ANTIBIOTIC PRESCRIPTION AUDIT AT UNIVERSITY TEACHING HOSPITALS IN RWANDA

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Declaration

I declare that this dissertation is my work except where specifically acknowledged and it has been passed through the antiplagiarism system and found to be compliant and this is the approved final version of the dissertation:

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Abstract

Background: Antibiotic resistance is becoming a public health threat worldwide. This assessment of antibiotic prescription in Teaching Hospitals in Rwanda (Centre Hospitalier Universitaire de Kigali (CHUK) and Centre Hospitalier Universitaire de Butare (CHUB) describes the antibiotic prescription patterns, the compliance to the standards treatment guidelines (STGs) while prescribing antibiotics, and describes the awareness of the prescribers of the STGs.

Methods: Data were collected in patients' files for those admitted to Clinical Departments from July to December 2019. Only patients who received antibiotics were selected. With a questionnaire, we collected data on the rate of use of standards treatment guidelines while prescribing antibiotics and the degree of satisfaction of medical doctors with the functionality of the Drug and Therapeutic Committees (DTC). Questionnaires have been filled by medical doctors. The research has been conducted from May 2020 to August 2021.

Results: The assessment of quality indicators of prescription of antibiotics shows gaps in antibiotics prescriptions. Prescriptions were not fully completed and the end date and route of administration were less recorded (27.7% and 79.8% respectively). Antibiotics prescribed were at 99.4% in-hospital drug formulary lists and were prescribed by generic names at 84.8%. Potential drug-drug interactions were observed at a rate of 47.46% with the antibiotics prescribed to the patient for which 9.69% were major, 10.17% minor, and 27.6% moderate.

Conclusion and recommendations: Antibiotic prescription in teaching hospitals in Rwanda needs to make adequate interventions to improve the clinical use of antibiotics. Prescribers should prescribe according to STGs with all relevant information as required. Uniform treatment sheets should be developed in CHUB to avoid medication errors. Monitoring of the use of antibiotics should be done to reduce the use of non-indicated antibiotics, duplicated antibiotics, and antibiotics with potential interactions which may lead to an increase in antibiotic resistance, increase the risk of harm to patients and increase healthcare costs. There is a need for hospitals to hire clinical pharmacists to deal with the rational use of medications. DTCs in teaching hospitals need to improve their functionality and put in place antibiotic stewardship programs to address deficiencies in antibiotic rational use.

Key words

Antibiotics, medical prescription, prescribing audit, antimicrobial resistance, drug formulary, standard treatment guideline

Abbreviations

CHUB	Centre Hospitalier Universitaire de Butare
CHUK	Centre Hospitalier Universitaire de Kigali
CSF	Cerebrospinal fluid
DNA	Deoxyribonucleic acid
DTC	Drug and Therapeutics Committee
ESBL	Extended-spectrum beta-lactamases
KPC	Klebsiella pneumoniae carbapenemase
MDR	Multidrug resistance
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *S. aureus*
NSAIDs	Nonsteroidal anti-inflammatory drugs
STG	Standard treatment guidelines
US FDA	The United States Food and Drug Authority

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CHAPTER ONE: GENERAL INTRODUCTION

1.1 Background

Infectious diseases have been a leading cause of mortality historically. Out of the top ten primary causes of mortality in 1900, infectious diseases accounted for one-third of all deaths.(1) However, during the twentieth century, advances in medicine and public health lowered the burden.

Antibiotics have substantially reduced deaths and complications caused by bacterial infections even if their widespread use is associated with emergence and spread of resistant strains.[2]

Many factors contribute to antibiotic resistance. Aastha Choksh and associates(2) describe some of these factors. Key factors identified in developing countries included: a. Lack of monitoring of resistance development, b. availability of antibiotics with poor quality, c. clinical misuse, and d. ease access to antibiotics. In developed countries, key factors identified: a. weak hospital-level regulation and b. excessive use of antibiotic in food-producing for animals. Another factor mentioned by the above authors is the lack of economic incentives for new antibiotic development.

The clinical misuse of antibiotics has led to many types of research around the world and some of them will be discussed in the following paragraphs.

The study on the Clinical pattern of antibiotic overuse and misuse in primary healthcare hospitals in the southwest China (3) revealed that overuse of antibiotics for uncomplicated respiratory infection and the use of cephalosporins, macrolides, and injection antibiotics in primary care are the major problems of clinical practice in rural areas of Guizhou.

The same as the previous research, the overuse of antibiotics was reported in a research on antibiotic prescribing in public and private practice in primary care clinics in Malaysia. (4) The antibiotic prescribing rates are high in both public and private primary care settings, especially in the private. This research provides evidence of overuse and misuse of excessive and inappropriate antibiotics.

One of the consequences of excessive and inappropriate antibiotic prescribing is the antibiotic resistance that all countries are facing in the world including Rwanda.

A study conducted in University Teaching Hospitals in Rwanda on ‘’Widespread antimicrobial resistance among bacterial infections in a Rwandan referral hospital’’ (5) found that 183 (75.9%) of 241 Gram-negative isolates screened for ceftriaxone were resistant. 66 (71.7 percent) of 92 Gram-negative isolates evaluated for the extended-spectrum beta-lactamase (ESBL) positive phenotype were ESBL positive.

A high rate of antibiotic resistance has been reported in the high prevalence of antimicrobial resistance among common bacterial isolates in a tertiary healthcare facility in a Rwandan study. (6) In total, 31.4 percent of E. coli isolates and 58.7% of Klebsiella isolates were resistant to at least one of the third-generation cephalosporins, according to the study. In addition, 8% of E. coli isolates were resistant to imipenem, and 82 percent and 6% of Staphylococcus aureus bacteria were resistant to oxacillin and vancomycin, respectively.

Another research found that all Escherichia coli isolates were cephalosporin resistant. (7) Data on antibiotic use was available for 165 of the 201 individuals that were enrolled. The majority of the patients were given antibiotics, mostly third-generation cephalosporins (n=149; 90%) and/or metronidazole (n=140; 85%). As a result, 80 patients (54%) were discovered to be at high risk of antibiotic treatment failure or death. All *Escherichia coli* specimens tested positive for cephalosporin resistance in this investigation.

E. Ishimwe and T. Rogo (7) found similar results in their study among children hospitalized with bacteremia admitted to the largest tertiary hospital in Rwanda. They found that 60.0 percent of Staphylococcus aureus isolates were oxacillin resistant. 33.3 percent of Klebsiella species were resistant to cefotaxime, 77.3 percent to gentamicin, and 42.8 percent to ciprofloxacin. Ampicillin resistance was found to be 100 percent.

1.2. Problem statement

The above data show a high antimicrobial resistance rate in Rwanda which poses a serious problem in the treatment of common infections. Given that antibiotic use begins with prescription in health care settings, and that the effectiveness of an intervention on antibiotic prescribing is highly dependent on the specific prescribing behavior and change barriers, as demonstrated by a study on interventions to improve antibiotic prescribing practices in ambulatory care (8), we decided to assess antibiotic prescription practices in teaching hospitals. The assessment described the antibiotic prescription patterns, the compliance to the standards treatment guidelines while prescribing antibiotics, and described the awareness of the prescribers of the STGs.

The research aimed to promote good clinical practices in antibiotic use at the teaching hospital level in Rwanda. The results from this study will be used by hospital authorities to put in place adequate interventions to improve the clinical use of antibiotics, thus reducing the antibiotic-resistant bacteria burden for the better health of the population.

1.3. Objectives of the study

1.3.1. General objective

The main objective was to assess the antibiotic prescription patterns at University Teaching Hospitals in Rwanda for good control and containment of antibiotic resistance.

1.3.2. Specific objectives

1. Describe antibiotic prescription patterns at university teaching hospitals in Rwanda;
2. Describe the compliance to standards treatment guidelines (STG) and
3. Describe the Medical doctor's awareness of STGs

CHAPTER TWO: A LITERATURE REVIEW

This chapter will define key definitions and describe the general concepts of antibiotics. We will discuss the reason for doing an audit of medicine use, characteristics of antibiotics, classes of antibiotics, mechanism of actions of antibiotics, when to start antibiotics, usage of antibiotics, problems related to their usage, and the management of antibiotics resistance.

2.1. Key definitions and concepts

2.1.1. Prescription

In the medical field, a physician's order for the preparation and administration of a medicine or equipment for a patient is known as a prescription. There are various parts to a prescription. They include the superscription or heading with the symbol "R" or "Rx", which stands for the word recipe (meaning, in Latin, to take); the inscription, which contains the names and quantities of the ingredients (dose and dosage form); the subscription or directions for compounding the drug (how much medication to take, how to take it, and how often to take it); and the signature which is often preceded by the sign "s" standing for signa (Latin for mark), giving the directions to be marked on the container. (9)

Prescribers should fill out all of the relevant information in the prescription because insufficient information can lead to poor treatment outcomes and harm to the patient. (10) To declare a prescription paper complete, the prescribers must complete all of the parameters listed on the prescription paper. (10) In our study, we are going to assess the completeness of antibiotic prescriptions using the treatment sheets and progress notes in patient’s files.

2.1.2. Audit

Among other definitions, an audit is an official examination of records or an investigation of a business's accounts, usually by professionals from outside the business, or an official assessment of the quality or condition of something.(11)

2.1.3. Prescription audit

A prescription audit is a quality improvement approach that tries to enhance patient care and outcomes through a systematic examination of care against specific criteria and the implementation of change as part of a comprehensive clinical audit. (12) According to the same source, prescription auditing can improve the prescription quality for the best quality care of the patient if it is done regularly to promote the education of prescribers. As far as antibiotics are concerned in our study, we are going to assess the scale of the problem of antibiotic

prescriptions to develop various interventional strategies designed to reduce their use. WHO drug use indicators will be referred to.

2.1.4. Antibiotics

In the strictest sense, antibiotics are antibacterial substances produced by diverse microorganisms (bacteria, fungi, and actinomycetes) that inhibit the growth of other microorganisms. Synthetic antimicrobial compounds, such as sulfonamides and quinolones, are frequently included in the word antibiotics. (1)

Others use terminology like antimicrobial, antibiotic, and anti-infective to refer to a wide range of medicinal compounds including antibacterial, antifungal, antiviral, and antiparasitic medications. (13) Antibacterial agents are the most frequently used and the one this study is going to focus on. They are used to prevent and treat bacterial infections.

2.1.5. Antibiotic resistance

Antibiotics, as previously stated, are medications that are used to prevent and treat bacterial infections. Antibiotic resistance occurs when bacteria change in response to the use of these medicines[3]. This change goes in the sense of becoming less effective in response.

Others define antibiotic resistance as bacteria's potential to change in a way that they resist drug effects — "the germs are not killed, and their growth is not reduced.".(14) As a result, when bacteria are exposed to drugs, resistance develops spontaneously. According to the same source, antibiotic overuse, on the other hand, accelerates the process, and numerous causes can contribute to its spread. In the following paragraphs, we will discuss how antibiotic resistance spreads, the misuse of antibiotics, and how to manage antibiotic resistance.

2.1.6. Standard treatment guidelines

The World Health Organization defines the Standard Treatment Guidelines (STG) are systematically developed statements designed to support practitioners and patients in making decisions about appropriate health treatment for specific clinical circumstances. (15) Studies have shown that when STGs are used and adhered to, resistant microorganisms' introduction declines in numbers. (16) According to the same source, the essential stakeholders must be involved and committed for the STGs to work effectively. Drug and therapeutics committees (DTC) in hospitals are responsible for providing support and mentoring to prescribing physicians. They must educate them and make STGs available to them. (18) Adherence to STGs must also be monitored on a regular basis, as this lowers hospital expenditures associated

with medications. In our study, we are going to assess the compliance to the standards treatment guidelines while prescribing antibiotics and assess the awareness of prescribers on the existence of treatment guidelines and the DTC.

2.1.7. Formulary list

Formulary lists represent the medicines of choice for a hospital, as defined by the competent medical authority, and represent one way to optimize the use of medicines. (17) This list is established by DTC and should be regularly updated. Non-adherence to such hospital policy may be caused by many reasons. Some of the reasons are that prescriptions are listed by brand names while medicines are stocked and dispensed under generic names, medicines on the formulary list not available in the hospital and prescribers which are not aware of the existence of the list or are not in agreement with the list.

2.1.8. Drug Interaction

A drug interaction occurs when the clinical effects of one drug are altered by the administration of another. The result may be an increase or decrease in either the beneficial or harmful effects of the second agent. (18) There are 3 classes of interactions. (19) An interaction is classified as major when highly clinically significant and the combination should be avoided, a moderate interaction is moderately clinically significant and the combination should be used only under special circumstances and interaction is minor when minimally clinically significant with minimum risks. A combination with minor interaction can be used after assessment of risks, consideration of alternative drugs, or after the establishment of a monitoring plan. (19) We will have to check possible interactions with prescribed medications with patients of our study population.

2.1.9. Therapeutic duplication

Therapeutic duplication is defined as the prescribing and dispensing of two or more medications from the same therapeutic class in such a way that the combined daily dose puts the recipient at risk of an adverse medical outcome or adds to more expenditures without providing extra therapeutic benefits (20) Duplication of antibiotics prescribed to patients of our study population will be assessed.

2.2. Characteristics of antibiotics, classes of antibiotics, and mechanism of action

Before talking about the usage of antibiotics and problems related to their usage, it is important to talk about their characteristics, their mechanisms of action, and their classes.

2.2.1. Characteristics of antibiotics

Kenneth Todar (21) listed characteristics of antibiotics as follow: On a variety of bacteria, antibiotics can have a cidal (killing) or static (inhibitory) action. The spectrum of action of an antibiotic refers to the range of bacteria or other microorganisms that it can kill. The spectrum of action of an antibiotic refers to the number of bacteria or other microorganisms that it affects. We have broad-spectrum antibiotics that kill or inhibit a wide range of Gram-positive and Gram-negative bacteria, narrow-spectrum antibiotics that are primarily effective against Gram-positive or Gram-negative bacteria, and antibiotics with a limited spectrum that are only effective against a single organism or disease when it comes to the spectrum of action.

Surbhi Leekha and colleagues (15) categorized bactericidal medications as drugs that cause bacterial cell death and disruption, medications that predominantly operate on the cell wall (eg, b-lactams), cell membrane (eg, daptomycin), or bacterial DNA (eg, fluoroquinolones). They have classified bacteriostatic agents as medicines that inhibit bacterial multiplication without killing the organism by inhibiting protein synthesis. Among bacteriostatic agents, we have sulfonamides, tetracyclines and macrolides. They added that the distinction is not absolute. An agent can be bactericidal against certain organisms and be bacteriostatic against others and vice versa even though this distinction is in most situations insignificant in vivo. According to the same source, in the case of serious illnesses like endocarditis and meningitis, bactericidal drugs are recommended to obtain a quick cure.

2.2.2. Classes of antibiotics and their mechanism of action

In the table below we are giving an overview of different classes of antibiotics. We will focus on current antibiotics on the National Essential Drugs list and antibiotics available on the local market.

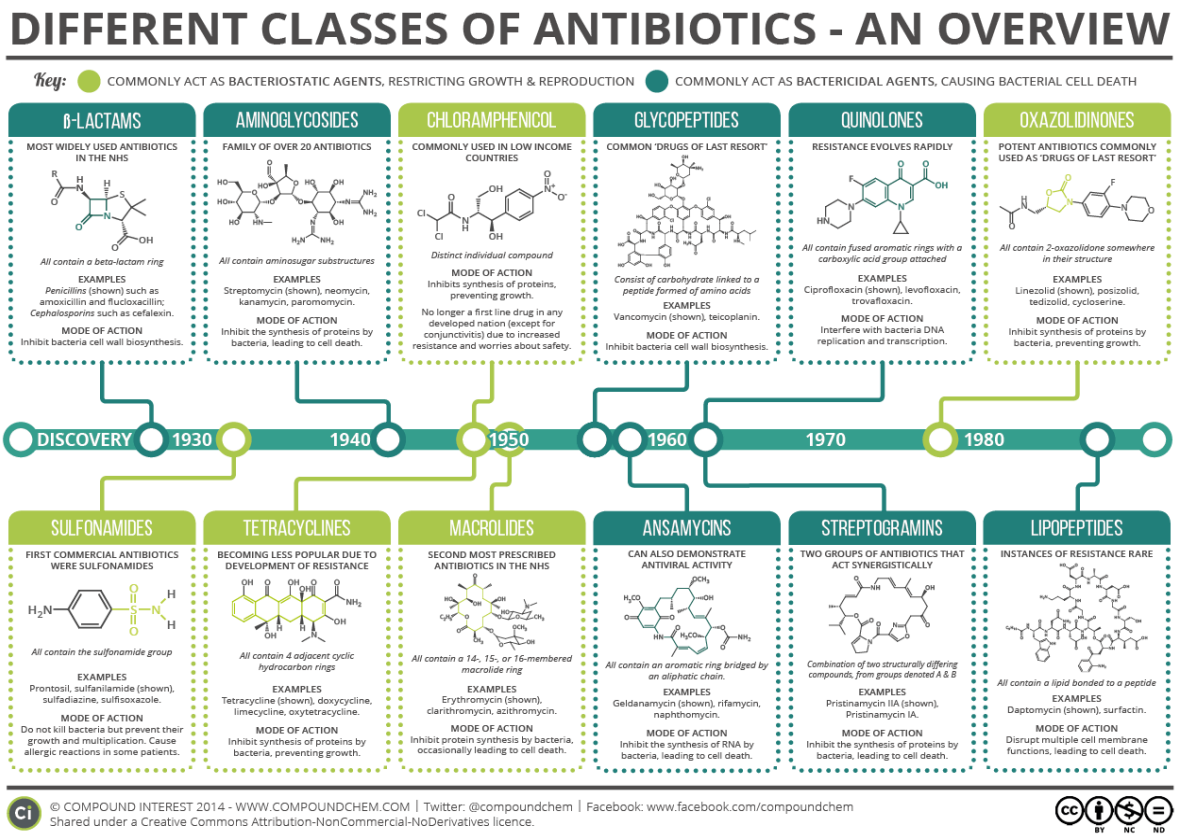


Figure 1: Different classes of antibiotics with their mechanisms of action(22)

From figure 1, we are going to have a brief presentation on different classes. In addition to these classes in figure 2, we find some other important classes of antibiotics such as lincomycins, polypeptides, fusidanes, nitroimidazoles, and nitrofurans.

a. Beta-Lactams

Beta-lactams are a class of antibiotics, the first of which was discovered in 1928 by Alexander Fleming (24) and named penicillin. A beta-lactam ring is found in all beta-lactam antibiotics; they work by interfering with the formation of peptidoglycan, a key component of the bacterial cell wall, and are most commonly used against gram-positive bacteria. Bacteria, on the other hand, can develop resistance to beta-lactams through different mechanisms, including the synthesis of enzymes that break down the beta-lactam ring. Beta lactams include the following:

