14%) were the most commonly used, consistent with first-line recommendations for bacterial URTIs like tonsillitis and pharyngitis [25,26]. However, the use of azithromycin (22%) was unexpectedly high, given that it is typically reserved for patients with penicillin allergies. This trend is concerning due to its higher cost and the potential for fostering antimicrobial resistance. Although azithromycin was widely used during the COVID-19 pandemic, there is no evidence to support its use for viral URTIs [27].

Despite established guidelines advising against routine antibiotic use for URTIs, some clinicians prescribe them to prevent complications [28]. However, our findings showed no increased risk of complications in the intervention arm. There was a non-significant 3.7% reduction in complication rates (p = 0.096) compared to the control arm. Pneumonia (38.9%) and pharyngotonsillitis (33.3%) were the most common complications.

Patient recovery within five days was slightly higher in the control arm, where over half received antibiotics. However, more than three-quarters of patients in the intervention arm also recovered within five days, despite lower antibiotic use, highlighting one measure of the intervention's effectiveness. Since bacterial URTIs may take several days to resolve, many patients in the control group likely received unnecessary antibiotics [29,30].

Most patients presented with mild symptoms, such as the common cold and flu-like illness. Empiric antibiotic therapy should be reserved for patients with suspected bacterial infection (i.e., high-grade fever, purulent nasal discharge, difficulty swallowing, or persistent worsening symptoms), particularly when the risk of complications is high [13,31]. Broader implementation of

this CDSA-based intervention may further reduce unnecessary antibiotic use, helping mitigate stockouts, reduce treatment costs, and slow the development of antimicrobial resistance [32].

This study has some limitations. The study area (Maputo and Matola cities) was chosen by convenience sampling, which limits generalizability across the whole country. However, the study sites were selected by random sampling. The study was conducted in a primary healthcare setting where access to accurate diagnosis was limited because of a lack of laboratory support. Contamination between study arms may have occurred due to earlier engagement during the pre-implementation and adaptation phases. Recruitment rates differed slightly between the two arms but did not affect the overall interpretation of results.

Conclusion

Our CDSA, coupled with education and audits with feedback, effectively reduced antibiotic usage. Furthermore, when decisions were made to withhold antibiotics for URTI, this approach did not increase the incidence of new symptoms or complications. In our six study sites, the intervention worked, but larger studies need to be performed with this CDSA across Mozambique to see if these results also hold up elsewhere. Thus, advocacy should be maintained with the Ministry of Health to implement this CDSA-based intervention in larger sites through an implementation science approach using frameworks that can measure effectiveness outcomes.

Abbreviations

ARV	Antiretroviral
AWaRe	Access, watch, and reserve the WHO antibiotic classification system
CDSA	Clinical decision support algorithm
CI	Confidence interval
HIV	Human immunodeficiency virus
PI	Principal investigator
RCT	Randomized controlled trial
REDCap	Research electronic data capture
RR	Relative risk
SD	Standard deviation
SPSS	Statistical package for social sciences
URTI	Upper respiratory tract infection
WHO	World Health Organization

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Authors contributions

All authors made substantial contributions to the study's concept and design. CF monitored and audited the implementation process, data collection, and analysis, and drafted the manuscript. ES supervised the data collection and analysis, commented on the entire manuscript, and critically revised it. TDM and MS made substantial revisions to the entire manuscript. GA made substantial revisions to the data analysis and results. All authors read and approved the final version of the manuscript.

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Availability of data and materials

Data not publicly available. All generated data will be available from the corresponding authors upon reasonable request and are deposited at the Faculty of Medicine, University Eduardo Mondlane data repository with limited access.

Declarations

Ethics approval and consent to participate

The Mozambican National Bioethics Committee for Health (Comité Nacional de Bioética para Saúde, CNBS) approved the study protocol on 14 August 2023 (register number 52/CNBS/2023). Participants were enrolled in the study after providing informed consent. The study was conducted following the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

Not applicable

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Table 1. Sociodemographic and clinical characteristics of the study participants

Characteristic	Intervention	Control	Total	p-value
Patient Sex (n=379)				0.875
Male	44 (24.2%)	49 (24.9%)	93 (24.5%)	
Female	138 (75.8%)	148 (75.1%)	286 (75.5%)	
Patient Age (n=379)				0.051
18-35 years	35 (19.2%)	60 (30.5%)	95 (25.1%)	
36-45 years	65 (35.7%)	51 (25.9%)	116 (30.6%)	
46-59 years	62 (34.1%)	65 (32.9%)	127 (33.5%)	
≥60 years	20 (11.0%)	21 (10.7%)	41 (10.8%)	
Patient Marital Status (379)				0.276
Married	67 (36.8%)	70 (35.5%)	137 (36.6%)	
Divorced	6 (3.3%)	4 (2.0%)	10 (2.7%)	
Single	106 (58.2%)	113 (57.4%)	219 (57.0%)	
Widower	3 (1.6%)	10 (5.1%)	13 (3.7%)	
Level of Education (n=361)				<0.001
Illiterate	6 (3.4%)	14 (7.6%)	20 (5.5%)	
Primary	78 (44.1%)	47 (25.5%)	125 (34.6%)	
Secondary/technical	88 (49.7%)	105 (57.1%)	193 (53.5%)	
Higher	5 (2.8%)	18 (9.8%)	23 (6.4%)	
Fever (n=231)				<0.001
Low grade	11 (6.6%)	19 (29.7%)	30 (13%)	
High grade	3 (1.8%)	3 (4.7%)	6 (2.6%)	
No fever	153 (91.6%)	42 (65.6%)	195 (84.4%)	
Clinical signs/symptoms (n=379)				
Rhinorrhea	113 (62.1%)	113 (57.4%)	226 (59.6%)	0.349
Sore throat	80 (44%)	106 (53.8%)	186 (49.1%)	0.055
Cough < 10 days	139 (76.4%)	145 (73.6%)	284 (74.9%)	0.534
Cough > 10 days	11 (6%)	12 (6.1%)	23 (6.1%)	0.985
Nasal congestion < 10 days	89 (48.9%)	115 (58.4%)	204 (53.8%)	0.065
Nasal congestion > 10 days	5 (2.7%)	5 (2.5%)	10 (2.6%)	0.899
Chills	66 (36.3%)	67 (34%)	133 (35.1%)	0.646
Runny nose	61 (33.5%)	45 (22.8%)	106 (28%)	0.021
Headache	114 (62.6%)	112 (56.9%)	226 (59.6%)	0.251
Place of Study (n=379)				0.516
Maputo	119 (65.4%)	135 (68.5%)	254 (67%)	
Matola	63 (34.6%)	62 (31.5%)	125 (33%)	
Clinician Sex				0.162
Male	4 (28.6%)	2 (10%)	6 (17.6%)	
Female	10 (71.4%)	18 (90%)	28 (82.4%)	
Clinician Age Range				0.192
18 – 35 years	10 (71.4%)	17 (85%)	27 (79.4%)	
36 – 45 years	4 (28.6%)	1 (5%)	5 (14.7%)	
46 – 59 years	---	2 (10%)	2 (5.9%)	
Clinician Category				0.760
Nurse	---	3 (15%)	3 (8.8%)	
Clinical technician	13 (92.9%)	17 (85%)	30 (88.2%)	
General practitioner	1 (7.1%)	---	1 (3%)	
Clinician Years of Experience				0.677
≤ 10 years	10 (71.4%)	15 (75%)	25 (73.5%)	
11 – 20 years	4 (28.6%)	3 (15%)	7 (20.6%)	
≥ 21 years	---	2 (10%)	2 (5.9%)	