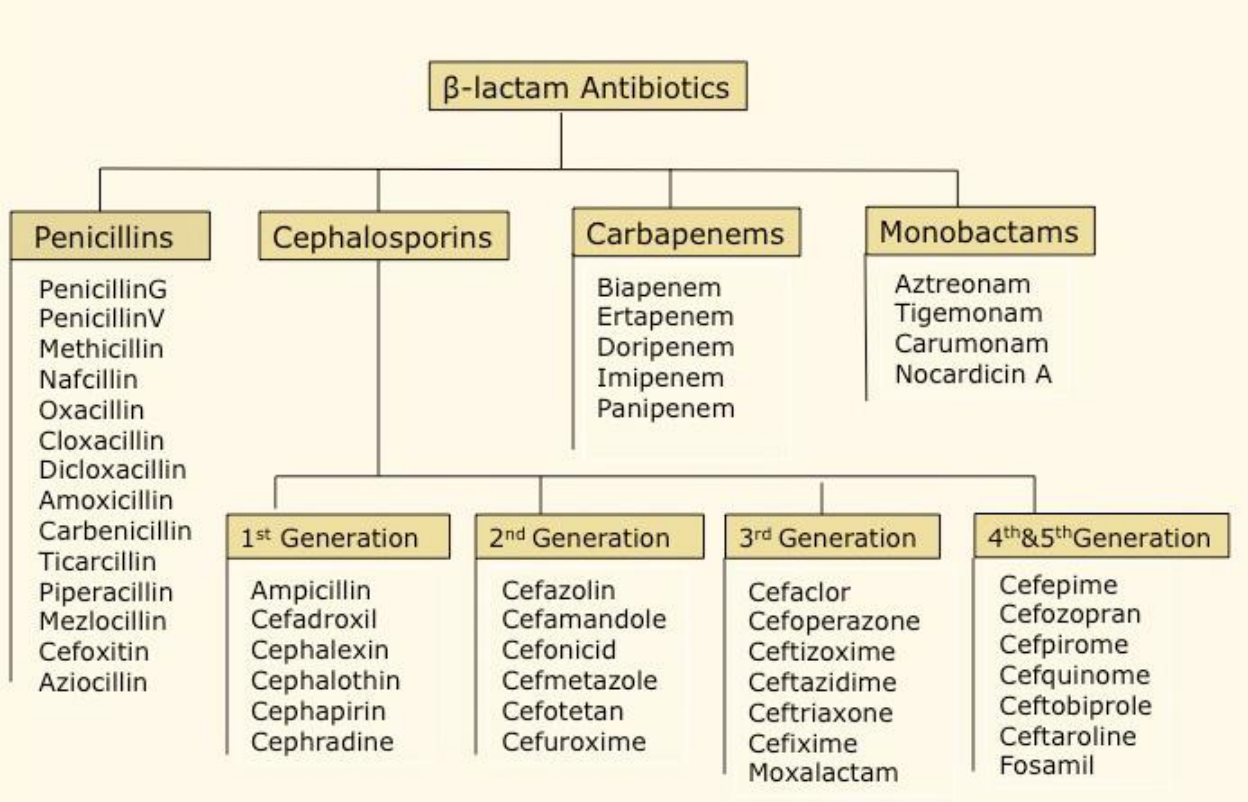


Figure 2 Beta-lactams antibiotics

a.1. Carbapenems

Carbapenems are active against Gram-positive and Gram-negative bacteria and are used with aminoglycosides to enhance the effectiveness of both antibiotics. Cilastatin and relebactam are not antibiotics and are used with carbapenems to protect them from being broken down. (23) They include imipenem and meropenem.

a.2. Monobactams

Aztreonam is active against anaerobes and acts synergistically with aminoglycosides. (24)

a.3. Cephalosporins

a.3. 1. Cephalosporins 1st generation are antibiotics that are effective against Gram-positive bacteria and are commonly used to treat skin and soft tissue infections caused by staphylococci and streptococci. Endocarditis caused by methicillin-resistant, S. aureus and prophylaxis before cardiothoracic, orthopedic, abdominal, and pelvic surgery are common uses for parenteral cefazolin. (25) They include cefazolin, cefadroxil, cephalexin. Note that ampicillin is not included in this class as it is in the figure above.

a.3.2. Cephalosporins 2nd generation and cephamycins (drugs that were originally produced by Streptomyces but are now synthetic) are classified together and are active against Gram-

positive cocci, gram-negative bacilli, and anaerobes, such as Bacteroides. They are often used for polymicrobial infections that include gram-negative bacilli and gram-positive cocci. Because cephamycins are active against Bacteroides species, they can be used when anaerobes are suspected (eg, in intra-abdominal sepsis, decubitus ulcers, or diabetic foot infections). (25) They include cefaclor, cefuroxime, cefoxitin, and cefotetan. Cefoxitin and cefotetan are among cephamycins. (25)

a.3.3. Cephalosporins 3rd generation are active against *Hemophilus Influenza* and some Enterobacteriaceae (eg, *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis)* that do not produce AmpC beta-lactamase or extended-spectrum beta-lactamase (ESBL) and also against some gram-positive species, especially streptococci including some strains with reduced penicillin susceptibility. Oral cefixime and ceftibuten have little activity against *S. aureus* and, if used for skin and soft-tissue infections, should be restricted to uncomplicated infections due to streptococci. Ceftazidime is active against Pseudomonas aeruginosa but has no appreciable gram-positive activity. Adding avibactam to ceftazidime increases its spectrum to include *Enterobacteriaceae* that produce AmpC, Extended-spectrum beta-lactamases (ESBL), or *Klebsiella pneumoniae carbapenemase* (KPC). (25) They include also ceftriaxone, cefixime, cefotaxime, ceftibuten, and ceftazidime + avibactam.

a.3.4. Cephalosporins 4th generation are active against Gram-positive cocci (similar to cefotaxime), Gram-negative bacilli (enhanced activity), including P. aeruginosa (similar to ceftazidime), and some AmpC beta-lactamase-producing Enterobacteriaceae, such as Enterobacter species. When necessary, they are used with other drugs to cover anaerobes or enterococci. (25) They include Cefepime.

a.3.5. Cephalosporins 5th generation are active against Methicillin-resistant *S. aureus* (MRSA), Penicillin-resistant streptococci and Ampicillin-susceptible, and beta-lactamase-producing *Enterococcus faecalis*. Their activity against other gram-positive cocci and gram-negative bacilli is similar to that of 3rd-generation cephalosporins. (25) The 5th-generation cephalosporins are not active against Pseudomonas species. They include ceftaroline and ceftobiprole.

a.3.6. Novel cephalosporins

They are cephalosporins that are against multidrug resistance (MDR) gram-negative bacteria. They are used to treat complicated intra-abdominal and urinary tract infections and nosocomial

pneumonia and display activity against several MDR Gram-negative strains(25). They include Cefiderocol and Ceftolozane+ tazobactam,(25)

a.4. Penicillins

They include 4 classes:

a.4.1. Natural penicillins are active against gram-positive and gram-negative. They are the ones derived from *Penicillium fungi* and used first in clinical practice. (26) Are included in the class, penicillin G benzathine, Penicillin V potassium, Penicillin G benzathine/Procaine penicillin, penicillin G benzathine, penicillin G potassium, and procaine penicillin.

a.4.2. Beta-lactamase resistant or inhibitors penicillins are effective against Gram + and Gram – bacteria. They block the activity of beta-lactamase enzymes (also called beta-lactamases), preventing the degradation of beta-lactam antibiotics. Individually, they don't have a lot of antimicrobial activity. Beta-lactamases include sulbactam, tazobactam and clavulanic acid. (26)

a.4.3. Aminopenicillins are active against both gram-positive and gram-negative bacteria, and they are not destroyed by acid hydrolysis, making them suitable for oral administration. They are, however, sensitive to beta-lactamase hydrolysis and are consequently sometimes combined with beta-lactamase inhibitors. Amoxicillin and ampicillin are two of them. (28)

a.4.4. Antipseudomonal penicillins are used to treat pseudomonal infections, Enterococcus, and Klebsiella. They are active against both gram-positive and gram-negative bacteria. Like other penicillins, they are usually susceptible to hydrolysis by beta-lactamases and are given with beta-lactamase inhibitors. They are not consistently active against Staphylococcus, some gram-negative rods, and certain beta-lactamase-producing gram-negative anaerobes. Combination of antipseudomonal penicillins with aminoglycosides produce a synergic effect and prevent development of resistant strains of bacteria. (26) Antipseudomonal penicillins include piperacillin, ticarcillin and carbenicillin.

b. Sulfonamides

Prontosil, a sulfonamide, was the first commercially available antibiotic, developed in 1932. Thereafter, a big number of broad-spectrum sulfonamide antibiotics were developed acting on both Gram-positive and Gram-negative bacteria. (22) They act by inhibiting the bacterial synthesis of the B vitamin folate, thus preventing the growth and reproduction of the bacteria.

Nowadays they are rarely used as they present as subject to hepatotoxicity and development of bacterial resistance. (22) They include sulfadiazine and Sulfamethoxazole/Trimethoprim. (27)

c. Aminoglycosides

Aminoglycosides prevent bacteria from synthesizing proteins, resulting in cell death. They are only effective against certain Gram-negative bacteria and some Gram-positive bacteria. They should be injected to be absorbed. Streptomycin was the first medicine found to be useful in the treatment of tuberculosis; however, due to aminoglycoside toxicity, their use is currently limited.(22) Aminoglycosides include also kanamycin, amikacin, gentamycin and tobramycin.

d. Tetracyclines

Tetracyclines are antibiotics with a broad spectrum of activity against Gram-positive and Gram-negative bacteria. They, like sulfonamides, block protein synthesis, preventing bacteria from growing and reproducing. Due to the increase of bacterial resistance, their use is decreasing. However, they still find use in treatment of chlamydia infections, urinary tract, and respiratory tract infections and in the treatment of acne. Tetracyclines should be taken in empty stomach, often two hours before or after meal as they bind with food reducing their absorption. (22) Only doxycycline and minocycline are not affected. (28) Tetracyclines include also tetracycline.

e. Chloramphenicol

Chloramphenicol, a broad-spectrum antibiotic, works by blocking protein synthesis, and consequently bacterial growth and reproduction. It is also bactericidal against a limited number of bacteria. (22) Its use is restricted because it inhibits the production of blood cells in bone marrow, resulting in a significant reduction in the number of blood cells (blood cell counts), which can be irreversible and fatal in some people. As a result, this drug is only used when no other options are available. (31) Thiamphenicol and chloramphenicol and are two of them.

f. Macrolides

The macrolides, like the beta-lactams, are mostly effective against Gram-positive bacteria; however, they function in a bacteriostatic way, blocking protein synthesis and so stopping growth and reproduction. They have a little broader spectrum of activity than penicillins, and

they are effective against a number of bacteria that penicillins are not (24). They include erythromycin and azithromycin.

g. Glycopeptides

Vancomycin is one of glycopeptides that is widely used as a "drug of last resort" when other antibiotics have failed (24). Glucopeptides are used to treat infections caused by multi-resistant Staphylococcus aureus (MRSA) and enterococcus infections resistant to beta-lactams and other antibiotics. They are also used when people are allergic to beta-lactams (32).

h. Oxazolidinones

Oxazolidinones are antibacterial that inhibit protein synthesis and thereby growth and reproduction in Gram-positive bacteria. Although cycloserine has been used as a second-line tuberculosis treatment since 1956, linezolid was the first marketed antibiotic in the family. Linezolid is expensive and not usually used even if resistance seems to be developing relatively slowly since its introduction (24).

i. Ansamycins

Ansamycins are antibiotics effective against Gram-positive as well as Gram-negative bacteria. They prevent the production of RNA, which plays a key biological role inside the bacteria's cells, and therefore cause the bacteria's cells to die (24). They are used to treat tuberculosis and leprosy. Ansamycins can also have antiviral properties, which itself is uncommon (24). They include, rifabutin, rifamycins, rifapentine, rifampicin, and rifampicin.

j. Quinolones

Quinolones are bactericidal antimicrobials which interfere with the replication and transcription of DNA in bacteria cells. They are broad-spectrum antibiotics commonly used to treat urinary tract infections and other hospital-acquired illnesses where resistance to previous antibiotic classes is suspected (24). Quinolones should be used only when absolutely necessary, as resistance might develop quickly. (24) Among quinolones we have ofloxacin, nalidixic acid, levofloxacin, ciprofloxacin and norfloxacin.

k. Streptogramins

Streptogramins are used normally in combination of two antibiotics from different group within the class: streptogramin A and streptogramin B. The combination presents a synergistic impact and makes the combination able to directly kill the bacteria cell by inhibiting the synthesis of proteins, while the use of one antibiotic, only the growth inhibiting activity is observed. Streptogramins are frequently used to treat infections that are resistant to other antibiotics, although resistance to streptogramins themselves has been reported. (24)

l. Lipopeptides

Lipopeptides are the most recent class of antibiotics, having been discovered in 1987. They are bactericidal against Gram-positive bacteria (24). Daptomycin is the most commonly used of the class; it has a unique method of action that disrupts multiple elements of bacterial cell membrane making incidences of resistance to the drug to be rare – though they have been reported. Daptomycin is given as an injectable to treat skin and tissue infections (24).

m. Lincomycins

Lincomycins block translation (protein synthesis) and are active against Gram-positive and Gram-negative bacteria esp. anaerobic Bacteroides. Lincomycin derivatives are reserved for the treatment of infections due to susceptible strains of pneumococci, staphylococci, and streptococci(29). They include clindamycin and lincomycin.

n. Polypeptides

Polypeptides damage cytoplasmic membranes and inhibit steps in murein (peptidoglycan) biosynthesis and assembly, making them effective against both Gram-positive and Gram-negative bacteria (34). Bacitracin is primarily used to treat Staphylococcus infections of the skin. Colistin and polymyxin B can cause kidney damage, thus they are only used for serious infections where bacteria have developed resistance to all other antibiotics and there are no other options (34).

o. Fusidanes

Fusidanes inhibit protein synthesis and are active against gram + bacteria. Fusidic acid is one of fusidanes.

p. Nitroimidazoles

Nitroimidazoles are anaerobic Gram+ and Gram- bacterium inhibitors of DNA replication. Metronidazole is used to treat infections in the pelvis, abdomen, soft tissues, gums, and teeth, as well as abscesses in the lungs and brain. Protozoal infections are also treated with it. Tinidazole and metronidazole interfere with alcohol. (35)

q. Nitrofurans

Nitrofurans work against both gram+ and gram – bacteria by inhibiting translation (protein synthesis). Nitrofurantoin is a drug that is used to prevent or treat simple bladder infections. It should not be administered to people who have renal or red blood cell problems (36).

2.3. Usages of antibiotics.

Antimicrobial resistance has become a public health issue as we mentioned previously, and will be discussed in the following paragraph. We will also discuss when to start antibiotics, the factors that determine the susceptibility and resistance of microorganisms to antibacterial agents, antibiotic combinations, common misuses of antibiotics, and how to manage antibiotic resistance.

2.3.1. When to start antibiotherapy?

In a normal way before antibiotics prescription, it is advised that in vitro testing of sensitivity and resistance of specific infections to a wide range of antimicrobial drugs to provide adequate treatment regimens to patients .(1) The test is used to help identify which antibiotic is most likely to be effective against the infection. The testing is also recommended as antibiotic use is often linked to the selection of resistant microbes. Antibiotic resistance increases as more bacteria are exposed to them (18). Leekha and associates (13) give us some critical situations where antibiotherapy may be initiated empirically: in critically ill patients, such as those in septic shock, febrile neutropenic patients, and patients with bacterial meningitis.

2.3.2. How does antimicrobial resistance occur?

To discuss how does antimicrobial resistance occurs, we will use figures picked from the Global eLearning training materials (30). Some microbes are pre-programmed to be resistant to certain types of antimicrobials. This is known as inherent or intrinsic resistance(30). For example, Gram-negative bacteria have a cell wall covered by an outer membrane that physically blocks some antibiotics from working(30). Microbes can also acquire genes that code for resistance, known as acquired resistance, through two ways, vertical and horizontal

transmission shown in the figure below. The microbial resistance may occur at the cell level or the molecular level.

2.3.3.1. Occurrence of the antimicrobial resistance at the cellular level

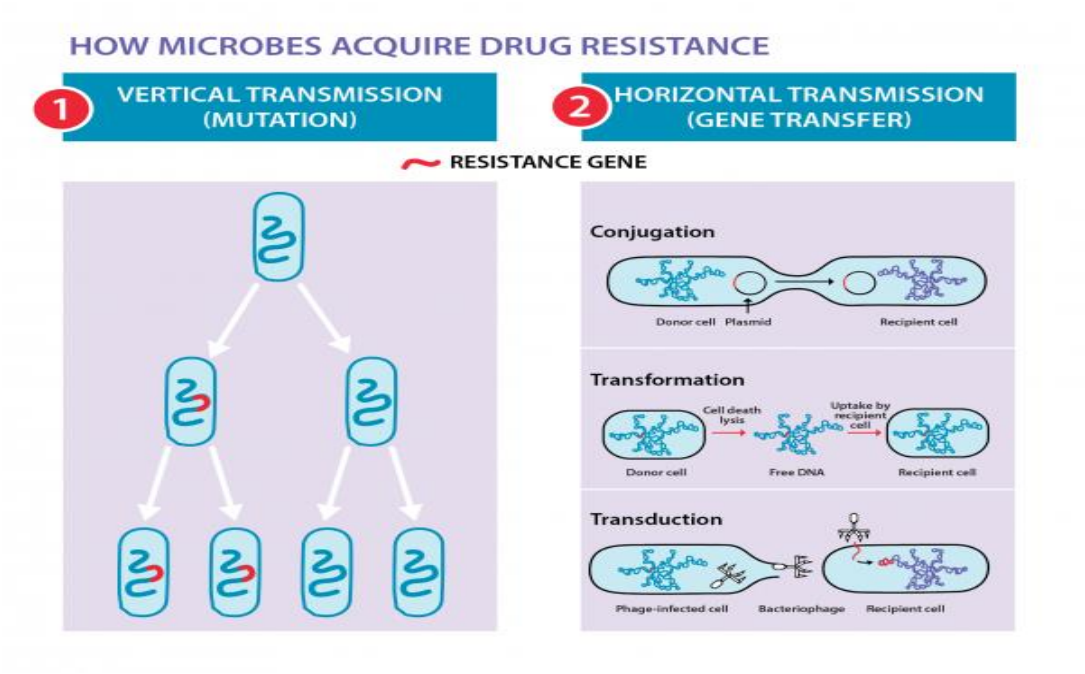


Figure 3:Microbe acquisition of drug resistance(30)

From the figure above, we have two processes: vertical transmission and horizontal transmission.

1. Vertical transmission

Vertical transmission is the spontaneous gene mutation during replication. Genetic mutations are rare spontaneous changes or errors that happen when microbes replicate(30). Occasionally, these mutations will confer a change in the microbe that helps it resist the effect of an antimicrobial. The new resistant genes are passed on to the microbe's progeny.

2. Horizontal transmission

Horizontal transmission is the exchange of genes between microbes(30). The microbes acquire resistance by a genetic material exchange between microbes via 3 different mechanisms.

a. Conjugation:

The bacteria come in direct contact with each other and small circular pieces of DNA found in the cytoplasm (plasmids) are transferred. Conjugation is the main mechanism of horizontal transmission.

b. Transformation:

The bacteria pick up bits of DNA from the external environment.

c. Transduction

IN this mechanism, there is a transfer of DNA from bacteria to specific viruses known as bacteriophages.

2.3.3.2. Occurrence of the antimicrobial resistance at the molecular level

At the molecular level, microbes have developed several key ways to resist the effects of antimicrobials(30) as shown by the figure below:

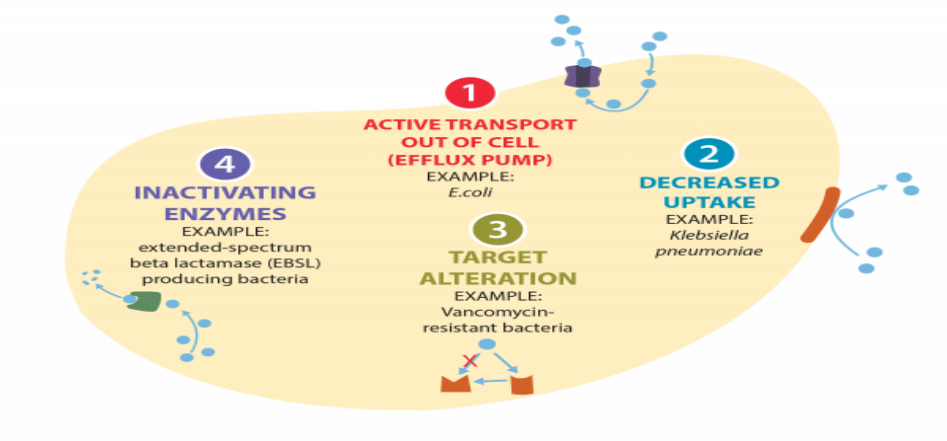


Figure 4: Microbe acquisition of drug resistance at a molecular level(30).

From the figure above, we have:

- Mechanisms 1 and 2: the microbe physically blocks or removes the antimicrobial from the cell
- Mechanism 3: the microbe alters the target site so that it is no longer recognized by the antimicrobial
- Mechanism 4: the microbe chemically modifies the antimicrobial

Microbes that acquire resistance genes, either through vertical or horizontal transmission, will survive in the presence of a specific antimicrobial while the ones without the resistance gene will die. This process is called selective pressure.

2.3.3.3. Selective pressure

The selective pressure will leave resistant microbes behind, and with no competition for growth, they will multiply and spread. Antimicrobials can create a situation where resistant microbes flourish. The following figure illustrates the selective pressure:

Figure 5: Microbe selective pressure(30).

When microbes acquire resistance genes to more than one type of antimicrobial drug, they are referred to as multidrug-resistant organisms.

2.3.4. How does antimicrobial resistance spread?

Antimicrobials are used for both human (medical) and animal (agricultural) purposes, both of which can facilitate the spread of antimicrobial resistance.

2.3.4.1. Improper use in animals

Antimicrobial products are used extensively for agricultural purposes, including the treatment and prevention of illnesses and increased growth promotion. Most antibiotics used in agriculture are also used in humans. In the United States, of the 41 antibiotics approved to use in food-producing animals, 31 are also used for humans(30).

2.3.4.2. Accumulation in the environment

Excessive and inappropriate use of antimicrobials in both humans and animals also means that these compounds are accumulating in the environment through wastewater and runoff. The impact of such an accumulation on the emergence of antibiotic resistance should not be understated. Most legislation on water quality does not include provisions to monitor the concentrations of antimicrobial-resistant microbes in sewage or treatment plants(30).

2.3.5. Factors that determine the susceptibility and resistance of microorganisms to antimicrobial agents

The minimal inhibitory concentration is used to determine susceptibility and resistance (MIC). The minimal concentration of an antibiotic required to suppress bacterial growth is known as the MIC (38). Antimicrobial therapy for an infection is ultimately determined by the MIC at the infection site. If host defenses are intact and active, a minimum inhibitory effect, such as that provided by bacteriostatic agents may be sufficient(1). On the other hand, if host defenses are impaired, antibiotic-mediated killing may be required to eradicate the infection. The author specifies that the concentration of drugs at the site of infection not only must inhibit the organism but also must remain below the level that is toxic to human cells. If this can be achieved, the microorganism is considered susceptible to the antibiotic. When an inhibitory or bactericidal concentration is higher than what can be safely achieved in vivo, the microorganism is said to be resistant to the antibiotic.(14)

2.3.6. Antibiotic combination

The combination of antibiotics is recommended only in specific cases. It is vital to understand the effects of interactions between the antibiotics to be used in order to make an appropriate combination, as they can affect the infectious agent or the host. Antibiotics acting on a variety of targets can increase or alter overall antimicrobial activity. (14) One of the effects of the interaction between antimicrobials is increased toxicity. For example, vancomycin administered alone generally has minimal nephrotoxicity while when associated with an aminoglycoside, the toxicity of aminoglycosides is increased. (1) We will assess the use of a combination of antibiotics in our study population.

For empirical therapy of an infection whose source is unclear, for the treatment of polymicrobial infections, to increase antimicrobial action (i.e., synergism) for a specific infection, and to prevent the emergence of resistance (15), a combination of antimicrobial drugs is indicated (39).

Disadvantages of Combinations of Antimicrobial Agents

Disadvantages of antimicrobial combinations include increased risk of toxicity from two or more agents, selection of multiple-drug-resistant microorganisms, eradication of normal host flora with subsequent superinfection, and increased cost to the patient. (1)·(31). Combination antimicrobial therapy should be considered for the treatment of serious Gram-negative

infections caused by Enterobacter cloacae, Pseudomonas aeruginosa, Serratia marcescens, and certain Gram-positive infections caused by Enterococcus spp. and Staphylococcus spp. (31).

2.3.7. Common misuses of antibiotics

Goodman and Gilman(1) have described some current misuses of antibiotics: treatment of nonresponsive infections, therapy of fever of unknown origin, improper dosage, inappropriate reliance on chemotherapy alone, and lack of adequate bacteriological information.

2.3.8. Use of antibiotics in special conditions

The management of antibiotics in some cases needs special considerations that Leekha S. and associates (13) describe some: antimicrobial therapy for the foreign body–associated infections (implants and prosthetic devices such as catheters and joint prostheses), use of antimicrobial agents as a prophylactic or suppressive therapy (pre-surgical antimicrobial prophylaxis, antimicrobial prophylaxis in immunocompromised patients, antimicrobial prophylaxis to prevent transmission of communicable pathogens to susceptible contacts and traumatic injuries with a high probability of infectious complications).

2.4. Management of antibiotic resistance

The use of antibiotics is associated with antibiotics resistance as discussed in the section on the occurrence of antibiotic resistance. In this section, strategies for the safe use of antibiotics will be discussed. A global report on antimicrobial resistance by WHO, published in April 2014, indicates alarmingly high rates of resistance in the bacteria which cause common infections in healthcare facilities as well as in the community(14). For the safe use of antibiotics, WHO made strategies for their safe management(32). In health facility settings, the strategies were formulated based on education (education of patients, community, prescribers, and dispensers), management of guidelines and formularies, link professional registration requirements for prescribers and dispensers to requirements for training and continuing education, the establishment of effective infection control and drug and therapeutic committees, availability of effective diagnostic facilities and control/monitor pharmaceutical company promotional activities within the hospital environment. Later, the WHO made a classification of antibiotics into three stewardship groups(33): access, watch, and reserve, to emphasize the importance of their optimal uses and potential for antimicrobial resistance. The access group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while also showing lower resistance potential than antibiotics in the other

groups(34). They are used as first- or second-choice empiric treatment options for specified infectious syndromes. The watch group includes antibiotics that have higher resistance potential and they are at relatively high risk of selection of bacterial resistance(34). Antibiotics in the Watch group should be prioritized as key targets of stewardship programs and monitoring. They are used as first- or second-choice empiric treatment options for specified infectious syndromes. The reserve group includes antibiotics and antibiotic classes that should be reserved for the treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Antibiotics in the reserve group should be used by specific patients and settings when all alternatives have failed or are not suitable. They should be accessible but controlled, involving monitoring and utilization reporting to preserve their effectiveness. (34) The study done by Masoko Ntšekhe and associates (16) shows that antibiotic resistance is an inevitable problem. The more microorganisms are exposed to antibiotics; the more resistance emerges. Rationalizing and managing prescribing patterns of antibiotics is one way that the process can be slowed(16) by using approaches that have been proven to work(16) which are the following:

Use of and Adherence to STGs: Studies have shown that when STGs are used and adhered to, resistant microorganisms decline in numbers(16). According to the same source, STGs work well when relevant stakeholders are involved and committed. DTCs have an important role to play by providing support and mentorship to the prescribing doctors. They need to educate them and make the STGs available. There also has to be consistent monitoring of adherence to STGs as this also reduces the hospital costs related to pharmaceuticals(16).

Formulary Restrictions*:* limit access to certain antibiotics, especially broad-spectrum antibiotics. Only a certain category of doctors should be allowed to prescribe those antibiotics that are controlled(16). The DTC should play a role by making restrictions and monitoring the adherence to the restrictions.

Antibiotic Rotation: this means that a medicine or a class of antibiotics is withdrawn for a specified period and then reintroduced again later, resulting in a continuous, successive alteration in antibiotic selection pressures(16). The rotation can be done between two classes of antibiotics with different mechanisms of action.

As seen above, the use and adherence to STGs and the role of DTC are key in the rational use of medicine and especially in the containment of antibiotic resistance. This brought us to assess the compliance to STGs and the awareness of the availability of STGs by medical doctors and their degree of satisfaction with the functionality of DTCs in our study population.

2.5. Conclusion

Appropriate use of antimicrobial agents involves obtaining an accurate diagnosis, determining the need for and timing of antimicrobial therapy, understanding how dosing affects the antimicrobial activities of different agents, tailoring treatment to host characteristics, using the narrowest spectrum and shortest duration of therapy, and switching to oral agents as soon as possible. Also, non-antimicrobial interventions, such as abscess drainage, are equally or more important in some cases and should be pursued diligently in comprehensive infectious disease management. The use and adherence to STGs to reduce the resistance of microorganisms to antibiotics. DTCs have a role to play by providing support and mentorship to the prescribing doctors.

CHAPTER THREE: METHODOLOGY

3.1. Type of study (study design)

We have described retrospectively the antibiotic prescribing practices in University Teaching Hospitals in Rwanda. The study aimed at obtaining data on antibiotic prescription patterns at University Teaching Hospitals in Rwanda and establishing whether there was awareness and adherence to standards treatment guidelines.

3.2.Location of the study

The study was conducted at University Teaching Hospitals in Rwanda including two hospitals, the University Teaching Hospitals of Butare (CHUB) and the University Teaching Hospitals of Kigali (CHUK). The CHUB is located at Mamba, village, Butare Cell, Huye District in the Southern Province of Rwanda. It is a National Referral Teaching Hospital which serves the Southern Province's populations and others from some Districts of Western Province. According to the last assessment of the population carried out in 2012, the total population to be served by CHUB is more than 3,772,230 people. The CHUK is the largest hospital located in the District of Nyarugenge at KN 4 Ave, Kigali City. It is also the biggest referral hospital in the country with a capacity of 519 beds. The two hospitals host both undergraduate and postgraduate programs. These hospitals were chosen for the study as the potential targets for quality improvement may have a positive impact on the education of health professionals and the patients would benefit from rational antibiotic use at a large scale.

The inpatient department includes internal Medicine, Pediatrics (which includes neonatology which was considered separately for its population), Surgery, Anesthesiology and Critical care, and Gynecology and Obstetrics. All departments were included in the study. This was necessary to identify the patterns of antibiotic prescription in various departments.

3.3.Study population.

The study population is, on one hand, patients admitted from July 1, 2019, to December 31, 2019, at CHUB and CHUK who received antibiotics. On the other hand, Medical Doctors working in admitting departments constitute our study population for the questions directed to Medical Doctors. The research was conducted on all inpatient departments within the hospitals.

3.4.Inclusion and exclusion criteria

3.4.1. Inclusion criteria

The medical records of inpatients admitted from July to December 2019 on antibiotics were reviewed for the study. All inpatients' wards within the hospitals were included. Medical doctors prescribing antibiotics for inpatients responded to questionnaires.

3.4.2. Exclusion criteria

Outpatients and daytime admission for ambulatory patients for procedures such as endoscopy or renal dialysis were excluded from the study. Patients admitted to accident and emergency departments were also excluded. Antiretroviral drugs used for HIV and the antituberculosis drug were excluded as frequently used in high numbers for long periods and frequently followed separately. The ones included in the data were the ones administered with other antibiotics to check for drug interactions. Antifungal products were also excluded. Incomplete files were excluded. Medical Doctors not prescribing antibiotics to inpatients were excluded from the study.

3.5.Sampling

3.5.1. Sample size calculation

Calculation of patient's files

As a prevalence study, to have the number of files to be used, we used Fischer's formula (35) to calculate the number of files.

$n = Z^2 p(1-p) / d^2$

Where the following represents:

n: sample size,

Z: statistic corresponding to the level of confidence,

P: expected prevalence

d: precision (corresponding to effect size). Considering the confidence interval of 95% and assuming that the prevalence is 80 %, a total of 384 patient files was required. We collected data from 412 patients' files.

Number of prescribers

In CHUB, the number of Medical Doctors actively prescribing antibiotics is 54 and in CHUK is 84. We planned to have the questionnaire be filled by at least 50% of the total population.

3.5.2. Sampling technique

The sample calculated for our study is 384 for the two hospitals.

Patients' files

The patient's files were selected randomly within the hospitals, departments, and wards. The sample calculated for our study was 384. The minimum number of files was 192 per hospital as we had two hospitals (192 divided by 2). Patient files were collected from five clinical departments with a minimum of 38 files (192/5). A minimum of 38 files were taken from all units of the departments equally were possible. See table 1.

Table 1: Patient's files sample

Ward/department	Name of hospital		
	CHUB	CHUK	Total
	N	n	N
GYN&OBS	33	36	69
ICU	28	36	64
IM	35	43	78
NEONATOLOGY	10	10	20
PEDIATRICS	41	35	76
SURGERY	64	42	106
Total	211	202	413

GYN&OBS: gynecology and obstetrics

ICU: intensive care unit

IM: internal medicine

Medical doctors

The questionnaire was randomly filled by 83 prescribers representing 60.1% of the total number of prescribers from all clinical departments and each department was represented at least by 10% of its prescribers.

3.6. Participant recruitment

Patient' files

The sample population was obtained from all patients who received antibiotics. A random sample was obtained from electronic software which manages patients in CHUK (Openclinc), and from patients' files in archives in CHUB. Relevant information was collected from the medical records of only those patients who received antibiotics. From the open clinic, we could find all patients who received antibiotics during the study period by the department and by ward. The files were selected randomly and the hospital patient's identification numbers were used to retrieve the files in the hospital archives. In CHUB archives, patients' files are kept by

date and by the department. Within the study period, we selected patients' files randomly, and only files of patients who received antibiotics were retained.

Medical doctors

Questionnaires were given to 80% of medical doctors of all departments but only 60% were received filled. At least every department had 10% of filled questionnaires as it was in covid 19 pandemic, we could not meet our expectations of 50% of filled questionnaires by departments.

3.7.Research instruments

Two data collection forms and a questionnaire were used. Data collections used in a study done in Lesotho(16) were adapted for our study in teaching hospitals in Rwanda. One data collection form, ''the data collection sheet'', contained details such as the patient demographic characteristics, history of present illness, presenting symptoms, medication prescribed previously, and the present provisional diagnosis. The data collection sheet on appendix 1 also contained the list of medicines (with details on strength, frequency, dosages, duration, and route of administration), number of antibiotics prescribed by generic name, microbiological and sensitivity tests requested, specimens sent to the lab for microbiological tests, availability of provisional results of culture sensitivity test, availability of final results of culture sensitivity test, change of antibiotic prescription with provisional or final results and other untreated medical conditions for the patient. The data collection form was filled only for patients on antibiotics. The Medicine Therapy Assessment Worksheet, the second data collection form contained the summarized information on the data collection to facilitate the data entry and the analysis. The questionnaire was filled by medical Doctors. It contains details on the existence of DTC in the hospital and how it was active, the existence of STGs in consultation rooms, consultation of STGs before prescription of antibiotics, and the need for improvement of antibiotic prescriptions in the hospital.

3.8.Study validity

Validity refers to how a test or research instrument measures what is supposed to measure. This was achieved by piloting the research instruments under the same procedures as in the main study. The piloting helped to identify internal inconsistencies in the research instruments that were likely to introduce measurement bias. Other possible threats to internal validity included

information bias. This was avoided by prior training of data collectors on the research instruments and the data collection techniques.

3.9.Data collection technique

Data collection was performed using the data collection sheet and the questionnaire (see appendix1 and 2 in English and Kinyarwanda). The Medicine Therapy Assessment Worksheet was filled with information from the data collection sheet (see appendix 3 in English and Kinyarwanda). It contained information on the correlation between medicine therapy and medical problem, antibiotherapy regimen, therapeutic duplication, interactions, and laboratory information. The source of information for completing the data collection sheet was from a review of patient's files. All patients' wards participated in the study and all medical doctors working in admitting departments were included in the study. The departments were grouped into internal Medicine, Pediatrics, Surgery, Anesthesiology and Critical care, and Gynecology and Obstetrics.

3.10. Data management

Independent variables

These included the patient demographic characteristics such as age, sex, and diagnosis.

Dependent variables

They compromised the type of antibiotics prescribed (with details on strength, frequency, dosages, duration, and route of administration), the number of antibiotics prescribed by generic name, microbiological and sensitivity tests requested, specimens sent to the lab for microbiological tests, availability of provisional results of culture sensitivity test, availability of final results of culture sensitivity test, change of antibiotic prescription with provisional or final results and other untreated medical conditions for the patient.

3.11. Data analysis and presentation

The study sought to answer some questions relating to antibiotic prescribing patterns at University Teaching Hospitals in Rwanda, data was collected and used to identify the prescribing patterns within the hospitals.

The use of antibiotics was compared to the use of other medications. Since this study only enrolled patients who had been prescribed antibiotics, we assessed the relative use of antibiotics as a total of all prescribed medicines by determining the number of antibiotics prescribed as a percentage of the total number of medicines prescribed for the same encounters.

The average number of antibiotics prescribed to patients was calculated as well details on class and antibiotics most prescribed.

Quality indicators of antibiotics prescriptions were assessed. We assessed the completeness of prescriptions, antibiotic prescriptions consistent with the drug formularies, and prescriptions by generic names using hospital lists provided by pharmacists, potential drug-drug interactions, duplication of antibiotics, prescriptions following STGs, and use of microbiological and sensitivity tests. To check the completeness of antibiotic prescriptions we recorded for each antibiotic prescribed details on strength, frequency, dosages, duration, and route of administration. Depending on the design of the patient file we could find a clear start date and end date while in other files we could not find them. For this case, we considered the start date as the date on which the antibiotics were prescribed.

Potential drug-drug interactions and antibiotic duplications were checked using an online checker on the website ‘’www.drugs.com/interactions-check.php’’. The potential interactions identified include interactions between antibiotics, interactions between antibiotics with other medications prescribed to the patients, and interactions between other medications prescribed to the patients. The interactions were classified by severity, major, moderate, and minor. The high level of severity was considered in case of the possibility of multiple types of interactions.

During this assessment, adherence to the national STGs was measured per prescription.

Measuring adherence to the guidelines is an important indicator of the rational use of medications. Various guidelines were used to assess adherence to STGs. Priority was given to national guidelines and when there were not available, WHO guidelines were used, and then other available international STGs. Some guidelines stipulate the use of specific antibiotics; others stipulate the use of antibiotics without specificity. When the guideline did not specify the antibiotic to be used, a broad-spectrum prescription was considered adequate.

Empirical therapy for infection uses most of the time combination of antibiotics or broad coverage antibiotics to ensure that the regimen includes an agent that is active against the potential pathogen. Microbiological and sensitivity tests should be performed as soon as possible to identify the responsible pathogen of the infection and use selective antibiotics. We checked microbiological and sensitivity tests requested specimens sent to the lab for microbiological tests, availability of provisional results of culture sensitivity tests, availability

of final results of culture sensitivity tests, and prescriptions that changed with provisional or final results.

The existence of DTCs in the hospital, the availability of STGs in consultations rooms, and the need for antibiotic prescriptions improvement helped to assess the awareness of the medical doctors on STGs.

The prescriptions patterns and outcome variables were discussed by demographic characteristics, by the hospital and wards.

Results were presented in the form of pie charts, tables, and graphs. SPSS V.21 and Microsoft Excel were used for data analysis and presentation.

3.12. Logistics and ethical consideration

Ethical approval was obtained from the College of Medicine and Health Sciences ethical committee reference number 136/CMHS IRB/2020. Further approval was obtained from CHUB and CHUK, references respectively RC/UTHB/011/2020 and EC/CHUK/058/2020. Before commencement of the study. Confidentiality of the data was highly regarded. The data were collected in a secured (with access limitations) area in hospital archives. The hardcopy records were kept in a locked area. The electronic records were password protected accessible only by the principal investigator. Before data collection, consent forms were signed by the participants/medical doctors (see appendix 4: consent forms in English and Kinyarwanda).

CHAPTER FOUR: RESULTS

4.1. Clinical and demographic characteristics of participants

4.1.1. Demographic characteristics of the study population

1. Distribution of the study population by ward, gender, and hospital

The study was conducted among 413 patients. Apart from the department of gynecology and obstetrics department where all patients are females, the surgery department had more males than females in both hospitals. In CHUB we had 43 males against 21 females while in CHUK we had 32 males against 21 females. (See figure 6).