Table 3. Antibiotic prescribing patterns

Antibiotic name	Class	Spectrum of action	Prescription level*	AwaRe 2023	Day 0 (recruitment visit)	Day 5 (1st follow-up visit)	Day 10 (2nd follow-up visit)	Day15 (3rd follow-up visit)	Total
Amoxicillin	Penicillin	Broad	1	Access	88 (51.5%)	9 (32.1%)	1 (25.0%)	----	98 (47.8%)
Amoxicillin-clavulanic acid	Beta-lactamase inhibitor	Broad	3	Access	3 (1.8%)	3 (10.7%)	1 (25.0%)	----	7 (3.4%)
Azithromycin	Macrolides	Broad	3	Watch	39 (22.8%)	4 (14.3%)	1 (25.0%)	1 (50.0%)	45 (21.9%)
Cefixime	Third-generation-cephalosporins	Broad	3	Watch	4 (2.3%)	2 (7.1%)	----	----	6 (2.9%)
Chloramphenicol	Amphenicols	Broad	2	Access	----	----	----	1 (50.0%)	1 (0.5%)
Cotrimoxazole	Sulfonamide	Broad	1	Access	10 (5.8%)	4 (14.3%)	---	----	14 (6.8%)
Erythromycin	Macrolides	Broad	2	Watch	2 (1.2%)	----	----	----	2 (1.0%)
Metronidazole	Imidazole	Broad	1	Access	2 (1.2%)	1 (3.6%)	----	----	3 (1.5%)
Phenoxymethylpenicillin	Penicillin	Narrow	1	Access	23 (13.4%)	5 (17.9%)	1 (25.0%)	----	29 (14.1%)

* Prescription level according to Mozambique National Medicines Formulary 2007

Table 4. Time to complete recovery between the two treatment arms.

Time to recovery	Intervention	Control	Total	*p-value*
	N (%) *	N (%) *	N (%) *	
Day 5	134 (77%)	158 (80%)	291 (78%)	0.378
Day 10	162 (93%)	195 (99%)	357 (96%)	**0.010**
Day 15	172 (99%)	197 (100%)	369 (99%)	0.488
Day 20	174 (100%)	197 (100%)	371 (100%)	---
Mean ± SD	6.5 ± 3.2	6.0 ± 2.2	6.3 ± 2.7	