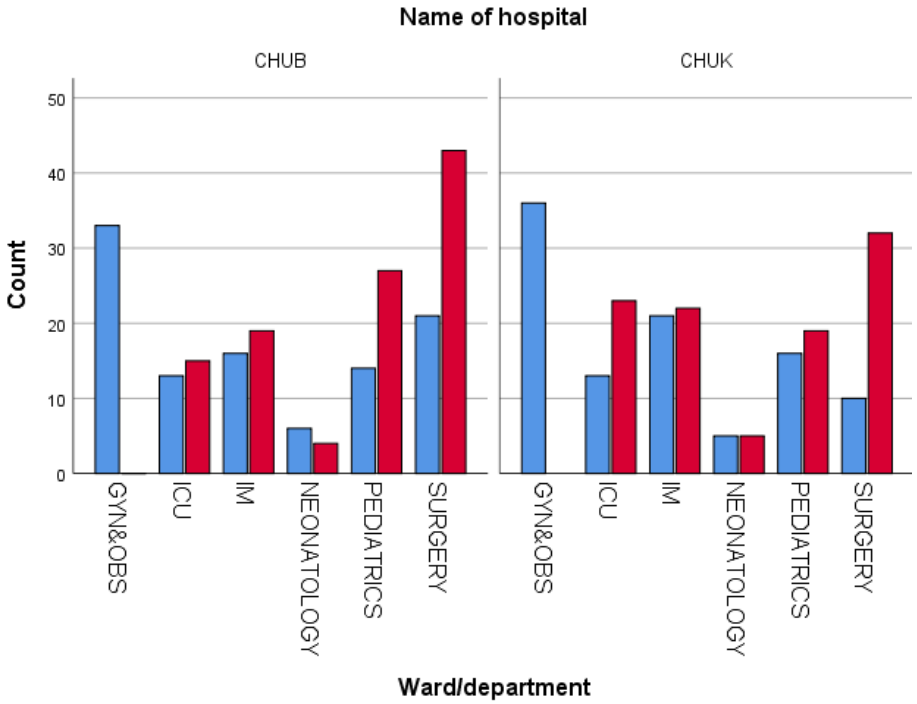


Figure 6 Distribution of participants per gender, ward, and hospital

2. **Distribution of participants per age group, ward, and hospital**

In CHUB, we found that in gynecology and obstetrics the large population was in the age group from 16 to 35years, 2 patients and 8 other patients were in the age group from 36 to 65 years while in pediatrics, 35 patients were in the age group from 0 to 5 years, 1 patient in 16 to 35 years and 5 patients in 6- 15 years. In CHUK, in gynecology and obstetrics, 27 patients were in the age group from 16 to 35 years and 9 patients in the age group from 36 to 65 years while in surgery, 4 patients were in the age group from 0 to 5 years, 2 patients in 6-15 years, 19 patients in 16 to 35 years, 13 patients in 36 to 65 years and 4 patients in the age group from 66 years and above. (See figure 7).

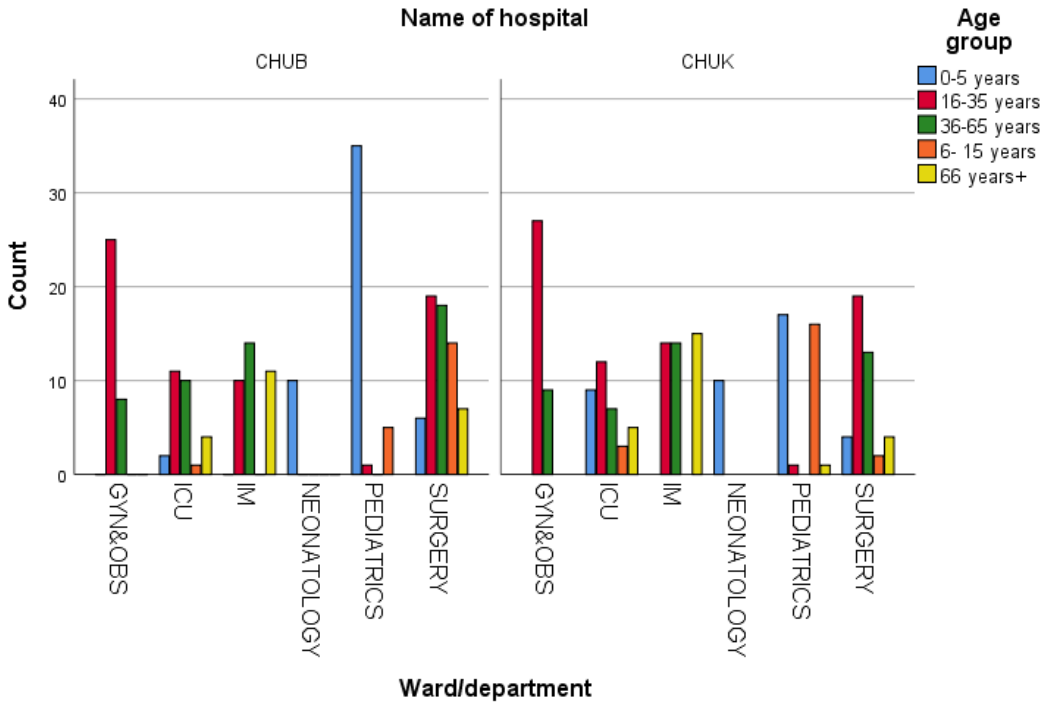


Figure 7: Distribution of participants by age group, ward, and hospital

IM: internal medicine
ICU: Intensive care unit
GYN&OBS: gynecology and obstetrics

4.1. 2. Clinical characteristics of participants

1. Overall indications for antibiotics

The antibiotics were given to patients in our study population for different diagnoses and the most frequent are presented in table 2. The most frequent indication was sepsis followed respectively by injury and abscess. More sepsis diagnosis was found in CHUB (65.7%), more injuries were found in CHUK (63.6%) and more abscesses were found in CHUB (59.1%).

Table 2: Indication of antibiotic use per hospital

Diagnosis	Name of hospital					
	CHUB		CHUK		Total	
	N	%	N	%	N	%
Abscess	**13**	**59.1**	**9**	**40.9**	**22**	**100**
Adenotonsilar hypertrophy	7	100	0	0	7	100
Burn	2	33.3	4	66.7	6	100
C-section	9	50	9	50	18	100
Cardiopathy	3	60	2	40	5	100
Cellulitis	5	71.4	2	28.6	7	100
Gastric cancer	5	100	0	0	5	100
Gastroenteritis	4	50	4	50	8	100
Hemorrhage	6	54.5	5	45.5	11	100
Injury	**12**	**36.4**	**21**	**63.6**	**33**	**100**
Ischemic encephalopathy	1	50	1	50	2	100
Meningitis	8	57.1	6	42.9	14	100
Neonatal infection	13	81.3	3	18.8	16	100
Peritonitis	4	33.3	8	66.7	12	100
Pneumonia	11	55	9	45	20	100
Pulmonary TB	0	0	5	100	5	100
Respiratory distress	2	28.6	5	71.4	7	100
Rupture of membrane	10	90.9	1	9.1	11	100
Sepsis	**23**	**65.7**	**12**	**34.3**	**35**	100
Urinary tract infection	4	36.4	7	63.6	11	100
Others	69	43.7	89	56.3	158	100
Total	211	51.1	202	48.9	413	100

2. Indication for antibiotic use in the study population per ward

Inside the department/ward, the indications for antibiotic use are presented in table 3. The ICU and Pediatrics had a high rate of sepsis (37.1% each) followed by IM (14.3%). Injuries were

most frequent in surgery (69.7%) and ICU (24.2%) and abscesses were most frequent in surgical (40.9%) and IM (22.7%).

Table 3: Indication for antibiotic use per ward

Diagnosis	Ward/department													
	GYN&OBS		ICU		IM		NEONATOLOGY		PEDIATRICS		SURGERY		Total	
	n	%	n	%	n	%	n	%	N	%	N	%	N	%
Abscess	4	18.2	1	4.5	5	**22.7**	0	0	3	13.6	9	**40.9**	22	100
Adenotonsilar hypertrophy	0	0	0	0	0	0	0	0	0	0	7	100	7	100
Burn	0	0	2	33.3	0	0	0	0	0	0	4	66.7	6	100
C-section	18	100	0	0	0	0	0	0	0	0	0	0	18	100
Cardiopathy	1	20	2	40	1	20	0	0	0	0	1	20	5	100
Cellulitis	1	14.3	1	14.3	1	14.3	0	0	1	14.3	3	42.9	7	100
Gastric cancer	0	0	0	0	4	80	0	0	0	0	1	20	5	100
Gastroenteritis	0	0	0	0	3	37.5	0	0	3	37.5	2	25	8	100
Hemorrhage	6	54.5	1	9.1	1	9.1	0	0	0	0	3	27.3	11	100
Injury	0	0	8	**24.2**	1	3	0	0	1	3	23	**69.7**	33	100
Ischemic encephalopathy	0	0	0	0	0	0	1	50	1	50	0	0	2	100
Meningitis	0	0	1	7.1	7	50	0	0	5	35.7	1	7.1	14	100
Neonatal infection	0	0	1	6.3	0	0	5	31	10	63	0	0	16	100
Peritonitis	4	33	6	50	0	0	0	0	0	0	2	17	12	100
Pneumonia	0	0	8	40	5	25	1	5	5	25	1	5	20	100
Pulmonary TB	0	0	0	0	4	80	0	0	1	20	0	0	5	100
Respiratory distress	0	0	1	14	0	0	6	86	0	0	0	0	7	100
Rupture of membrane	9	82	0	0	0	0	0	0	1	9.1	1	9.1	11	100
Sepsis	2	5.7	13	**37**	5	**14**	1	2.9	13	**37**	1	2.9	35	100
Urinary tract infection	2	18	0	0	6	55	0	0	2	18	1	9.1	11	100
Others	22	14	19	12	35	22	6	3.8	30	19	46	29	158	100
Total	69	17	64	16	78	19	20	4.8	76	18	106	26	413	100

4.2. Antibiotic prescription patterns at University Teaching Hospitals in Rwanda

4.2.1. Use of antibiotics compared to other medications

A total number of 895 antibiotics were prescribed to patients in CHUB and CHUK. A large number of 324 patients have prescribed 2 antibiotics while 7 patients were prescribed 7 antibiotics. In CHUB patients were prescribed from one to 7 antibiotics with a large number of patients who received 2 antibiotics (166 patients out of 211) while in CHUK, patients were prescribed up to six antibiotics. The majority (158 patients out of 202 patients) also received 2 antibiotics. See table 4.

Table 4: Number of antibiotics prescribed to the patients per hospital

Number of antibiotics prescribed to patients	Name of hospital					
	CHUB		CHUK		All	
	Number of patients	Total number of antibiotics prescribed to patients	Number of patients	Total number of antibiotics prescribed to patients	Number of patients	Total number of antibiotics prescribed to patients
1	80	80	45	45	125	125
2	83	166	79	158	162	324
3	31	93	43	129	74	222
4	14	56	26	104	40	160
5	2	10	7	35	9	45
6	0	0	2	12	2	12
7	1	7	0	0	1	7
Total	211	412	202	483	413	895

Patients were also prescribed other medications from one to twelve other medications with antibiotics in CHUB and from one to seven in CHUK. A total number of 551 other medications were prescribed in CHUB and 561 in CHUK. See table 6. An overall of 2007 drugs prescribed to patients, 44.6% were antibiotics (895). By hospital, in CHUB, out of 963 medications prescribed, 412 were antibiotics equivalent to 42.8%, and in CHUK, out of 1044 medications prescribed to patients, 483 were antibiotics (46.3%). Patients who received only antibiotics without any other medications are 31 (20 in CHUB and 11 in CHUK). See table 6.

Table 5: Other medications prescribed to patients with antibiotics per hospital

Number of other drugs prescribed with antibiotics	Name of hospital					
	CHUB		CHUK		Total	
	Number of patients	Total number of antibiotics prescribed to patients	Number of patients	Total number of antibiotics prescribed to patients	Number of patients	Total number of antibiotics prescribed to patients
1	40	40	36	36	76	76
2	58	116	49	98	107	214
3	52	156	44	132	96	288
4	12	48	29	116	41	164
5	16	80	23	115	39	195
6	1	6	6	36	7	42
7	3	21	4	28	7	49
8	4	32	0	0	4	32
9	2	18	0	0	2	18
10	0	0	0	0	0	0
11	2	22	0	0	2	22
12	1	12	0	0	1	12
n/a	20	0	11	0	31	0
Total	211	551	202	561	413	1112

n/a: Number of patients who did not receive other medications with antibiotics (only antibiotics)

4.2.2. Number of antibiotics prescribed per prescription

1. Number of antibiotics per prescription

In general, 30.27 % of the patients were prescribed one antibiotic, 39.23% were prescribed two antibiotics, 17.92% were prescribed 3 antibiotics and 9.69% were prescribed 4 antibiotics. Other patients were prescribed more than four antibiotics. See figure 8. The average number of antibiotics prescribed to patients was 2.17 with a standard deviation of 1.086.

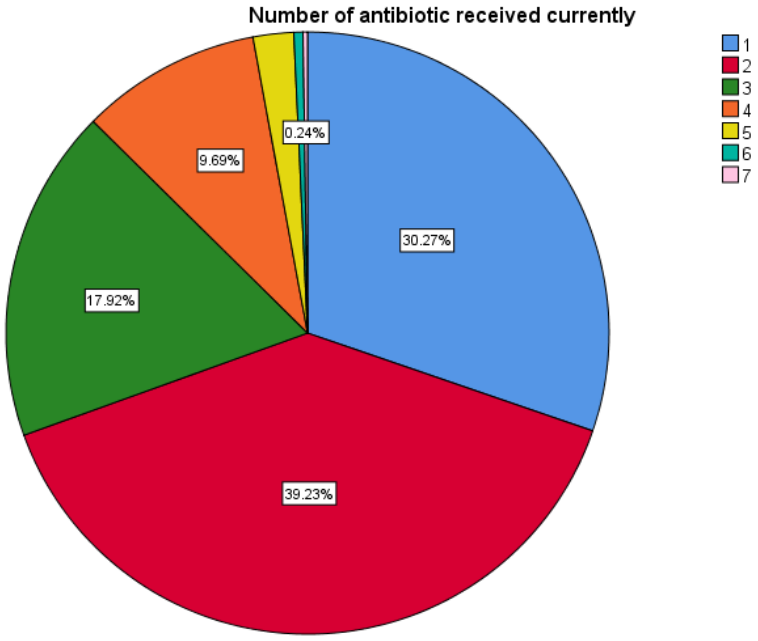


Figure 8: Overall number of antibiotics prescribed

2. Number of antibiotics per prescription per hospital

In general, fewer antibiotics were prescribed in CHUB than CHUK. Almost 40% of patients in CHUB were prescribed one antibiotic while in CHUK less than 25% received one antibiotic. Patients who received two antibiotics were quite similar for the two antibiotics (almost 40%). See figure 9.

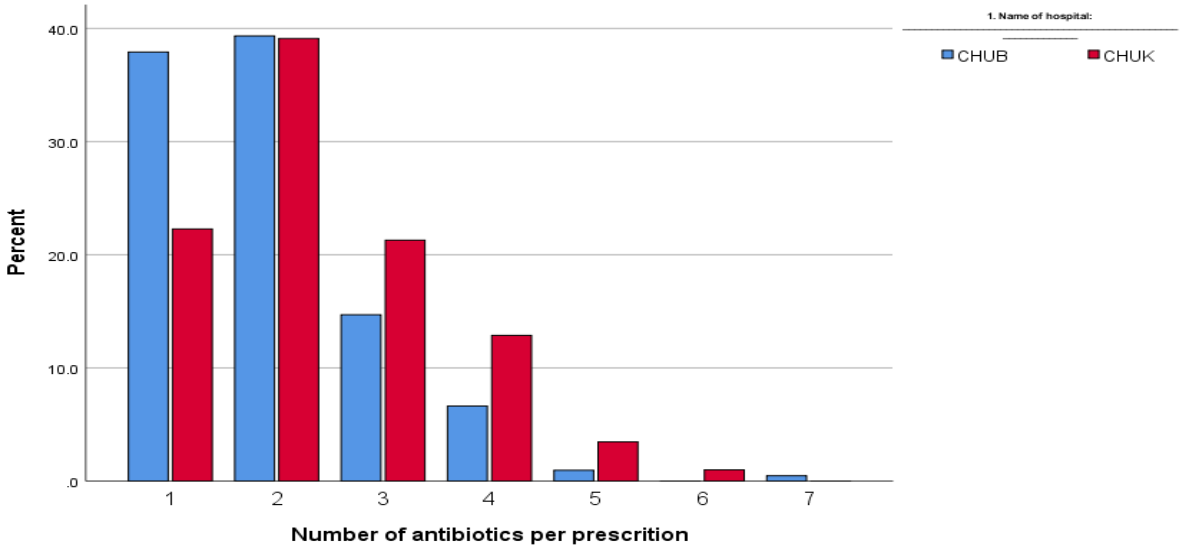


Figure 9: Number of antibiotics per prescription and per hospital

3. Number of antibiotics prescribed per prescription per wards

Among the patients who received one antibiotic, the surgery department comes at the first line with almost 50% followed by Gynecology and obstetrics and neonatology comes in the last

line. For the patients who received two antibiotics, representing the big portion of patients, neonatology comes at the first line with 60% followed by pediatrics. See figure 10.

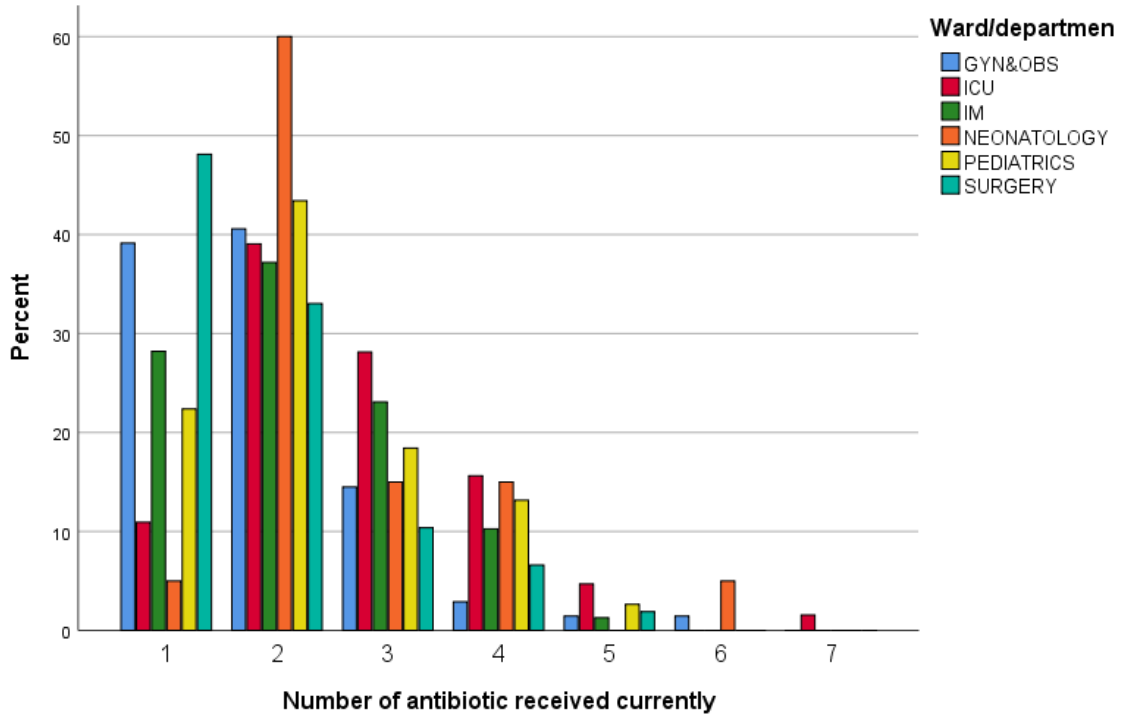


Figure 10: Number of antibiotics per prescription per wards

4.2.3. Specific antibiotics most prescribed to patients

1. Specific antibiotics most prescribed per hospital

Ceftriaxone is the most prescribed antibiotic (22.7%) followed by metronidazole (14.7%), then cefotaxime (13.1%), cloxacillin (7.9%), ampicillin (5.8%), ciprofloxacin (5%), doxycycline (4.8%), meropenem (4.6%), gentamicin (3.8%) and vancomycin (2.9%). Other antibiotics had the least proportion of prescribing. (Table 5).