* Accumulated frequency

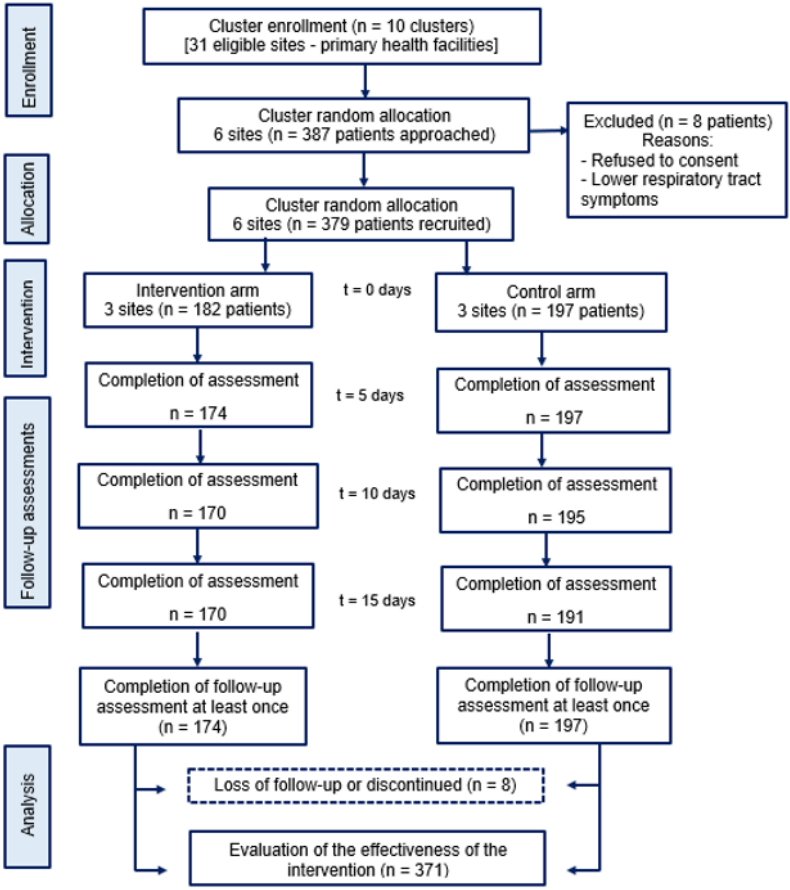


Figure 1. **Study flow diagram: enrollment, intervention, and assessments**

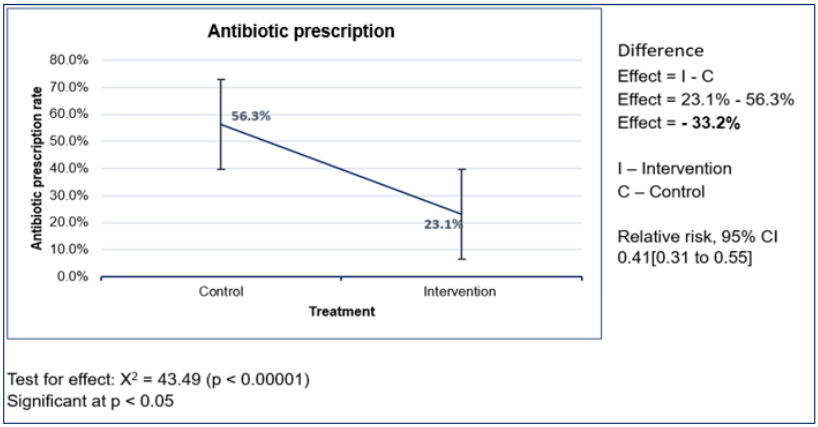
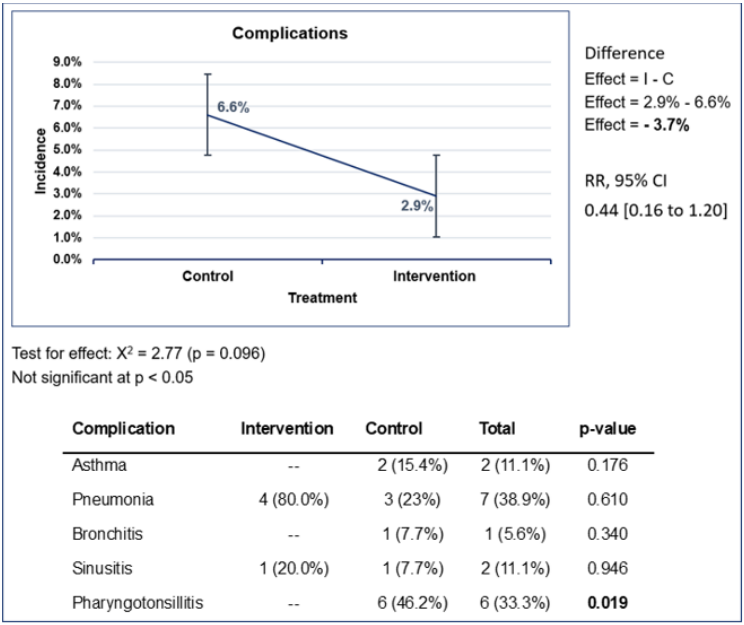


Figure 2. Comparison of antibiotic prescribing rates between intervention and control arms on the day of recruitment (Day 0). A reduced frequency is observed in the intervention arm. Pearson's chi-square test was used to test the significance of the reduction ($p < 0.001$). RR was less than 1, meaning that the intervention had a protective effect.



Complication	Intervention	Control	Total	p-value
Asthma	--	2 (15.4%)	2 (11.1%)	0.176
Pneumonia	4 (80.0%)	3 (23%)	7 (38.9%)	0.610
Bronchitis	--	1 (7.7%)	1 (5.6%)	0.340
Sinusitis	1 (20.0%)	1 (7.7%)	2 (11.1%)	0.946
Pharyngotonsillitis	--	6 (46.2%)	6 (33.3%)	**0.019**

Figure 3. Comparison of the incidence of complications between intervention and control arms. A reduced incidence of complications is observed in the intervention arm. Pearson's chi-square test was used to test the significance of the reduction ($p = 0.096$). Although the reduction was insignificant, the RR was less than 1, meaning that the intervention reduced the risk of developing a complication.

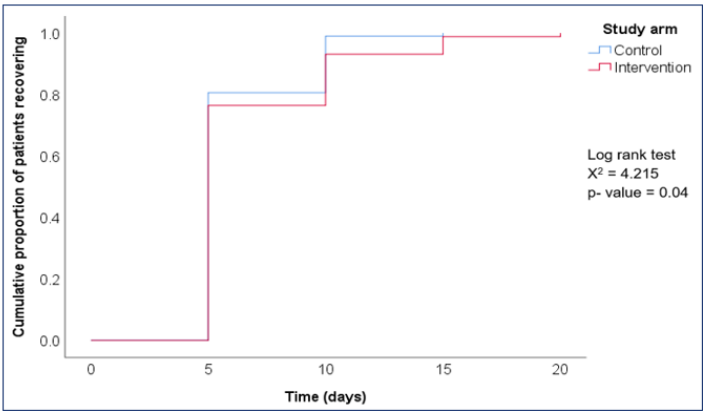
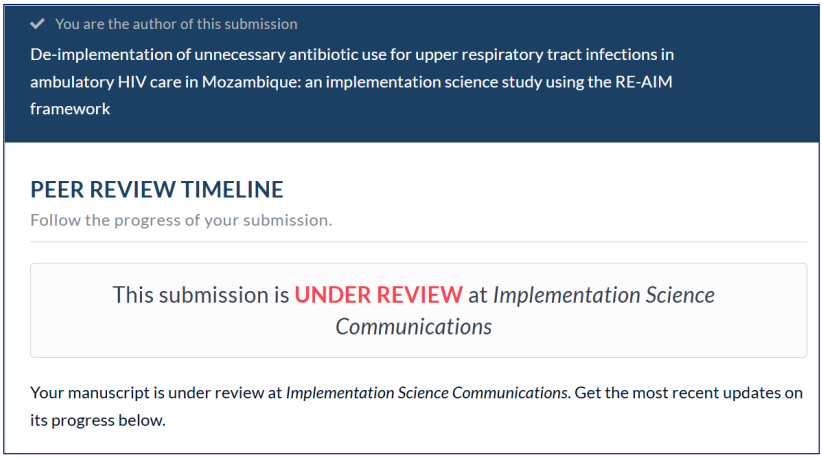


Figure 4. **Cumulative probability of patients recovering stratified by control and intervention arms**. Irrespective of study arms, all participants are fully recovered in about 2 weeks of symptom onset. Log-rank test was used to test for equality of recovery distributions between the two curves (i.e., intervention and control). Statistically significant differences were observed around days 10 and 15 of follow-up visits, favoring control, but with no clinical significance.

Paper V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De-implementation of unnecessary antibiotic use for upper respiratory tract infections in ambulatory HIV care in Mozambique: an implementation science study using the RE-AIM framework

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Abstract

Background: Antibiotics are commonly overused to treat upper respiratory tract infections (URTIs) in HIV-infected adults in primary healthcare settings, even though viruses cause most URTIs. Therefore, a de-implementation of unnecessary antibiotic prescribing for URTIs was implemented in these settings. Thus, in this study, we evaluated a strategy to de-implement unnecessary antibiotic prescriptions among ambulatory HIV-infected adults with acute URTI symptoms using the reach-effectiveness-adoption-implementation-maintenance (RE-AIM) framework.

Methods: We conducted a three-phase, hybrid type II effectiveness-implementation study utilizing a two-arm, parallel cluster-randomized controlled trial design involving HIV-infected adults recruited from six primary healthcare facilities in Mozambique. Quantitative data were collected from June to September 2024, whereas qualitative data were collected between October and December 2024. The intervention included a clinical decision support algorithm (CDSA), training and supervision of clinicians, and prescription audits. The intervention was evaluated based on the assessment of four dimensions of the RE-AIM framework: *reach*, *effectiveness*, *adoption*, and

implementation. We used Pearson's chi-square test and relative risk to assess the effect of the intervention.

Results: *Reach*: Among 387 HIV-infected adults approached, 379 (97.9%) were successfully recruited, with 182 (48%) in the intervention and 197 (52%) in the control group. Among the recruited patients, the mean age was 44±12.3 years, and 286 (75.5%) were female. *Effectiveness*: The intervention resulted in 33.2% fewer antibiotics prescribed compared to controls. The antibiotic prescribing rate was 23.1% for the intervention and 56.3% for the control group. *Adoption*: All three intervention sites (100%) and all clinicians (100%) demonstrated a commitment to de-implementing antibiotics. *Implementation*: The implementation protocol was delivered as planned. Almost all participants (n=21) in focus group discussions (FGD) were either satisfied or very satisfied with the intervention. They reported the effectiveness of the CDSA and the change in attitudes and antibiotic prescribing practices.

Conclusions: Based on the RE-AIM evaluation, the implementation of the planned intervention was successful as it effectively promoted de-implementation and reduced unnecessary antibiotics for URTIs. The strategy employed in this study can be applied in other settings, particularly in the current context of the growing burden of antibiotic resistance as a global problem.

Trial registration ISRCTN, ISRCTN88272350. Registered 16 May 2024, https://www.isrctn.com/ISRCTN88272350

Keywords: Antibiotics, De-implementation, Clinical decision support algorithm, Upper respiratory tract infections, HIV, Mozambique

Contributions to literature

- The change in attitudes and practices of inappropriate antibiotic prescription is possible through a well-developed and implemented strategy.
- Findings from this study highlight the potential effect of our strategy to reduce unnecessary antibiotic use for URTIs that could broadly be used to combat antimicrobial resistance.
- The study employs an innovative methodological approach that enables the evaluation of implementation outcomes while effectiveness is being established.

Background

Antibiotics are commonly overprescribed to treat upper respiratory tract infections (URTIs) among adult patients in primary care settings (1). Over 80% of all URTIs are of viral etiology, self-limiting, and generally resolve without further complications; therefore, prescribing antibiotics may not be required (2,3). Despite this, over two-thirds of patients with URTI end up being prescribed antibiotics (4,5). Excessive or inadequate antibiotic prescribing for URTIs is considered an unnecessary practice, with a waste of often valuable resources (6). Also, the use of unnecessary antibiotics contributes to antibiotic resistance, making future infections harder and more expensive to treat (7). This can also disrupt the gut microbiome and increase the risk of secondary infections, such as *C. difficile* (8).

Several strategies to reduce antibiotic use have been tested in different contexts (9,10,11,12). Clinical decision support algorithms (CDSA) were among these effective approaches to promote

the reduction of antibiotic use, mainly when combined with education of healthcare providers and prescription audits (9,11). The CDSAs for managing respiratory tract infections have shown significant implementation effectiveness (9). Many of these tools have been integrated into electronic prescribing platforms and are associated with reduced inappropriate antibiotic prescribing (9,13). Low-income countries (LICs) have been facing challenges in integrating electronic prescribing. However, in Tanzania, the CDSA was used in printed (26%) or electronic (25%) forms, with a significant reduction in antibiotic use compared to the control (70%) arm (13).

In Mozambique, the management of URTIs in primary healthcare settings is primarily empirical and often results in an overprescription of antibiotics despite compelling evidence of viral etiology. The country can benefit from the implementation and dissemination of evidence-based interventions to improve health outcomes. It is, therefore, critical to evaluate interventions to inform future decisions and ensure that the best available interventions and strategies are implemented (14,15).

An implementation science framework, RE-AIM (*Reach, Effectiveness, Adoption, Implementation, and Maintenance*), is often used to evaluate the implementation of health interventions, addressing individual- and setting-level outcomes essential to assess the impact and sustainability of an intervention or program (16,17). All domains of the RE-AIM framework can be used, but systematic reviews of the literature on RE-AIM have found that four dimensions (reach, effectiveness, adoption, and implementation) are evaluated and reported more often than the other dimension (maintenance) (18,19,20).

Research around responsible antibiotic use should include interventions to promote the de-implementation of unnecessary antibiotic usage, mainly for URTIs. We developed an intervention research protocol to promote responsible antibiotic prescribing in treating URTIs among HIV-infected individuals, and thus de-implementing unnecessary prescriptions (21). This study aimed to evaluate the reach, effectiveness, adoption, and implementation of a strategy to de-implement unnecessary antibiotic prescriptions for URTIs among HIV-infected adults attending primary healthcare facilities using the RE-AIM framework.

Methods

Study design

We conducted a hybrid type II effectiveness-implementation study guided by the Dynamic Adaptation Process (DAP) framework, consisting of three phases: a pre-implementation phase, adaptation & implementation phase, and a post-implementation phase **(Figure 1)**.

Figure 1. The Dynamic Adaptation Process (DAP) that guided the implementation strategy

Furthermore, we employed a multi-center, two-arm, parallel cluster-randomized controlled trial design with a mixed-methods approach. We used the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) planning and evaluation framework to evaluate the effectiveness and implementation of this study (17). Reporting follows the Standards for Reporting Implementation Studies (StaRi) (22). The analysis presented in this paper represents phase three (post-implementation), focusing on the evaluation of the intervention's implementation. Our study protocol has been published elsewhere (21).

resulted in a sample size of 345 participants to be assigned to either the intervention or control groups in a 1-to-1 ratio. Allowing for an attrition rate of 10%, we aimed to recruit a total of 380 HIV-infected patients with URTIs to ensure refusals or loss of patients' follow-up or their information.

Data collection, measures, and analysis

Quantitative data were collected from June to September 2024, whereas qualitative data were collected between October and December 2024. A structured questionnaire and a case record notebook were used to collect quantitative data. The on-site study coordinator was responsible for collecting data in close coordination with the clinicians. Data quality checks were performed by the Principal Investigator (PI) twice per month for completeness and accuracy and to address inconsistencies. Quantitative data were collected to evaluate the reach, effectiveness, adoption, and implementation of the intervention.

Reach

The "*reach*" outcome included two categories: recruitment rate and attrition rate. The *recruitment* rate was calculated as the proportion of patients recruited among those approached to participate in the study. The *attrition* rate was calculated as the proportion of patients who did not attend any of the follow-up visits among those recruited. These data were collected from the structured questionnaire. For analysis, we compared the reach outcomes between the intervention and control groups.

Effectiveness

For "*effectiveness,*" we measured the antibiotic prescribing rate as the primary outcome, the incidence of complications, and the mean time for complete recovery from the first medical visit as the secondary outcomes. The antibiotic prescribing rate was calculated as the number of patients who received at least one antibiotic prescription among those recruited on the day of enrollment (day 0). Antibiotic prescribing data were collected from the structured questionnaire in the section on prescribed medication. The complications and the time for complete recovery from the first medical visit were collected from the structured questionnaire in the section on follow-up visits. The complication rate was measured as the proportion of patients who experienced complications among those recruited and who completed the first follow-up visit (day 5). The mean time for complete recovery was calculated as the average time it took for patients to recover from their symptoms completely. For analysis, Pearson's chi-square test was used to compare the effect of the intervention between the intervention and control sites, with a significance level of 5%. To ascertain the magnitude of the intervention's effect, the relative risk (RR) was calculated, and the effectiveness ratio (1–RR) was used to estimate the intervention's effectiveness.