Table 6: Specific most prescribed antibiotics per hospital

Antibiotics	Name of hospital					
	CHUB		CHUK		All	
	n	%	n	%	N	%
Ceftriaxone	107	26	96	19.9	203	22.7
Metronidazole	64	15.5	68	14.1	132	14.7
Cefotaxime	52	12.6	68	14.1	120	13.4
Cloxacillin	31	7.5	40	8.3	71	7.9
Ampicillin	34	8.3	18	3.7	52	5.8
Ciprofloxacin	11	2.7	37	7.7	48	5.4
Doxycycline	15	3.6	28	5.8	43	4.8
Meropenem	19	4.6	22	4.6	41	4.6
Gentamicin	5	1.2	27	5.6	32	3.6
Vancomycin	12	2.9	14	2.9	26	2.9
Others	62	15	65	13.5	127	14.2

2. Specific antibiotics most prescribed per wards

In general, the most prescribed antibiotics per ward were ceftriaxone (22.7%) and metronidazole (14.7%) except in pediatrics and neonatology where the most prescribed were cefotaxime (29.1%) and cloxacillin (14.3%) in pediatrics and ampicillin (34.6%) and cefotaxime (26.9%) in neonatology. Ceftriaxone was prescribed at 28.6% in gynecology and obstetrics, 21.5% in ICU, 29.8% in IM, and 31.3% in surgery. Metronidazole was prescribed at 26.3% in gynecology and obstetrics, 17.4% in ICU, 16.4% in IM, and 16.4% in surgery. See table 6.

Table 7: Antibiotics prescribed to patients by ward

Antibiotics	Ward/ department													
	GYN&OBS		ICU		IM		NEONATOLOGY		PEDIATRICS		SURGERY		Total	
	n	%	n	%	N	%	n	%	n	%	N	%	n	%
Ampicillin	8	6	2	1.2	1	0.6	18	**35**	20	11.4	3	1.6	52	5.8
Cefotaxime	9	6.8	15	8.7	16	9.4	14	**27**	51	**29**	15	7.8	120	13.4
Ceftriaxone	38	**29**	37	**22**	51	**30**	0	0	17	9.7	60	**31**	203	**23**
Ciprofloxacin	3	2.3	12	7	15	8.8	1	1.9	9	5.1	9	4.7	49	5.5
Cloxacillin	5	3.8	17	9.9	6	3.5	1	1.9	25	**14**	17	8.9	71	7.9
Doxycycline	9	6.8	6	3.5	24	14	0	0	3	1.7	1	0.5	43	4.8
Gentamicin	1	0.8	4	2.3	3	1.8	7	13.5	5	2.9	12	6.3	32	3.6
Meropenem	1	0.8	19	11	3	1.8	4	7.7	10	5.7	4	2.1	41	4.6
Metronidazole	35	**26**	30	**17**	28	**16**	1	1.9	6	3.4	32	**17**	132	**15**
Vancomycin	0	0	8	4.7	0	0	4	7.7	13	7.4	1	0.5	26	2.9
Others	24	18	22	12.8	24	14	2	3.8	16	9.1	38	19.8	126	14.1
Total	133	82	172	87.2	171	86	52	96.2	175	90.9	192	80.2	895	100

3. Specific antibiotic combinations most prescribed per prescription and hospital

The most prescribed antibiotic combination was the combination of ceftriaxone and metronidazole with 13.3% overall (17.1% for CHUB and 9.4% for CHUK) followed by the ampicillin-cefotaxime combination with 4.4% overall (CHUB: 7.6% and CHUK: 1%) and cefotaxime-cloxacillin with 2.9% in overall (2.4% in CHUB and 3.5% in CHUK). In CHUK, ceftriaxone -metronidazole combinations are followed by cefotaxime-cloxacillin. (Table 7)

Table 8: Specific antibiotic combinations prescribed per prescription and hospital

Specific Antibiotic combinations	Name of hospital					
	CHUB		CHUK		Total	
	n	%	n	%	N	%
Amoxicillin + clavulanic acid	5	2.4	0	0	5	1.2
Ampicillin, Cefotaxime	16	**7.6**	2	1	18	**4.4**
Ampicillin, Gentamicin	0	0	6	**3**	6	1.5
Cefotaxime, Cloxacillin	5	**2.4**	7	**3.5**	12	**2.9**
Cefotaxime, Doxycycline	0	0	2	1	2	0.5
Cefotaxime, Metronidazole	0	0	3	1.5	3	0.7
Ceftriaxone, Doxycycline	3	1.4	5	2.5	8	1.9
Ceftriaxone, Gentamicin	0	0	5	2.5	5	1.2
Ceftriaxone, Metronidazole	36	**17.1**	19	**9.4**	55	**13.3**
Cloxacillin, Ceftriaxone	5	2.4	1	0.5	6	1.5
Others	141	66.8	152	75.2	293	70.9
Total	211	100	202	100	413	100

4.2.4. Number of classes of antibiotics prescribed per prescription

1.Number of class of antibiotics combined per prescription

The antibiotic class combinations were wide. The range went from 2 to 5 combinations. The large portion was the combination of two classes which was 52.54 % and 14.24% of a combination of 3 classes. See figure 12.

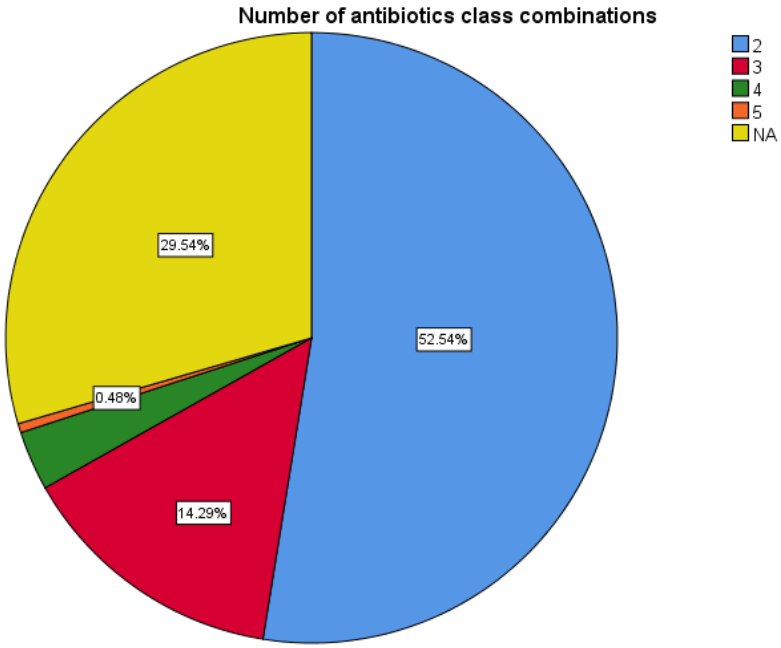


Figure 11: Number of antibiotic class combinations

NA: No class combination (single antibiotic or antibiotics from the same class)

2. Number of the class of antibiotics combined per prescription and per hospital

Figure 11 shows that among antibiotic combinations, 70% had 2 antibiotics combined (80% in CHUB and 70% in CHUK). (Figure 12)

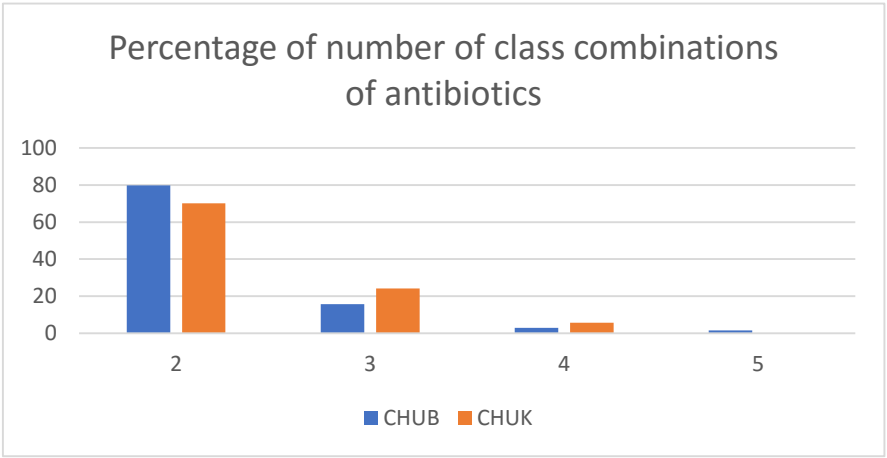


Figure 12: Number of the class of antibiotics combined per patient and per hospital

3. Number of the class of antibiotics combined per patient and per ward

A large number of prescriptions of antibiotics in Pediatrics were prescribed one class of antibiotics, almost 60%. Pediatrics is followed by Surgery in prescribing one class of antibiotics

as shown by figure 11. The same figure shows also that all wards prescribed two classes of antibiotics in a range between 30 and 50%. See figure 13.

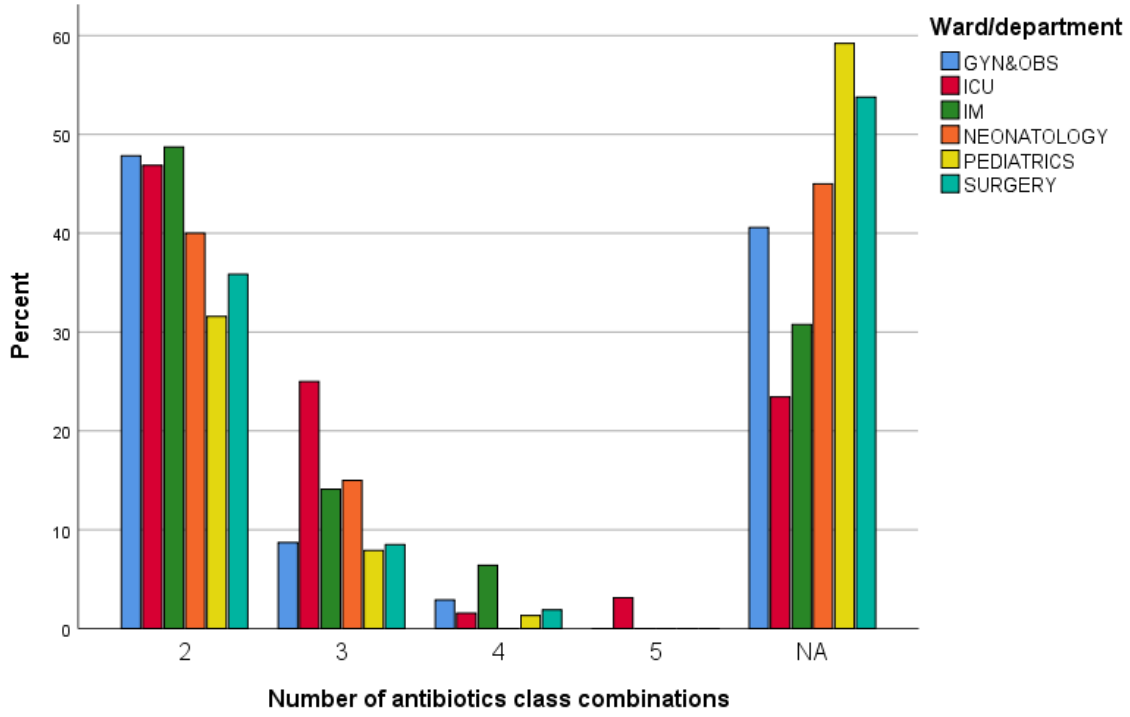


Figure 13: Number of classes combinations of antibiotics

4.2.5. Classes of antibiotics prescribed to patients

1. **Specific classes of antibiotics most prescribed to patients**

The cephalosporins 3rd generation class of antibiotics had the highest proportion of prescriptions (36.3%) followed by nitroimidazoles (14.7%) and penicillins (13.7%). Among the most prescribed, glycopeptides had the least proportion of antibiotic prescribing (2.9%). See Table 8.

Table 9: Specific classes of antibiotics most prescribed to patients

Antibiotic class	Name of hospital					
	CHUB		CHUK		Total	
	n	%	N	%	N	%
Aminoglycosides	5	1.2	27	5.6	32	3.6
Carbapenems	19	4.6	22	4.6	41	4.6
Cephalosporins 3rd generation	159	**38.6**	164	**34.0**	323	**36.1**
Glycopeptides	12	2.9	14	2.9	26	2.9
Nitroimidazoles	64	**15.5**	68	**14.1**	132	**14.7**
Penicillins	65	**15.8**	58	**12.0**	123	**13.7**
Quinolones	12	2.9	37	7.7	49	5.5
Tetracyclines	15	3.6	28	5.8	43	4.8
Others	61	14.8	65	13.5	126	14.1
Total	412	100.0	483	100.0	895	100.0

3. Specific class combinations of antibiotics most prescribed per hospital

The most prevalent class combinations of antibiotics among the most prescribed combinations of antibiotics were beta-lactams and nitroimidazoles (47.5%) followed by combinations of beta-lactams (33.3%) in general. In CHUB the trend was the same with 50% of the combination of beta-lactams and nitroimidazoles and 42.9% of beta-lactams. In CHUK, the most combinations were beta-lactams and nitroimidazoles (44%) followed by beta-lactams $ aminoglycosides (22%). (Table 9)

Table 10: Specific classes combinations of antibiotics most prescribed per hospital

Specific class combinations of antibiotics	Name of hospital					
	CHUB		CHUK		Total	
	n	%	N	%	N	%
Beta-lactams	30	**42.9**	10	20.0	40	**33.3**
Beta-lactams $ Aminoglycosides	0	0.0	11	**22.0**	11	9.2
Beta-lactams $ Nitroimidazoles	35	**50.0**	22	**44.0**	57	**47.5**
Beta-lactams $ Tetracyclines	4	5.7	7	14.0	11	9.2
Ceftriaxone, Metronidazole	1	1.4	0	0.0	1	0.8
Total	70	100.0	50	100.0	120	100.0

4. Specific class combinations of antibiotics most prescribed per ward

The most prevalent class combinations of antibiotics among the most prescribed combinations of antibiotics in GYN&OBS was beta-lactams and nitroimidazoles (94.4%) followed by combinations of beta-lactams and tetracyclines (5.6%). In ICU, the most prevalent combinations were combinations of beta-lactams and nitroimidazoles (52.9%) followed by combinations of beta-lactams (23.5%). In IM, the most combinations were combinations of beta-lactams (63.2%) followed by combinations of beta-lactams and tetracyclines (31.6%). In neonatology, the most frequent combinations were combinations of beta-lactams (66.7%) followed by beta-lactams and aminoglycosides (33.3%). In pediatrics, the trend is the same as in neonatology with 85.7% of combinations of beta-lactams and 9.5% of combinations of beta-lactams and aminoglycosides. In surgery, the most frequent combinations were combinations of beta-lactams and nitroimidazoles (47.5%) followed by combinations of beta-lactams (33.3%). (Table 10)

Table 11: Specific class combinations of antibiotics most prescribed by ward

Specific class combinations of antibiotics	Ward/department													
	GYN& OBS		ICU		IM		NEONATOLOG		PEDIATRICS		SURGERY		Total	
	n	%	n	%	n	%	n	%	n	%	N	%	n	%
Beta-lactams	0	0	4	**24**	0	0	8	**67**	18	**86**	10	**30.3**	40	**33**
Beta-lactams $ Aminoglycosides	0	0	2	12	0	0	4	**33**	2	**9.5**	3	9.1	11	9.2
Beta-lactams $ Nitroimidazoles	17	**94**	9	**53**	12	**63**	0	0	1	4.8	18	**54.5**	57	**48**
Beta-lactams $ Tetracyclines	1	**5.6**	2	12	6	**32**	0	0	0	0	2	6.1	11	9.2
Ceftriaxone, Metronidazole	0	0	0	0	1	5.3	0	0	0	0	0	0	1	0.8
Total	18	100	17	100	19	100	12	100	21	100	33	100	120	100

4.2.6. Antibiotic duplications.

1. Duplications in combinations of antibiotics

Prescriptions of combinations of antibiotics showed duplications. The most duplicated antibiotics were cefotaxime and cloxacillin (17.2%) followed by ampicillin and cefotaxime (16.4%) then ceftriaxone and cloxacillin (10.9%) and others as shown in figure 14.

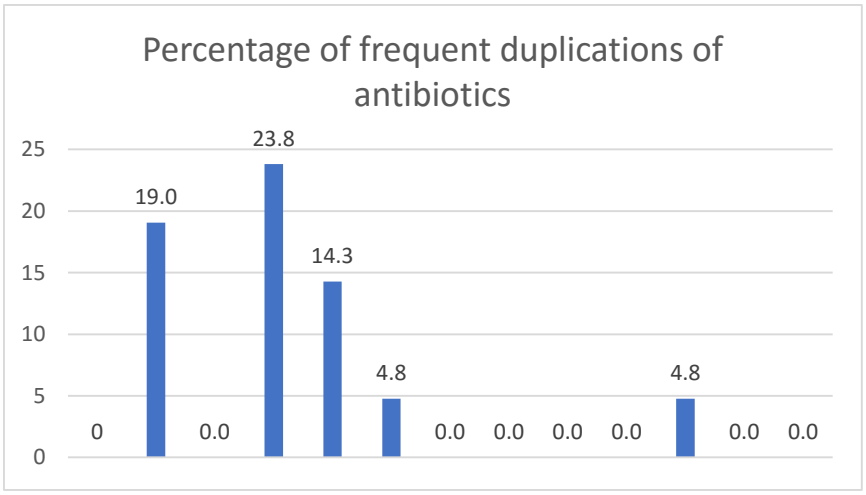


Figure 14: Frequent duplications of antibiotics

2. Duplications in the combination of antibiotics per hospital

The most frequent duplications in antibiotics combinations were combinations of cefotaxime and ampicillin in CHUB (27%) followed by cefotaxime and cloxacillin (14.3%). In CHUK, the

most frequent were combinations of cefotaxime and cloxacillin (20%) followed by ceftriaxone and cloxacillin and cefotaxime and ceftriaxone with 9.2% each, See table 11.

Table 12: Combinations of antibiotics with duplications per hospital

Antibiotic duplications	Name of hospital					
	CHUB		CHUK		Total	
	n	%	n	%	n	%
Cefotaxime $ Cloxacillin	9	**14.3**	13	**20.0**	22	**17.2**
Ampicillin $ Cefotaxime	17	**27.0**	4	6.2	21	**16.4**
Ceftriaxone $ Cloxacillin	8	12.7	6	**9.2**	14	10.9
Cefotaxime $ Ceftriaxone	3	4.8	6	**9.2**	9	7.0
Ceftriaxone $ Meropenem	4	6.3	4	6.2	8	6.3
Ampicillin $ Cefotaxime $ Meropenem	5	7.9	0	0.0	5	3.9
Cefotaxime $ Ceftazidime $ Cloxacillin	0	0.0	4	6.2	4	3.1
Cefotaxime $ Cloxacillin $ Meropenem	1	1.6	3	4.6	4	3.1
Ampicillin $ cefotaxime $ Meropenem	3	4.8	0	0.0	3	2.3
Cefotaxime $ Ceftriaxone $ Cloxacillin	1	1.6	2	3.1	3	2.3
Amoxicillin + clavulanic acid $ Cefotaxime	1	1.6	1	1.5	2	1.6
Ampicillin $ Cefotaxime $ Cloxacillin	0	0.0	1	1.5	1	0.8
Ampicillin $ Ceftriaxone $ Cloxacillin	0	0.0	1	1.5	1	0.8
Ceftriaxone $ Cloxacillin	1	1.6	0	0.0	1	0.8
Others	10	15.9	20	30.8	30	23.4
Total	63	100.0	65	100.0	128.0	100.0

3. Duplications in combinations of antibiotics per wards

The most frequent duplications in GYN&OBS were duplications in the combinations of cefotaxime and cloxacillin (22.2%) followed by cefotaxime and ceftriaxone (11.1%). In ICU, the most frequent duplications were duplications of ceftriaxone and meropenem (18.5%) followed by cefotaxime and cloxacillin (14.3%). In internal medicine, all the above

duplications are observed at the same rate of 14.3%, while in neonatology the prevalent duplications were combination of ampicillin and cefotaxime with a rate of 61.5%. In pediatrics, the most frequent combinations were combinations of ampicillin and cefotaxime (25%) followed by the combinations of cefotaxime and cloxacillin (22.7%). The combinations of ceftriaxone and cloxacillin (23.8%) followed by the combinations of cefotaxime and cloxacillin (19%) were the most duplications found in surgery. See table 13.