Adoption

The "*adoption*" outcome was measured as the number of sites and intervention agents (i.e., clinicians) who effectively followed the CDSA and were committed to promoting the de-implementation of unnecessary antibiotics. To get this information, we reviewed the symptomatology, including the duration of symptoms and antibiotic prescriptions, for each

participant, and these data were collected from the structured questionnaire. The analysis was performed for the intervention group at two levels (facility level and health provider level).

Implementation

For the "*implementation*" outcome, we evaluated the intervention fidelity and the degree of health worker satisfaction with the intervention. To evaluate implementation fidelity, we reviewed fidelity logs and monitored the implementation protocol to ensure it was delivered as intended. The information to evaluate the degree of satisfaction was collected from a survey with health providers in the intervention group. The degree of satisfaction was measured using a 5-point Likert scale, and for analysis, it was reduced to a binary category: dissatisfied (very dissatisfied, dissatisfied, neutral) and satisfied (very satisfied, satisfied).

To explore a deeper understanding of the implementation outcome, we collected qualitative data through focus group discussions (FGDs). The researchers approached the selected participants for FGDs with the help of the on-site study coordinator. The participants were invited to participate in the FGD after being informed of the study's purpose and the anonymous nature of the activities. After convening the group, eligible participants were again informed of the purpose of the FGD through a written participant information sheet, which included an informed consent form. Concurrently, the informed consent documents were read aloud to the participants, who were invited to ask questions to ensure comprehension before being asked to sign them. The time and place for FGDs were suggested by the participants and agreed with the research team.

Three FGDs were conducted, one at each health facility selected for the study. The FGD generated discussions and debates about the topic from the participants' perspectives. Each FGD involved 5 - 9 participants with similar characteristics, including male and female clinicians, pharmacists, laboratory technicians, and clinical managers. The FGDs were conducted by two researchers, a moderator, and an observer, who took notes on group dynamics and nonverbal communication. The FGDs occurred at each health facility and lasted roughly 40 - 50 minutes. It was structured around five thematic sections: (i) CDSA effectiveness, (ii) implementation barriers, (iii) implementation enablers, (iv) maintenance and dissemination of the use of the CDSA, and (v) pharmacy and laboratory perspectives regarding the implementation of the CDSA. All sections consisted of open-ended questions. FGDs were conducted in Portuguese (Mozambique's official language).

To analyze the qualitative data, we developed a matrix in which rows corresponded to participants' responses and columns to the questions posed. Responses were organized according to both predefined themes—based on the focus group discussion (FGD) guide—and themes that emerged during the analysis. The data were analyzed manually using a combination of content and thematic analysis, beginning with the organization and categorization of data under the predefined and emerging themes. Relevant quotes from participants were placed in the corresponding cells.

Results

Participants

A total of 34 clinicians, including clinical technicians (n=30, 88.2%), nurses (n=3, 8.8%), and physicians (n=1, 3%), provided care to a total of 379 HIV-infected patients with URTI symptoms. The majority of clinicians were females (82.4%), young (79.4%), with a mean age of 30.5 ± 8.5 years. Additionally, the majority had 10 years or less of work experience (73.5%). Among HIV-infected patients recruited, the majority were adults, with a mean age of 44 ± 12.3 years and a predominance of females (75.5%). Over half of the participants (57%) were single, and slightly more than half reported a secondary or technical (53.5%) level of education **(Table 1)**. Most presented with common cold and flu-like symptoms with no fever (84.4%). Around two-thirds (65.8%) received care in the city of Maputo.

Table 1. Demographic and clinical characteristics of the participants

Pre-implementation

Based on insights garnered from the pre-implementation phase of the study, we modified our implementation strategy to involve health facility leadership in coordinating and monitoring, as well as supervising the process on-site and reminding clinicians to utilize all available tools provided.

Adaptation and implementation

During the adaptation period, health providers were trained in the use of the CDSA and data collection tools. Afterward, they familiarized themselves with the intervention tools and implementation protocol to achieve the desired level of readiness for the start of the intervention. After a two-month adaptation period, we felt that all the health facilities and intervention agents had achieved the desired level of readiness. Then, a four-month implementation period followed, in which an implementation audit and continuous feedback were conducted to guarantee and monitor adherence to the implementation protocol.

Post-implementation

Reach

Reach was assessed at the individual (i.e., patient) level. A total of 387 HIV-infected patients deemed eligible were approached, and 379 (97.9%) agreed and were successfully recruited. Eight patients (2.1%) were excluded due to either refusal of consent or because they had a confirmed lower respiratory tract infection. Among the recruited patients, 182 (48%) were assigned to the intervention group, while 197 (52%) were assigned to the control group. The recruitment rate was high in both arms, 98.4% (182/185) in the intervention group and 97.5% (197/202) in the control group (Table 2). The overall attrition rate was less than 5%, indicating a low bias and no cause for concern.

Table 2. Intervention results according to the RE-AIM dimensions

Effectiveness

Among HIV-infected patients seen for URTI in the outpatient setting, the antibiotic prescribing rate was 23.1% (42/182) in the intervention group and 56.3% (111/197) in the control (Table 2). The overall rate (combining both groups) was 40.4% (153/379). The intervention resulted in a 33.2%

reduction in antibiotics compared to the control group. Individuals in the intervention group were less likely to receive an antibiotic prescription than those in the control group (RR = 0.41, 95% CI: 0.31 – 0.55).

Adoption

We evaluated the intervention adoption dimension to measure which sites and intervention agents (i.e., clinicians) adopted the de-implementation strategy of unnecessary antibiotics. Our direct observation found that the three sites (100%) and all intervention agents (100%) assigned to the intervention group showed commitment to promoting the de-implementation of unnecessary antibiotics (Table 2). Sixteen clinicians participated in the intervention group, comprising four doctors (25%) and 12 clinical officers (75%).

Implementation

Fidelity

The implementation protocol was delivered as intended. Overall, 100% (36/36) of clinicians in both groups adhered strictly to the implementation protocol, observing all stages of the implementation process. In both arms, patients were visited four times (on days 0, 5, 10, and 15). An additional follow-up visit was required in a few cases. Clinicians duly filled out the data collection forms and case record notebooks. Within 15 days of a follow-up visit, 100% (197/197) of patients in the control arm had recovered completely from their symptoms, and 99% (172/174) in the intervention arm. Only 1% (2/174) in the intervention arm required more than 15 days (i.e., 20 days) to completely recover.

Health providers' satisfaction

In total, 21 health providers from the intervention sites participated in the FGDs. This included 12 clinicians who were involved in providing direct patient care to HIV-infected adults, three pharmacists, two laboratory technicians, and one public health officer. The pharmacists, laboratory technicians, and the public health officer were additionally included in order to provide their opinions and experiences with how the intervention impacted their sectors of the healthcare facility **(Table 3)**. The majority were female (81%), young with an age range of 18 – 35 years (66.7%), and had a mean age of 31 ± 6 years. They had less than 10 years of service (76.2%) and were primarily clinical technicians (57.1%). Almost all participants were either satisfied or very satisfied with the intervention (i.e., whole CDSA, diagnosis procedure, and patient reference). Then, to explore the health providers' opinion regarding the implementation process, six major themes were extracted from the FGDs: (1) CDSA effectiveness, (2) changing attitudes and prescribing practices, (3) maintenance and dissemination of the use of the CDSA, (4) barriers to implementing the intervention, (5) enablers in implementing the intervention, and (6) reduction in requests for laboratory tests and antibiotics (**Supplementary file 2**).

CDSA effectiveness: Participants were asked about the effectiveness of the CDSA in improving symptoms without the use of an antibiotic. Respondents stated that most patients improved after the first intervention, even without antibiotic prescription. They received positive feedback from patients, indicating that they were feeling better, even without antibiotic use. When questioned about its effectiveness in reducing overprescription and adverse reactions, they stated that the

CDSA decreased the irrational use of antibiotics and helped prevent adverse events. Some said that the CDSA helped them avoid prescribing many medications for the same patient and reduce excessive prescriptions.

> *"There was a decrease in the excessive use of antibiotics compared to the period before and after the introduction of the algorithm. The algorithm helped us think logically, and we prescribed fewer medications for the same patient. Treatment is mild, and adverse reactions are rare. In most cases, we did not prescribe antibiotics and treated the patients symptomatically by giving them analgesics and decongestants/antihistamines."* (FGD 3)

Changing attitudes and prescribing practices: Participants realized that the CDSA has guided them in diagnosing and treating URTI symptoms appropriately. Clinicians were able to change their prescribing behavior in treating URTIs. They explained that, previous to our CDSA-based intervention, antibiotics were widely prescribed to relieve any URTI symptoms. Following this intervention, clinicians began to prescribe antibiotics less frequently and to avoid unnecessary antibiotic prescriptions.

> *"Truly, working with the algorithm helped us a lot. Before, every flu case was given antibiotics. I was able to assess when I should and should not give antibiotics"*. (FGD 1)

Maintenance and dissemination of the CDSA: Participants recognized the value of continuing to use the CDSA, as it enhances their practices and makes their work easier. They agreed that the tool should be used as standard guidance in the Mozambican National Health Service (NHS) in the management of URTIs in primary care settings for both HIV-infected and non-infected patients.

> *"The algorithm should be considered as standard and be used in other healthcare facilities, especially primary care. It should be recommended for use because it helps reduce the excessive prescription of antibiotics for URTIs. In addition to HIV-infected patients, it can also be used for HIV-uninfected patients. It should be used for all patients regardless of their HIV test status."* (FGD 1)

Barriers to implementing the intervention: FGD participants described several challenges in putting the intervention into practice. A common difficulty was managing patient expectations, as some patients anticipated receiving an antibiotic prescription—most often cotrimoxazole—which they believed would relieve their symptoms. Obtaining informed consent also posed challenges for patients who could not read or write, requiring the involvement of a witness to sign on their behalf. Limited availability of decongestants, such as nasal drops, in the NHS led clinicians to prescribe chlorpheniramine instead, which itself was sometimes out of stock. Follow-up by phone created further complications: when patients did not have a personal phone, contact numbers of relatives or friends were requested, raising concerns from the patient that their HIV status might be disclosed. In such cases, some patients refused to participate and were excluded from the study. Finally, FGD participants noted that at the start, unfamiliarity with the CDSA and a shortage of thermometers for all the consultation rooms further hindered the smooth implementation of the intervention.

> *"Decongestant drugs, such as nasal drops in the National Health System, are unavailable. So, we prescribed chlorpheniramine to perform this function, and sometimes it was not available in the facility. For patients who had no personal contact number, we asked for the confidant's contact details. Some of these patients thought that we were exposing their HIV status."* (FGD 2)

Enablers in implementing the intervention: We asked the participants what enabled the implementation of the intervention. Some stated that they adopted a practice of motivating patients to participate by informing them that, in cases of persistent or worsening symptoms, they could return to the healthcare facility and speak directly to the clinician who treated them, without needing to make an appointment, wait in line, or even make a phone call.

Others stated that the presence of an on-site intervention coordinator facilitated monitoring of the implementation process by reminding the clinicians to adhere strictly to the intervention protocol. Some participants agreed that what enabled the follow-up of some patients who were inaccessible or unreachable by phone calls is the availability of a database of HIV-infected patients undergoing antiretroviral therapy (ART), where there are alternative contact numbers.

> *"The patient did not have to wait in line and was told to speak directly to me, which motivated them to participate. I provided my telephone number so that the patient could call me if their symptoms worsened. The algorithm itself facilitated the implementation. In the beginning, the doctor, our supervisor, and coordinator reminded us to use the algorithm and not to prescribe antibiotics for URTI according to the algorithm."* (FGD 1)

Reduction in requests: We asked the participants about their perspectives on reducing requests for antibiotics and laboratory tests from the pharmacy and laboratory standpoints. They declared that a reduction in requests for unnecessary laboratory tests was observed during the implementation period. Previously, in any case of URTI, some clinicians were ordering a tuberculosis (TB) test. During the intervention period, no shortage of reagents and antibiotics was observed.

> *During the intervention, we did not have any stockouts. There was a reduction in antibiotic use, and we had a good stock of antibiotics due to the use of the algorithm by clinicians. There was a reduction in orders for unnecessary laboratory tests. Any URTI patient was requested to undergo a TB test. With the study, there was a reduction in orders, and no shortage of reagents was observed during the intervention period."* (FGD 1)

Discussion

This study evaluated a strategy to de-implement unnecessary antibiotic prescriptions among HIV-infected adults with URTIs using the RE-AIM framework. The main findings indicate that the reach, effectiveness, adoption, and implementation of the intervention were relatively high. We observed a high patient participation rate, indicating a high proportion of HIV-infected adult patients reached by the intervention among those approached. An increased participation rate in randomized controlled trials can be achieved when participants perceive that they will receive better care and extra attention (24). Therefore, the relatively high participation rate observed in this study is attributed to the clinicians, who provided better information about the study, including the risks

and benefits of participating, building trust, and establishing a collaborative relationship. Furthermore, the connection between the clinician and the patient, as well as the facilitation of rapid contact during the follow-up visit, which would not have occurred in other circumstances, enabled greater patient participation in the process of implementing the planned intervention.