Table 13: Combinations of antibiotics with duplications per ward

Antibiotic combinations	GYN& OBS	ICU	IM	NEONATOLOGY	PEDIATRICS	SURGERY	Total
Cefotaxime $ cloxacillin	11.1	**14.8**	**14.3**	**7.7**	**22.7**	**19**	17.2
Ampicillin $ Cefotaxime	11.1	0	7.1	**61.5**	**25**	0	16.4
Ceftriaxone $ Cloxacillin	**22.2**	7.4	0	0	11.4	**23.8**	10.9
Cefotaxime $ Ceftriaxone	**11.1**	3.7	**14.3**	0	4.5	14.3	7
Ceftriaxone $ Meropenem	0	**18.5**	**14.3**	0	0	4.8	6.3
Ampicillin $ Cefotaxime $ Meropenem	0	0	0	**7.7**	9.1	0	3.9
Cefotaxime $ Ceftazidime $ Cloxacillin	0	3.7	0	0	6.8	0	3.1
Cefotaxime $ Cloxacillin $ Meropenem	0	3.7	7.1	0	4.5	0	3.1
Ampicillin $ cefotaxime $ Meropenem	0	0	0	**7.7**	4.5	0	2.3
Cefotaxime $ Ceftriaxone $ Cloxacillin	0	3.7	0	0	2.3	4.8	2.3
Amoxicillin + clavulanic acid $ Cefotaxime	0	0	7.1	0	2.3	0	1.6
Ampicillin $ Ceftriaxone $ Cloxacillin	**11.1**	0	0	0	0	0	0.8
Ampicillin $ Cefotaxime $ Cloxacillin	0	3.7	0	0	0	0	0.8
Ceftriaxone $ Cloxacillin	0	0	0	0	2.3	0	0.8
Others	33.3	40.7	35.7	15.4	4.5	33.3	23.4

4.3. Quality indicators of prescription of antibiotics

4.3.1. Completeness of antibiotic prescriptions

Treatment sheets were incomplete concerning strength, dosage, end date, and route of administration. As the design of some treatment sheets does not allow us to know the starting date, we assumed that the start date was the date of prescription, which brought the results to be completed at 100%. The strength is recorded at 95.4%, the frequency at 92%, the dosage at 94%, and the start date at 100%. A big gap is observed in the omission of the end date (27.7% only completed) and the route of administration (79.8%). See figure 15.

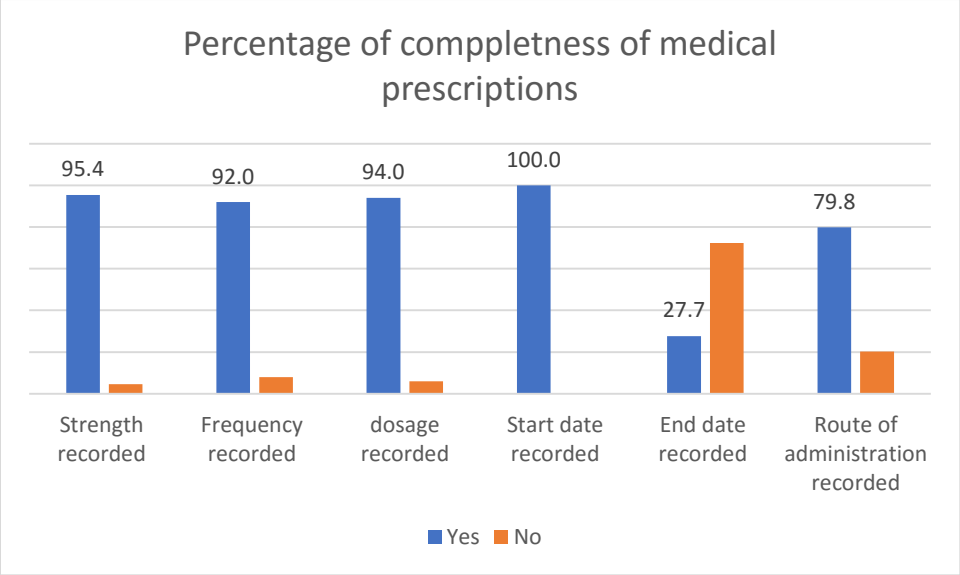


Figure 15: Completeness of medical prescriptions

4.3.2. Prescriptions of antibiotics by generic names

In general, antibiotics are prescribed at 84.8% by generic names. CHUK has the highest generic prescribing rate with 85.1% and CHUB has a rate of 84.5% (figure 16). The average number of antibiotics prescribed by generic names is 1.84.

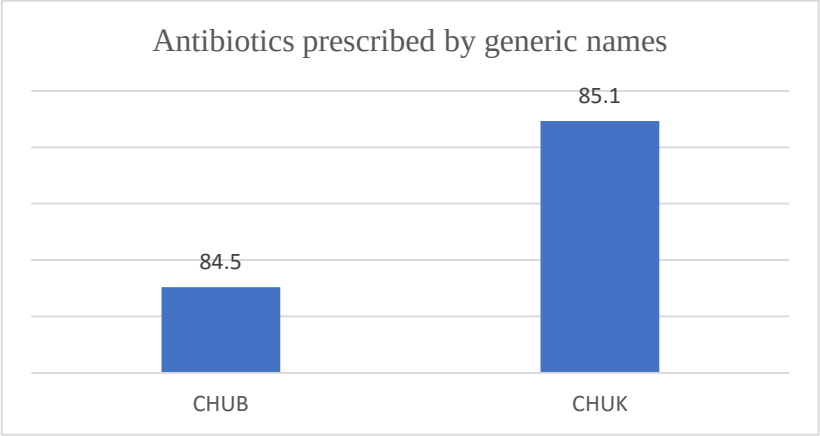


Figure 16: Percentage of antibiotics prescribed by generic names

4.3.3. Prescriptions of antibiotics on the hospital drug formulary

On average, 99.4% of the prescribed antibiotics across the two hospitals were on the drug formulary lists. In detail, CHUB performed at 100% and CHUK at 99% (figure 16). The average number of antibiotics prescribed on the drug formulary is 2.16.

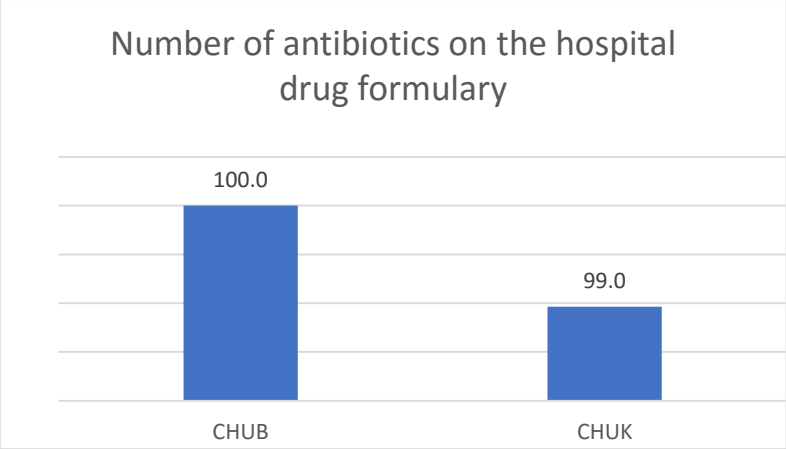


Figure 17: Percentage of antibiotics prescribed on the hospital drug formulary

4.3.4. Potential drug-drug interactions in antibiotic prescriptions

1. Potential drug-drug interactions in antibiotic prescriptions

The antibiotics prescribed in the CHUK and CHUB had potential drug-drug interactions at a rate of 47.46% for which 9.69% were major, 10.17% minor, and 27.6% moderate. (See figure 18)

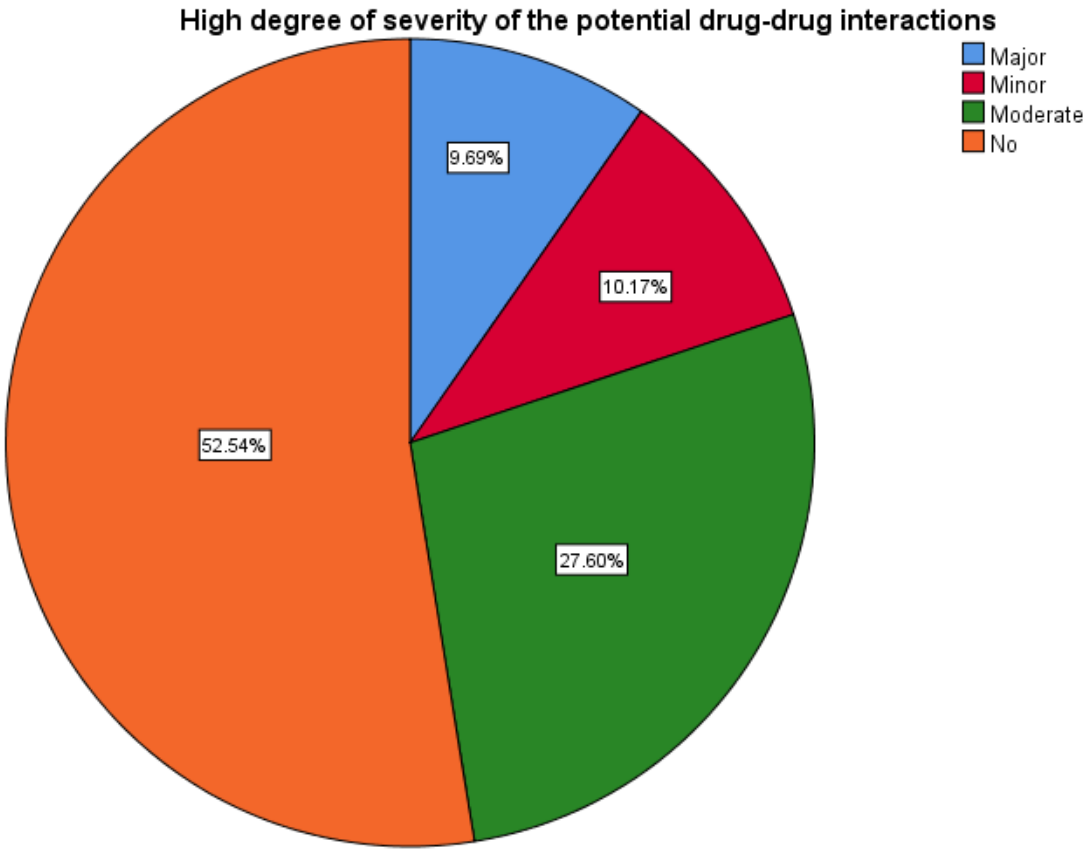


Figure 18: High degree of severity of drug-drug interactions.

2. Potential drug-drug interactions in antibiotic prescriptions per hospital

Antibiotics prescribed in CHUB had potential drug-drug interaction at 40% while in CHUK it was almost 55%. See figure 19.

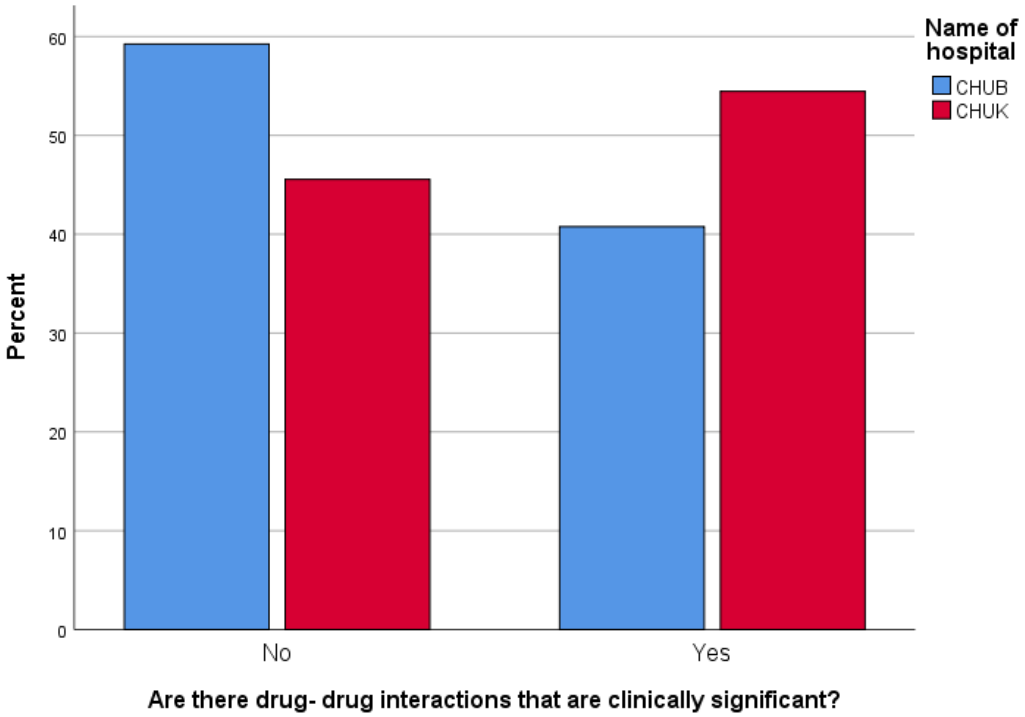


Figure 19: Percentage of potential drug-drug interactions per hospital

In terms of the degree of severity of the potential drug-drug interactions, we found that in CHUB, 9 % were major, almost 11% minor, and 20% moderate. In CHUK, 10% were major, 9% minor, and 36% moderate. See figure 20.

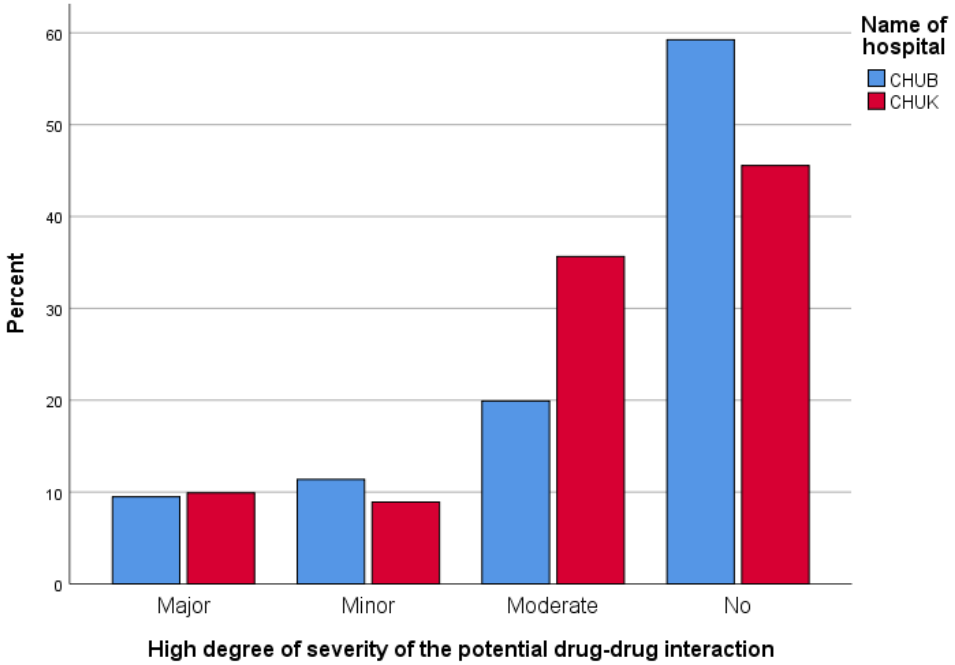


Figure 20: Percentage of the high degree of severity of drug-drug interactions per hospital

3. **Potential drug-drug interactions in antibiotic prescriptions per ward**

Antibiotics prescribed in ICU had potential drug-drug interactions at almost 65%. The ICU was followed by IM (almost 60%) and surgery (above 50%). Neonatology had a low rate of almost 37%. See figure 21.

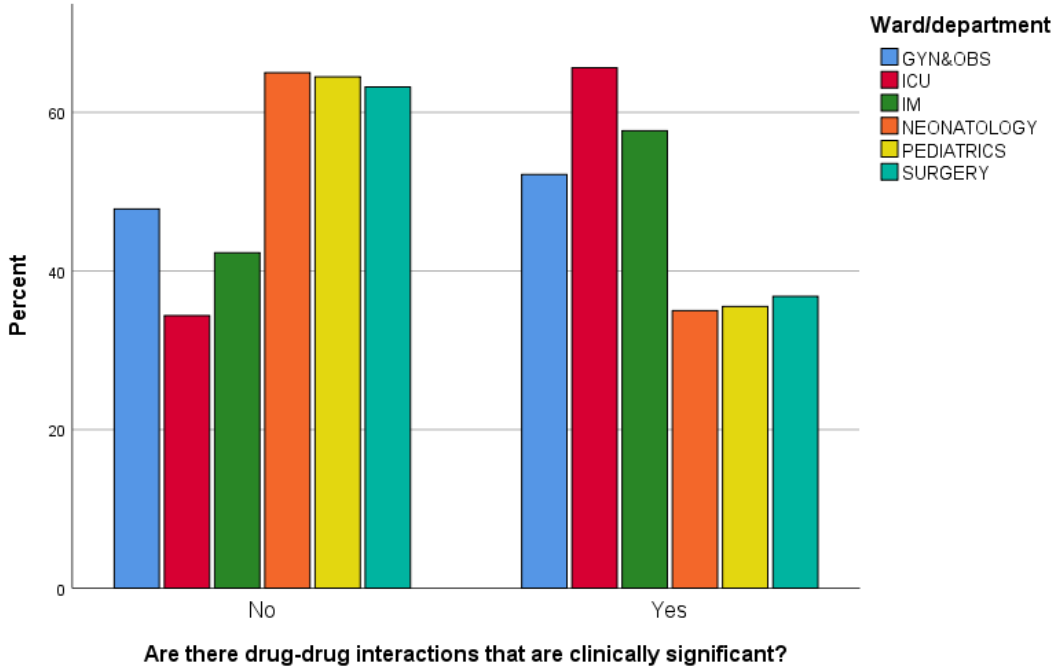


Figure 21: Percentage of potential drug-drug interaction by ward

Per degree of severity, the ICU had the higher rate of major potential drug-drug interactions with almost 18% followed by IM. Surgery had the highest rate of moderate potential drug-drug interactions (almost 30%) but also among the prescriptions without potential interactions (almost 70%). See figure 22.