We report a productive deployment of our strategy in the intervention group, translated by both facilities and health providers into de-implementing unnecessary antibiotic prescriptions for HIV-infected patients with URTIs. As a result of the adoption of the de-implementation strategy, the intervention was effective in reducing the antibiotic prescribing rate by approximately one-third (33.2%) compared to the control. This decrease in the antibiotic prescribing rate is supported by health providers' opinions regarding the implementation of the intervention. They reported that the intervention enabled them to change their attitudes and prescribing practices, resulting in a reduction of unnecessary prescription of antibiotics.

The antibiotic prescribing rate in the intervention group (23.1%) aligns with the WHO reference of 20 – 26.8% (19). In our control sites, in the absence of the intervention, the antibiotic prescribing rate (56.3%) was nearly double the WHO reference. These findings reveal the strong effect of our intervention in reducing antibiotic prescriptions. Our findings are aligned with those reported in Tanzania, where the intervention showed a significant reduction in antibiotic use (26%) compared to the control (70%) (13).

Although some barriers were observed during the implementation process, all of them were successfully overcome, allowing the success of our intervention. The success reported in this study is due, in part, to the high fidelity of the intervention during implementation (25,26).

Health providers were satisfied with the implementation of the CDSA, and we felt that it would drive them to continue using the CDSA and promote a reduction in unnecessary antibiotic prescriptions for URTIs. The continued use of the CDSA, coupled with health providers' satisfaction, will reflect on the sustainability of the intervention, improving health outcomes in the mid and long term, thus contributing to the combat of unnecessary antibiotic use. However, health providers' ownership of the intervention is crucial for sustaining use of the CDSA even after the trial period (27).

An unexpected benefit of implementing our intervention was a simultaneous reduction in requests for unnecessary laboratory tests. This demonstrates the utility of our CDSA in contributing to the attitudes and behavior change in regards to antibiotic prescribing.

We used an innovative methodological approach, simultaneously evaluating both intervention effectiveness and implementation outcomes, utilizing a cluster-randomized controlled trial design. Implementation science frameworks share a common language and more efficiently contribute to generalized knowledge about clinician-changing behaviors (28). Using RE-AIM in this research allowed us to actively study the implementation while effectiveness was established, thus quantifying the health outcomes.

Some limitations were observed in this research. Due to limited resources, the research was conducted in only six healthcare facilities. The study area (Maputo and Matola cities) was chosen by convenience sampling. Contamination within the sites may have occurred due to earlier

activities in the pre-implementation and adaptation phases. The patient recruitment rates between the intervention and control arms differed slightly but did not impact the overall results presented in this study. The *maintenance* dimension, one of the five pillars of the RE-AIM framework, was not assessed due to the short timeline of the research project. Therefore, we focused on the other four dimensions: *reach, effectiveness, adoption*, and *implementation* of the intervention. Despite the limitations, the study provides evidence of the utility of our strategy in reducing antibiotic use.

Conclusions

This study revealed an effective and successful implementation of our intervention in the primary healthcare setting. The intervention was effective in de-implementing unnecessary antibiotic prescriptions for URTIs. The reach, adoption, and implementation outcomes were high. Future studies may be developed using our implementation strategy in other areas to determine if the same findings are observed elsewhere. Furthermore, new studies can use our approach in other settings, including in secondary and tertiary levels of the health system, and contribute to necessary changes in attitudes and prescribing behavior in order to contribute to more appropriate and evidence-based antibiotic prescription.

Abbreviations

ART	Antiretroviral therapy
CDSA	Clinical decision support algorithm
DAP	Dynamic adaptation process
FGD	Focus group discussion
HIV	Human immunodeficiency virus
LIC	Low-income country
NHS	National Health Service
PI	Principal investigator
RE-AIM	Reach-effectiveness-adoption-implementation-maintenance framework
RR	Relative risk
SD	Standard deviation
StaRi	Standards for reporting implementation studies
TB	Tuberculosis
URTI	Upper respiratory tract infection
WHO	World Health Organization

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Authors contributions

All authors made substantial contributions to the study's concept and design. CF monitored and audited the implementation process, data collection, and analysis, as well as drafted the manuscript. ES supervised the data collection and analysis, commented on the entire manuscript, and critically revised it. TM and MS made substantial revisions. All authors read and approved the final version of the manuscript.

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Availability of data and materials

All generated data will be available from the corresponding authors upon reasonable request and deposited at the Faculty of Medicine, University Eduardo Mondlane data repository.

Declarations

Ethics approval and consent to participate

The Mozambican National Bioethics Committee for Health (*Comité Nacional de Bioética para Saúde*, CNBS) approved the study protocol on 14 August 2023 (register number 52/CNBS/2023). Participants were enrolled in the study after providing informed consent.

Consent for publication

Not applicable.

Competing interests

Not applicable

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582 **Table 1**. Demographic and clinical characteristics of the participants