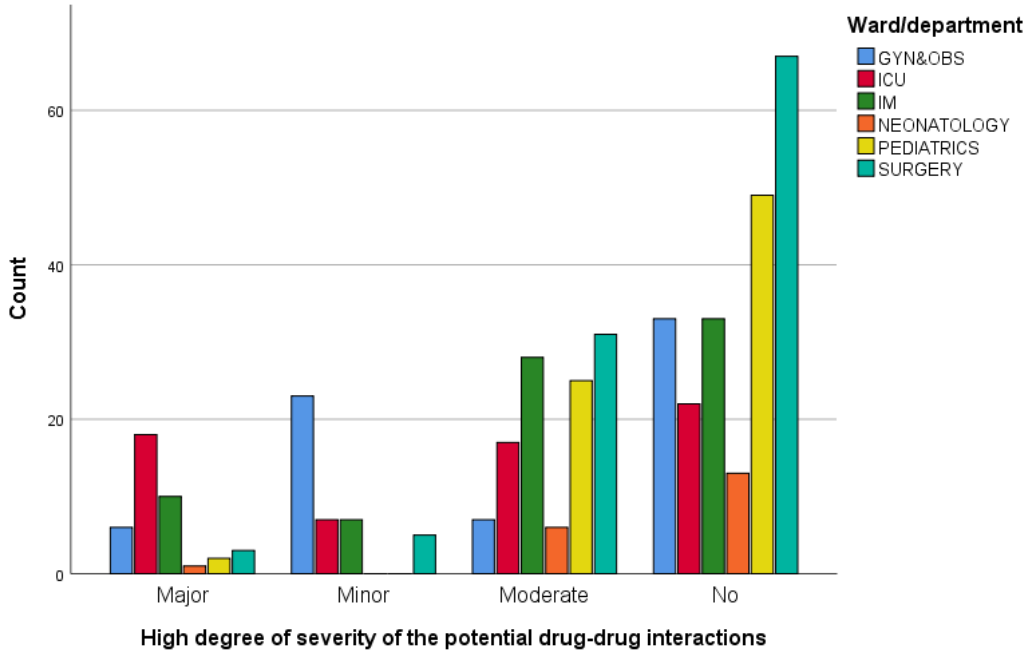
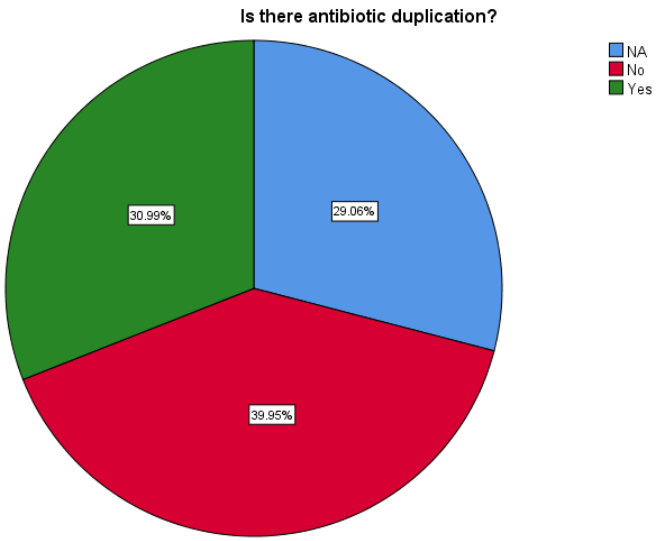


Figure 22: Percentage of the high degree of severity of potential drug-drug interactions per ward

4.3.5. Duplication in antibiotic prescriptions

1. Overall duplications

Antibiotics have been prescribed with duplications at a rate of 30.99%. In 39.95% there was no duplication in antibiotics prescriptions and 29.08% of prescriptions were single antibiotics. See figure 23.



NA (not applicable): Single antibiotic prescribed

Figure 23: Duplication in antibiotics prescriptions

2. Duplication in antibiotic prescriptions per hospital

Antibiotic combinations were prescribed with duplication at 43.7%. In CHUB, duplications were observed at 46.3%, and in CHUK, they were observed at 41.4%. See figure 24.

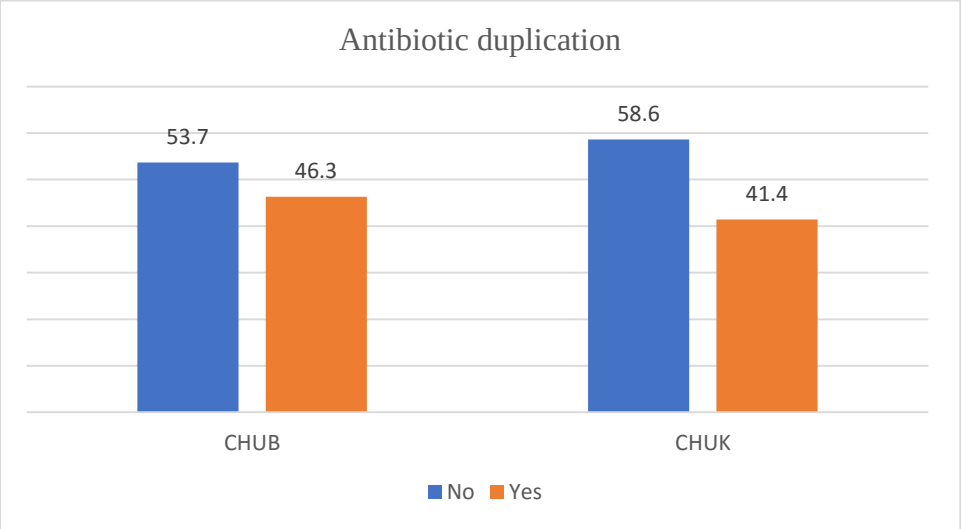


Figure 24: Duplication of antibiotics per hospital

3. Duplication in antibiotic prescriptions per ward

The pediatric ward had the highest rate of antibiotic duplications in antibiotic duplications with a rate of 74.6% followed by neonatology with a rate of 68.4%. The gynecology and obstetrics had less rate of antibiotic duplications with a rate of 21.4%. See figure 25.

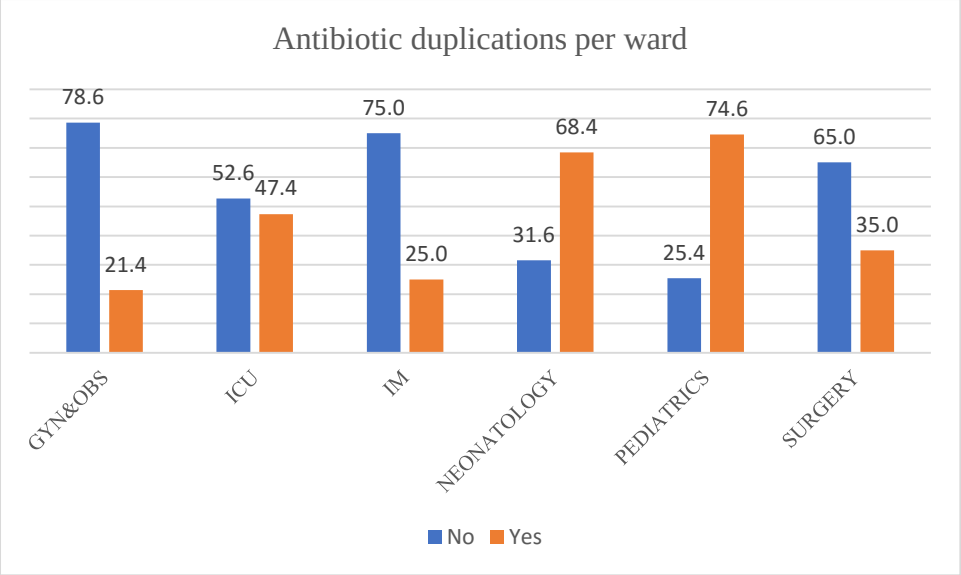


Figure 25: Duplication in antibiotic prescriptions per ward

4.3.6. Prescriptions following STGs

1. Specificity of antibiotics to use in STGs

The majority of the guidelines found in hospitals in our study (80%) specified the antibiotics to be used for the clinical problem followed by 16% of guidelines that not stipulated the use of antibiotics and 4 % of guidelines that stipulate the use of antibiotics without specificity of which antibiotics to be used. See figure 26.

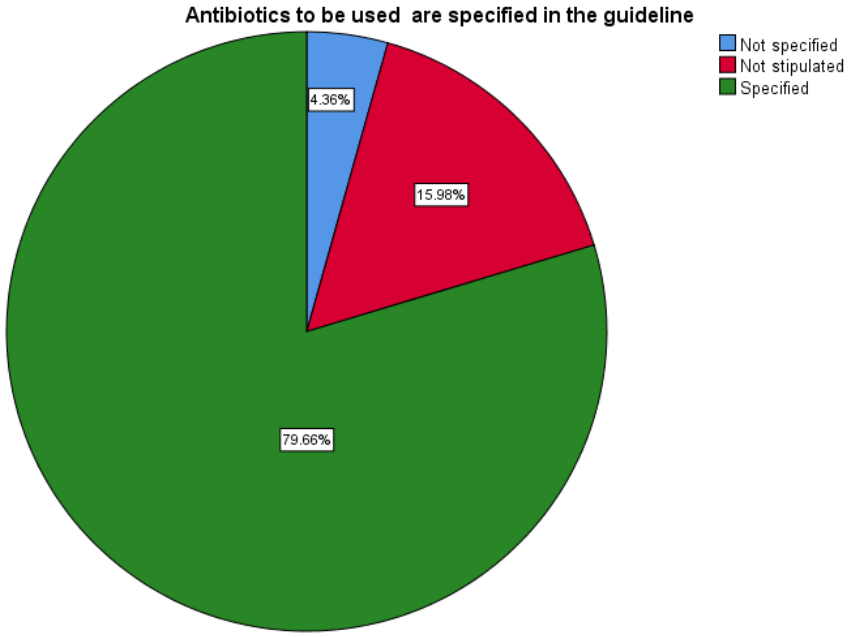


Figure 26: Antibiotics to be used for the clinical problem is specified in the guideline

2. **Antibiotic prescriptions following STGs**

The adherence was assessed per encounter. As seen above, 16% of guidelines do not specify which antibiotics to be used. The use of any broad-spectrum antibiotics was considered compliant with the guideline.

a. **Overall prescriptions following STGs**

The results indicate that there was generally a low adherence to the STGs. The overall score of adherence to STGs is 40.92%. See figure 27.

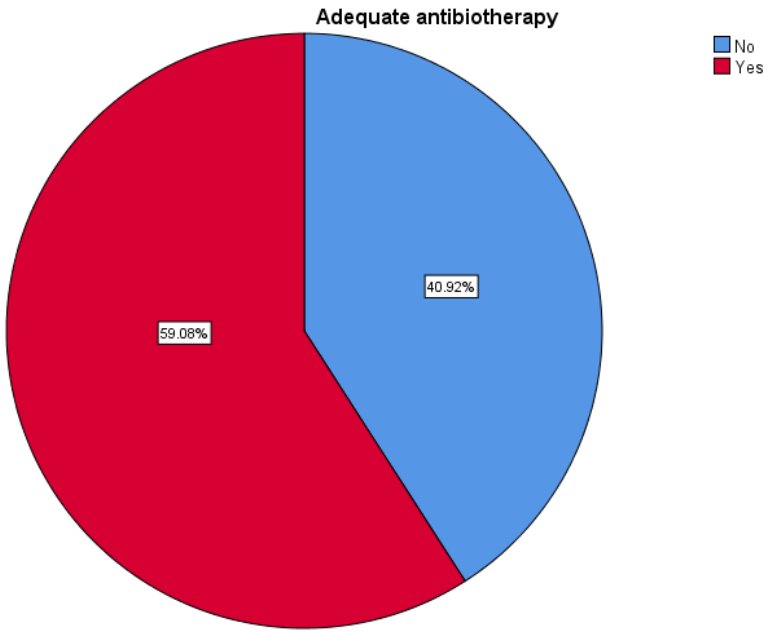


Figure 27: Overall prescriptions following STGs

b. **Prescription following STGs per hospital**

Antibiotics are more prescribed following STGs in CHUB than CHUK. The adherence rate is above 65% while CHUK has an adherence rate of almost 50%. See figure 28.

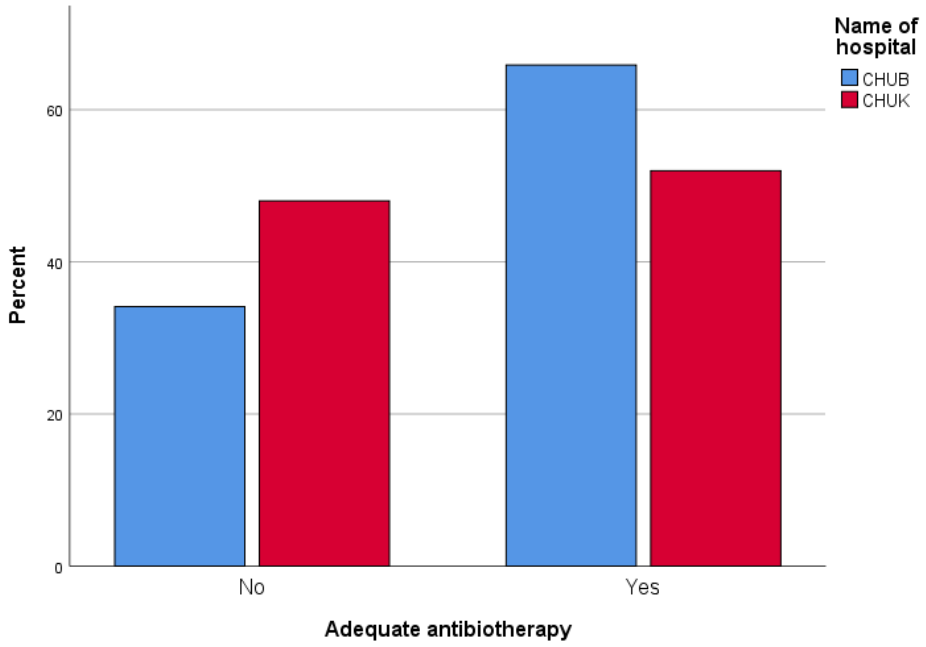


Figure 28: Prescriptions following STGS per hospital

c. **Prescription following STGs per wards**

Neonatology and pediatrics wards are the ones that adhere to the STGs than other wards with a rate of 80%. Surgery adheres less than other departments with a rate of almost 45%. See figure 29.

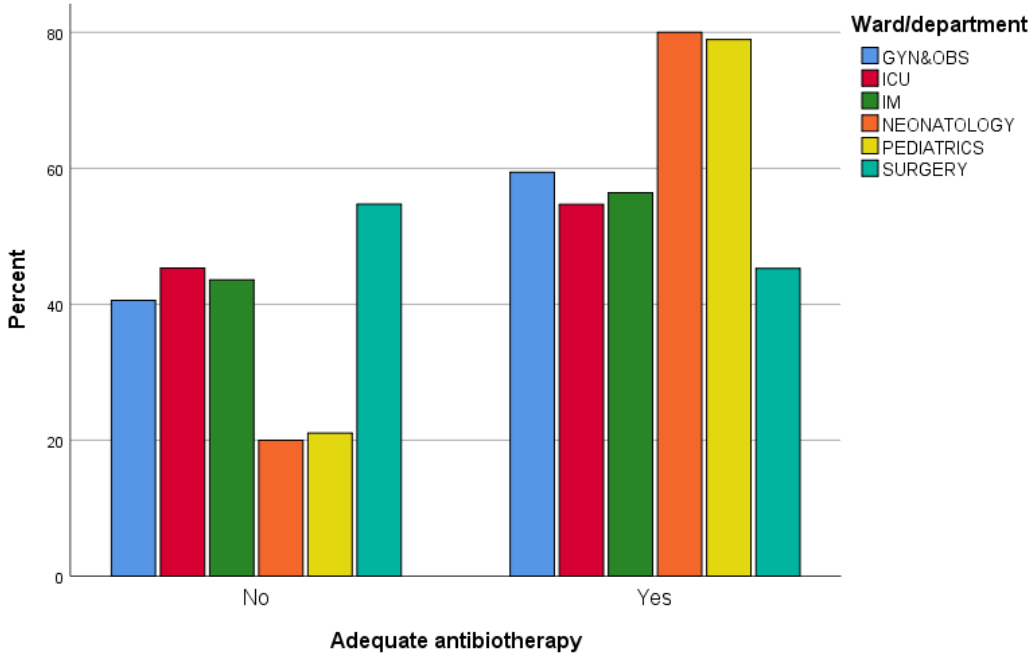


Figure 29: Prescription following STGs per wards

4.3.7. Microbiological tests and sensitivity use

Empirical therapy for infection uses most of the time combination of antibiotics or broad coverage antibiotics to ensure that the regimen includes an agent that is active against the potential pathogen. Microbiological and sensitivity tests should be performed as soon as possible to identify the responsible pathogen of the infection and use selective antibiotics.

Microbiological and sensitivity tests were requested for only 18.6% of all patients and the specimen was sent for only 11.9 % for all participants. Provisional results were available for 8 % and final results for 10.2%. Prescriptions of antibiotics changed with provisional results for 5.1% and with final results for 7.3%. (See table 13)

Table 14: Participants' clinical characteristics (microbiological tests requested, sent to the lab, provisional and final results, prescriptions change with provisional and final results) per hospital

Statement		Name of Hospital					
		CHUB		CHUK		Total	
		N	%	N	%	N	%
Did the microbiological and sensitivity tests been requested?	NO	179	84.8	157	77.7	336	81.4
	YES	32	15.2	45	22.3	77	18.6
	Total	211	100	202	100	413	100
Have specimens been sent to the lab for microbiological tests?	NO	196	92.9	166	82.2	362	87.7
	Not docume	1	0.5	1	0.5	2	0.5
	YES	14	6.6	35	17.3	49	11.9
	Total	211	100	202	100	413	100
If yes, are provisional results of culture sensitivity available?	N/A	197	93.4	167	82.7	364	88.1
	No	3	1.4	13	6.4	16	3.9
	Yes	11	5.2	22	10.9	33	8
	Total	211	100	202	100	413	100
Are final results of culture sensitivity available?	N/A	197	93.4	167	82.7	364	88.1
	No	3	1.4	4	2	7	1.7
	Yes	11	5.2	31	15.4	42	10.2
	Total	211	100	202	100	413	100
If yes, antibiotic prescription has changed with provisional results	N/A	200	94.8	180	89.1	380	92
	No	10	4.7	2	1	12	2.9
	Yes	1	0.5	20	9.9	21	5.1
	Total	211	100	202	100	413	100
Antibiotic prescription has changed with final results	N/A	200	94.8	171	84.7	371	89.8
	No	11	5.2	1	0.5	12	2.9
	Yes	0	0	30	14.9	30	7.3
	Total	211	100	202	100	413	100

Not documented: There was no information if the sample were sent to the lab or not.

4.4. Medical doctor's awareness of STGs

Medical doctors who responded to the questionnaire at CHUB represented 50.6% of all respondents while 49.4% were from CHUK.

We have seen previously that when STGs are used and adhered to, resistant microorganisms decline in numbers(16) and that the DTC provides support and mentorship to prescribing doctors by education and by availing the STGs.

Medical prescribers were asked if they knew of the existence of DTC, 81.9% of prescribers knew the existence of DTC in the two hospitals. All prescribers in CHUB were aware of the existence of the DTC while in CHUK only 63.4% knew its existence.