Characteristic		Intervention	Control	Total	p-value
Patient sex	Male	44 (24.2%)	49 (24.9%)	93 (24.5%)	0.875
	Female	138 (75.8%)	148 (75.1%)	286 (75.5%)	
Patient age range	Mean ± SD	45 ± 11.5	43 ± 12.9	44 ± 12.3	0.051
	18 – 35 years	35 (19.2%)	60 (30.5%)	95 (25.1%)	
	36 – 45 years	65 (35.7%)	51 (25.9%)	116 (30.6%)	
	46 – 59 years	62 (34.1%)	65 (32.9%)	127 (33.5%)	
	≥ 60 years	20 (11.0%)	21 (10.7%)	41 (10.8%)	
Patient marital status	Married	67 (36.8%)	70 (35.5%)	137 (36.6%)	0.276
	Divorced	6 (3.3%)	4 (2.0%)	10 (2.7%)	
	Single	106 (58.2%)	113 (57.4%)	219 (57.0%)	
	Widower	3 (1.6%)	10 (5.1%)	13 (3.7%)	
Patient's level of education	Illiterate	6 (3.4%)	14 (7.6%)	20 (5.5%)	<0.001
	Primary	78 (44.1%)	47 (25.5%)	125 (34.6%)	
	Secondary/Technical	88 (49.7%)	105 (57.1%)	193 (53.5%)	
	Higher	5 (2.8%)	18 (9.8%)	23 (6.4%)	
Signs and Symptoms	Fever low-grade	11 (6.6%)	19 (29.7%)	30 (13%)	<0.001
	Fever high grade	3 (1.8%)	3 (4.7%)	6 (2.6%)	
	No fever	153 (91.6%)	42 (65.6%)	195 (84.4%)	
	Rhinorrhea	113 (62.1%)	113 (57.4%)	226 (59.6%)	0.349
	Sore throat	80 (44%)	106 (53.8%)	186 (49.1%)	0.055
	Cough < 10 days	139 (76.4%)	145 (73.6%)	284 (74.9%)	0.534
	Cough > 10 days	11 (6%)	12 (6.1%)	23 (6.1%)	0.985
	Nasal congestion < 10 days	89 (48.9%)	115 (58.4%)	204 (53.8%)	0.065
	Nasal congestion > 10 days	5 (2.7%)	5 (2.5%)	10 (2.6%)	0.899
	Chills	66 (36.3%)	67 (34%)	133 (35.1%)	0.646
	Runny nose	61 (33.5%)	45 (22.8%)	106 (28%)	0.021
	Headache	114 (62.6%)	117 (57.9%)	227 (60.2%)	0.329
Place of patient care	Maputo	112 (64.0%)	136 (67.3%)	248 (65.8%)	0.497
	Matola	63 (36.0%)	66 (32.7%)	129 (34.2%)	
Clinician sex	Male	4 (28.6%)	2 (10%)	6 (17.6%)	0.162
	Female	10 (71.4%)	18 (90%)	28 (82.4%)	
Clinician age range	Mean ± SD	30.6 ± 6.3	30.4 ± 9.8	30.5 ± 8.5	0.192
	18 – 35 years	10 (71.4%)	17 (85%)	27 (79.4%)	
	36 – 45 years	4 (28.6%)	1 (5%)	5 (14.7%)	
	46 – 59 years	---	2 (10%)	2 (5.9%)	
Clinician category	Nurse	---	3 (15%)	3 (8.8%)	0.760
	Clinical technician	13 (92.9%)	17 (85%)	30 (88.2%)	
	Physician	1 (7.1%)	---	1 (3%)	
Clinician's years of experience	Mean ± SD	5.6 ± 4.7	6.6 ± 8.5	6.2 ± 7.2	0.677
	≤ 10 years	10 (71.4%)	15 (75%)	25 (73.5%)	
	11 – 20 years	4 (28.6%)	3 (15%)	7 (20.6%)	
	≥ 21 years	---	2 (10%)	2 (5.9%)	

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584 **Table 2**. Implementation outcomes according to the RE-AIM dimensions

RE-AIM	Indicator	Level	Group	N (%) or results
Reach	Patients recruited with URTI symptoms	Patients	Intervention	182/185 (98.4%) patients
			Control	197/202 (97.5%) patients
			Total	379/387 (97.9%) patients
	Attrition rate	Patients	Intervention	8/182 (4.4%) patients
			Control	0 patients
			Total	8/387 (2.1%) patients
	Patients recruited and completed at least one follow-up visit	Patients	Intervention	174/182 (95.6%) patients
			Control	197/197 (100%) patients
			Total	371/379 (97.9%) patients
Effectiveness	Patients who received antibiotic prescriptions	Patients	Intervention	42/182 (23.1%) patients
			Control	111/197 (56.3%) patients
			Total	153/379 (40.4%) patients
	Patients with complications (complication rate)	Patients	Intervention	5/174 (2.9%) patients
			Control	13/197 (6.6%) patients
			Total	18/371 (4.9%) patients
	Patients recovered within 5 days	Patients	Intervention	133/174 (76.4%) patients
			Control	158/197 (80.2%) patients
			Total	291/371 (78.4%) patients
	Patients recovered within 10 days	Patients	Intervention	162/174 (93.1%) patients
			Control	195/197 (98.9%) patients
			Total	357/371 (96.2%) patients
	Patients recovered within 15 days	Patients	Intervention	172/174 (98.8%) patients
			Control	197/197 (100%) patients
			Total	369/371 (99.5%) patients
Adoption	Intervention sites that successfully implemented the strategy	Health facility	Intervention sites	3/3 (100%) sites
	Clinicians who adopted the de-implementation strategy	Healthcare providers	Intervention	14/14 (100%) clinicians
Implementation	Clinicians who effectively followed the implementation protocol	Healthcare providers	Intervention	14/14 (100%) clinicians
			Control	20/20 (100%) clinicians
			Total	34/34 (100%) clinicians
Maintenance	Not assessed			

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590 **Table 3**. Degree of satisfaction of the FGD participants

Feature	Total n (%)	Satisfaction with the whole CDSA		Satisfaction with the diagnosis procedure in the CDSA		Satisfaction with patient reference in the CDSA	
		Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)
Sex							
Female	4 (19%)	4 (19%)	--	4 (19%)	--	4 (20%)	--
Male	17 (81%)	17 (81%)	--	17 (81%)	--	16 (80%)	1 (100%)
Age							
Mean ± SD	31 ± 6.0						
18 – 35 years	14 (66.7%)	14 (67%)	--	14 (67%)	--	13 (65%)	1 (100%)
36 – 45 years	7 (33.3%)	7 (33%)	--	7 (33%)	--	7 (35%)	--
Length of service							
Mean ± SD	6 ± 4.9						
≤ 2 years	6 (28.6%)	6 (28.6%)	--	6 (28.6%)	--	5 (25%)	1 (100%)
3 – 10 years	10 (47.6%)	10 (47.6%)	--	10 (47.6%)	--	10 (50%)	--
11 – 20 years	5 (23.8%)	5 (23.8%)	--	5 (23.8%)	--	5 (25%)	--
Job Category							
Clinical Technician	12 (57.1%)	12 (57.1%)	--	12 (57.1%)	--	11 (55%)	1 (100%)
General Physician	3 (14.3%)	3 (14.3%)	--	3 (14.3%)	--	3 (15%)	--
Pharmacist	3 (14.3%)	3 (14.3%)	--	3 (14.3%)	--	3 (15%)	--
Laboratory technician	2 (9.5%)	2 (9.5%)	--	2 (9.5%)	--	2 (10%)	--
Public health officer	1 (4.8%)	1 (4.8%)	--	1 (4.8%)	--	1 (5%)	--
Focus group							
1° de Maio	9 (42.9%)	9 (42.9%)	--	9 (42.9%)	--	9 (45%)	--
Bagamoyo	7 (33.3%)	7 (33.3%)	--	7 (33.3%)	--	6 (30%)	1 (100%)
Matola 2	5 (23.8%)	5 (23.8%)	--	5 (23.8%)	--	5 (25%)	--

591 Yes satisfaction (very satisfied or satisfied); No satisfaction (neutral, dissatisfied, very dissatisfied)

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