A good number of prescribers (44.6%) do not have STGs in their consultation rooms. More medical doctors in CHUB had STGs in consultation rooms (54.8%) than CHUK (34.1%). A large number of medical doctors (91.6%) felt that there was a need for the improvement of antibiotics prescriptions (90.5% in CHUB and 92.7% in CHUK). (Table 14)

Table 15: Prescriber's information on DTC and STGs

Statement		Name of Hospital					
		CHUB		CHUK		Total	
		N	%	N	%	N	%
Is there a Drug and Therapeutic committee in the hospital?	No	0	0.0	15	36.6	15	18.1
	Yes	42	**100.0**	26	**63.4**	68	**81.9**
	Total	42	50.6	41	100.0	83	100.0
Do you have a copy of the STGs in your consultation room?	No	19	45.2	27	65.9	46	55.4
	Yes	23	**54.8**	14	**34.1**	37	**44.6**
	Total	42	100.0	41	100.0	83	100.0
Do you think there is a need to improve the prescribing of antibiotics in this hospital?	No	4	9.5	3	7.3	7	8.4
	Yes	38	**90.5**	38	**92.7**	76	**91.6**
	Total	42	100.0	41	100.0	83	100.0

CHAPTER FIVE: DISCUSSIONS

The assessment of antibiotic prescription practices in teaching hospitals in Rwanda aimed at obtaining data on antibiotic prescription patterns at University Teaching Hospitals in Rwanda and establishing whether there was awareness and adherence to standards treatment guidelines. Data were collected from 413 patients' files who had been prescribed antibiotics (211 from CHUB and 202 from CHUK) from inpatients wards (GYN &OBS, ICU, internal medicine, neonatology, pediatrics, and surgery). Questionnaires were filled by 83 medical prescribers.

Antibiotic prescription patterns at University Teaching Hospitals in Rwanda

In our study antibiotics were prescribed most frequently for sepsis (35%), injuries (33%), and abscesses (22%) respectively. The ICU and pediatrics had a high rate of sepsis (37.1% each) followed by IM (14.3%). Injuries were most frequent in surgery (69.7%) and ICU (24.2%) and abscesses were most frequent in surgical (40.9%) and IM (22.7%). Our results are supported by the results from a study conducted in a tertiary hospital in India that found that antibiotics were prescribed for sepsis at the rate of 37%(36). Similar to our study, it is common that most patients admitted to ICU suffered from sepsis and the majority receive antibiotics as treatment(37).

Our study showed that in the overall of 2007 drugs prescribed to patients, 44.6% were antibiotics (895) in the two hospitals. In CHUB, out of 963 medications prescribed, 412 were antibiotics equivalent to 42.8%, and in CHUK, out of 1044 medications prescribed to patients, 483 were antibiotics (46.3%). Patients who received only antibiotics without any other medications were 31 (20 in CHUB and 11 in CHUK) which represents 7.5% of the total population.

In Ethiopia, a study on prescribing patterns of antibiotics using WHO prescribing indicators among inpatients(38) revealed that 52.3% of patients had at least one antibiotic. A similar study done in Ghana showed a rate of antibiotic use at 51.4%(39).

Our study revealed that a large number of patients (324) were prescribed 2 antibiotics (39.23%) in the two hospitals even if the number of antibiotics prescribed to patients wide-ranging from one to seven in CHUB and from one to six in CHUK. Patients who received two antibiotics were quite similar for the two antibiotics (almost 40%). The average number of antibiotics prescribed to patients is 2.17 in CHUB and CHUK. Nebyu Daniel Amaha and associates [1] found an average of 1.29 antibiotics prescribed per hospitalization. Another study of

prescribing pattern of antibiotics done in Ethiopia showed an average number of antibiotics per prescription of 2.01 [1], a similar rate to the one in our study (2.1), and the study was done in [1]. Polypharmacy is associated with the increased occurrence of inappropriate medication, drug-drug interactions, adverse drug reactions, and poorer health outcomes[1]. It has also a negative impact on the budget of the hospital as unnecessary drugs are consumed and should be kept at a minimum level when required.

The most prescribed antibiotic was ceftriaxone (22.7%) followed by metronidazole (14.7%), then cefotaxime (13.1%), cloxacillin (7.9%), ampicillin (5.8%), ciprofloxacin (5%), doxycycline (4.8%), meropenem (4.6%), gentamicin (3.8%) and vancomycin (2.9%). Other antibiotics had the least proportion of prescribing. Per wards, the trend was the same except for pediatrics and neonatology. The most prescribed antibiotics in pediatrics were cefotaxime (29.1%) and cloxacillin (14.3%) and in neonatology, ampicillin (34.6%) and cefotaxime (26.9%).

Similar results were found in Tanzania, where the most prescribed antibiotics were ceftriaxone (29.8%) and metronidazole (23.9%)(40). In Botswana, cefotaxime and metronidazole were the most prescribed in public hospitals with ceftriaxone the most prescribed antimicrobial in private hospitals(41).

The cephalosporins 3rd generation class of antibiotics had the highest proportion of prescribing (36.3%) followed by nitroimidazoles (14.7%) and penicillins (13.7%). Among the most prescribed, glycopeptides had the least proportion of antibiotic prescribing (2.9%). In many other studies, cephalosporins were found to be the most prescribed. The cephalosporin group (38.8%) was the most prescribed in Malaysia [1] and Ethiopia [1], in Pakistan, cephalosporins were extensively prescribed to patients followed by penicillins (42). Compared to our study, all study shows that cephalosporins and penicillins are the most antibiotics used in the study populations. As per WHO classification, these antibiotics are classified in a watch group, meaning that they have a high potential for resistance and should be monitored.

The most prescribed antibiotic combination was the combination of ceftriaxone and metronidazole with 13.3% overall (17.1% for CHUB and 9.4% for CHUK) followed by the ampicillin-cefotaxime combination with 4.4% overall (CHUB: 7.6% and CHUK: 1%) and cefotaxime-cloxacillin with 2.9% in overall (2.4% in CHUB and 3.5% in CHUK).

The most prevalent class combinations of antibiotics among the most prescribed combinations of antibiotics were beta-lactams and nitroimidazoles (47.5%) followed by combinations of

beta-lactams (33.3%) in general. In CHUB the trend was the same with 50% for the combination of beta-lactams and nitroimidazoles and 42.9% for beta-lactams. In CHUK, the most combinations were beta-lactams and nitroimidazoles (44%) followed by beta-lactams $ aminoglycosides. At Lift valley hospital provincial general hospital, the most prevalent antibiotic combinations were the combination of aminoglycosides and penicillins (20.7%) followed by the combination of cephalosporins and nitroimidazoles derivatives (9.5%)(43). The combinations are quite similar to the combinations of our study.

Antibiotics have been prescribed with duplications at a rate of 30.99% when they should not be antibiotic duplications. The most frequent duplications in antibiotics combinations were combinations of cefotaxime and ampicillin in CHUB (27%) followed by cefotaxime and cloxacillin (14.3%). In CHUK, the most frequent were combinations of cefotaxime and cloxacillin (20%) followed by ceftriaxone and cloxacillin and cefotaxime and ceftriaxone with 9.2% each. A study done in the USA found evidence of redundant antimicrobial coverage for 23 different antimicrobial combinations in 394 of the 505 (78%) hospitals, representing a total of 32,507 cases(44). According to the same source, high-frequency redundancies were observed in 3 anaerobic regimens, accounting for 22,701 (70%) of the cases. Of these, metronidazole and piperacillin-tazobactam accounted for 53% (n = 17,326) of all potentially redundant cases. The rate in this study (70%) is higher than the rate in our study (30.99%). Appropriate use of antimicrobials may reduce the risk of harm to patients and lower healthcare costs.

Quality indicators of prescription of antibiotics

Medical prescriptions should be completed 100%. To assess the completeness of medical prescriptions, we used a uniform treatment sheet used in CHUK but in CHUB, treatment sheets were different depending on the department. The completeness of treatment observed was as follows: the strength was recorded at 95.4%, the frequency at 92%, the dosage at 94%, and the start date at 100%. A big gap was observed in the omission of the end date (27.7% only completed) and the route of administration (79.8%).

The omission of the duration of treatment, strengths, and dosage forms may pose a problem for dispensing as most drugs are available in various strengths and dosage forms. Incomplete medical prescriptions may also lead to issues such as treatment failure, antibiotic resistance, and adverse drug reaction which are associated with underdosing or overdosing. A similar study was conducted on compliance with good practice in prescription writing at outpatient

clinics in Saudi Arabia(45) and results show that the strength of medication and dose units were indicated in 26.6% and 55.6% of prescriptions. A study on deficiencies in medical prescriptions in a Sudanese hospital(46) shows that 25.7% lacked the duration of treatment.

Comparing with our results, the compliance is higher for our study in terms of unit dosage recording (92% versus 55.6%), in terms of strength (95.4% versus 26.6%), and in terms of duration of treatment, the findings are quite similar (27.7% versus 25.7%).

In general, 99.4% of the prescribed antibiotics in CHUB and CHUK were on the drug formulary lists. In detail, CHUB performed at 100% and CHUK at 99%. Other studies showed similar findings. The percentage of drugs prescribed from the essential drugs list was 95.3%(47), 94.1%(48), all prescribed antibiotics were from the national essential medicine list in a study done in Ethiopia(38).

In general, antibiotics were prescribed at 84.8% by generic names while they should be prescribed at 100%. CHUK had a generic name prescribing rate of 85.1% and CHUB has a rate of 84.5%. The average number of antibiotics prescribed by generic names was 1.84. The majority (97.6%) of antibiotics were prescribed by their generic name in a study done in Ethiopia(38), the rate was 95.3% in another study[1]. The rate of prescription by generic names in our study (84.8%) is less than the rate in other studies.

The antibiotics prescribed in the CHUK and CHUB had potential drug-drug interactions at a rate of 47.46% for which 9.69% were major, 10.17% minor, and 27.6% moderate. At CHUB prescribed antibiotics with potential drug-drug interaction at 40% while in CHUK it was almost 55%. By degree of severity, we found that in CHUB, 9 % were moderate, almost 11% minor, and 20% moderate. In CHUK, 10% were major, 9% minor, and 36% moderate. A similar study conducted on potential drug-drug interactions with antimicrobials in hospitalized patients in Turkey shows that 26.4% of all interactions and 38% of major interactions were with antimicrobials(49). Our findings of 47% of potential interactions show that in our study population the rate was higher than the study done in Turkey (38%). For the safety of the patients, close monitoring should be done to mitigate the high level of potential interactions.

The adherence to the STG was assessed per prescription and results indicate that there was generally a low adherence to the STGs. The overall score of adherence to STGs is 40.92%. Antibiotics are more prescribed following STGs in CHUB (65%) than CHUK (50%). Neonatology and pediatrics wards are the ones that adhere to the STGs than other wards with a rate of 80%. Surgery adheres less than other departments with a rate of almost 45%. The

compliance to guidelines was 45.8% in Rift Valley Provincial General Hospital(50) which is quite similar to the results in our study population.

Microbiological and sensitivity tests were requested for only 18.6% of all patients and the specimen was sent for only 11.9 % for all participants. Provisional results were available for 8 % and final results for 10.2%. Prescriptions of antibiotics changed with provisional results for 5.1% and with final results for 7.3%. A study on empirical use of antibiotics and adjustment of empirical antibiotic therapies in a university hospital(51) has shown that in 2943 admitted patients the initial therapy was adjusted in 168 patients (31%). This rate of 31% is higher compared to the rate of our study which is 7.3% even if we have a lower rate in other studies. A study done in Ethiopia shows that culture and sensitivity testing were not performed in any of the cases(38) and another one shows that only 2 of 591 patients were prescribed antibiotics based on culture and antimicrobial susceptibility testing results(52). Empiric treatment with broad-spectrum or combination of antibiotics should be changed with provisional and final microbiological and sensitivity tests results when available to avoid toxicity, superinfection, selection of resistant microorganisms to several drugs and to avoid unnecessary expenses. Although the reluctance to change the antimicrobial agent is understandable when a favorable clinical response has occurred, the goal should be to use the most selectively active drug.

Medical doctor's awareness of STGs

Medical doctors who responded to the questionnaire at CHUB represented 50.6% of all respondents while 49.4% were from CHUK. Only 81.9% of prescribers knew the existence of DTC in the hospital. All prescribers in CHUB were aware of the existence of the DTC while in CHUK only 63.4% knew its existence. A good number of prescribers (44.6%) do not have STGs in their consultation rooms. More medical doctors in CHUB had STGs in consultation rooms (54.8%) than CHUK (34.1%). A large number of medical doctors (91.6%) felt that there was a need for the improvement of antibiotics prescriptions (90.5% in CHUB and 92.7% in CHUK).

We found similar results with a study done in Lesotho in six hospitals(16), some hospitals knew the existence of DTCs and others did not and some DTCs were more functional than others. The same feeling of the majority of prescribers to improve the antibiotic prescription is shared.

CONCLUSION AND RECOMMENDATIONS

Antimicrobial agents are among the most commonly used and misused of all drugs. The consequence of the widespread use of antimicrobial is the emergence of antibiotic-resistant pathogens and antibiotic resistance is becoming a public health threat worldwide. As rational prescribing is a primary step to ensure rational drug use, we decided to assess antibiotic prescription practices in Rwanda Teaching Hospitals. The assessment intended to describe the antibiotic prescription patterns, the compliance to the standards treatment guidelines while prescribing antibiotics, and describe the awareness of the prescribers of the STGs.

To answers the questions above, we collected data using a designed data collection form in patients' files admitted in clinical departments who were admitted in CHUK and CHUB from July to December 2019 and who received antibiotics. A questionnaire was administered to medical doctors prescribing antibiotics in clinical departments to assess the degree of satisfaction of the functionality of the Drug and Therapeutic Committees (DTC) and the usage of STGs while prescribing antibiotics.

We used SPPS, Microsoft excel, and drug-drug interactions online checker, to analyze and check for drug-drug interactions. The findings of the analysis of the data collected are discussed in the following paragraphs.

The assessment of quality indicators of prescription of antibiotics shows gaps in antibiotics prescriptions.

Treatment sheets were not fully completed. The strength of antibiotics was recorded at 95.4%, the frequency at 92%, the dosage at 94%, and the start date at 100%. A big gap was observed in the omission of the end date (27.7% only completed) and the route of administration (79.8%).

Antibiotics prescribed in CHUB and CHUK were at 99.4% in-hospital drug formulary lists and were prescribed by generic names at 84.8%. The prescriptions had potential drug-drug interactions at a rate of 47.46% for which 9.69% were major, 10.17% minor, and 27.6% moderate. The rate of potential drug-drug interaction was at 40% in CHUB and almost at 55% in CHUK.

Using standards treatment guidelines for provisional diagnosis in patient’s files, we found that from all prescriptions, 40.92 % of prescribed antibiotics were complying with treatment guidelines. Antibiotics are more prescribed following STGs in CHUB (65%) than CHUK

(50%). Neonatology and pediatrics wards are the ones that adhere to the STGs than other wards with a rate of 80%.

Microbiological and sensitivity tests were requested for only 18.6% of all patients and the specimen was sent for only 11.9 % for all participants. Provisional results were available for 8 % and final results for 10.2%. Prescriptions of antibiotics changed with provisional results for 5.1% and with final results for 7.3%.

Only 81.9% of prescribers knew the existence of DTC in the hospital (100% for CHUB and 63.4% for CHUK). A good number of prescribers (44.6%) do not have STGs in their consultation rooms and 91.6% of them feel that there is a need for the improvement of antibiotics prescriptions.

This audit on antibiotic prescription in Teaching Hospitals in Rwanda has given sufficient information needed to make adequate interventions to improve the clinical use of antibiotics. Studies on specific medical problems may give more details on adequate dosing and duration of treatment.

In general, antibiotic-prescribing practices in Teaching Hospitals in Rwanda need to be improved as rational prescribing is a primary step to ensure rational drug use. Prescribers should prescribe according to STGs and prescribe with all relevant information as required. Uniform treatment sheets should be developed in CHUB to avoid medication errors.

The use of non-indicated antibiotics, duplicated antibiotics, and antibiotics with potential interactions may lead to the increase of antibiotic resistance, increase of risk of harm to patients, and increase healthcare costs and should be avoided. Interventions of clinical pharmacists to be hired is really needed.

A culture to test the sensitivity and resistance of specific pathogens to a wide range of antimicrobial agents and the use of results should be encouraged to enable prescribers to institute proper treatment regimens for their patients.

DTCs in teaching hospitals need to improve their functionality and put in place antibiotic stewardship programs to address deficiencies in antibiotic rational use.

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APPENDIX 1: DATA COLLECTION SHEETS

Annex a. Data collection sheet

1. Name of hospital: _____

2. Patient number: _____Gender:_____Date of birth/age: ___

3. History of present illness:

_____

_____

_____

4. Presenting symptoms:

_____

_____

_____

5. Has the patient ever presented with the same condition before this visit?

Yes☐ No ☐

If 'Yes', what medication was prescribed to them the previous time?

Rx: a) _____

b)_____

c)_____

6. Present provisional diagnosis:

_____

List of medicines prescribed, (strength, frequency, dosages, duration, and route of administration)

Rx: a) _____

b)_____

c) _____

7. What is the number of antibiotics prescribed by generic name?

8. Did the microbiological and sensitivity tests have been requested? Yes ☐ No ☐

9. Have specimens been sent to the lab for microbiological tests? Yes ☐ No ☐

10. a) If yes, are provisional results of culture sensitivity available Yes ☐ No ☐

b) Are final results of culture sensitivity available? Yes ☐ No ☐

11. If yes, antibiotic prescription has changed with provisional results Yes ☐ No ☐

12. Antibiotic prescription has changed with final results. Yes ☐ No ☐

13. Are there any untreated medical conditions? Yes ☐ No ☐

Annex A

Umugereka a. Ifishi ifata amakuru

1. Izina ry'ibitaro: _____

2. Nomero y'umurwayi:_____Igitsina:_____Itariki yavukiye/Imyaka:

3. Amateka y'uburwayi afite ubu:

_____

_____

_____

4. Ibimenyetso agaragaza:

_____

_____

_____

_____

5. Umurwayi yaba yarigeze kugaragaza ibi bimenyetso mbere yuko aza?

Yego ☐ Oya ☐

Niba ari yego, ni iyihe miti yahawe icyo gihe?

Rx: a) _____

b) _____

c) _____

6. Uburwayi bukekwa:

_____

Imiti bamwandikiye, (Ingano y'umuti, inshuro awufata ku munsi, ingano y'umuti afatira rimwe, igihe azawufatira n'uko azawufata)

Rx:

a) _____

b) _____

c) _____

d) _____

7. Nuwuhe mubare wa antibiotike wanditswe na muganga akoresheje inyito rusange y'umuti?

_____

8. Haba hari ibizamini byo gupimwa mikorobe byasabwe? Yego ☐ Oya ☐

9. Amaraso y'umurwayi yaba yaroherejwe muli laboratoiri gupimwa mikorobe?

Yes ☐ No ☐

10. a) Niba ari yego, igisubizo cyibanze cyaba cyarabonetse? Yego ☐ Oya ☐

b) Igisubizo cya nyuma cyaba cyarabonetse? Yego ☐ Oya ☐

11. Niba igisubizo cyibanze cyarabonetse, haba hari icya hindutse kuli antibiotike yari yarandikiwe? Yego ☐ Oya ☐

12.Niba igisubizo cya nyuma cyarabonetse, antibiotike yandikiwe yaba yarahindutse bijyanye nibisubizo? Yego ☐ Oya ☐

13. Haba hari ubundi burwayi umurwayi afite bwaba butaravuwe? Yego ☐ Oya ☐

APPENDIX 2: QUESTIONNAIRE

ANNEX B. PRESCRIBER QUESTIONNAIRE

1. a) Is there a Drug and Therapeutic committee in the hospital? Yes ☐ No ☐

b) If yes, on a scale of 1-5, how active is it in your opinion? (5 being very active and 1 being not active at all)

2. a) Do you have a copy of the STGs in your consultation room? Yes ☐ No ☐

b) If no, why not?

_____

c) Have you tried to get a copy Yes ☐ No ☐

d) If yes, how often do you ever refer to the STGs when you prescribe antibiotics?

(Please indicate how often on a scale of 1-5, with 5 being always and 1 being you never refer to them.)

3. Do you think there is a need to improve the prescribing of antibiotics in this hospital?

Yes ☐ No ☐

Any other comments?

Thank you for your time!!!!!

UMUGEREKA B. IBIBAZO BISUBIZWA N'ABAGANGA BANDIKA IMITI

1. a) Ese mu bitaro hari komite ishinzwe imikoreshereze y'imiti? Yes ☐ No ☐

   b) Niba ihari, ugendeye ku kigero kiva kuli 1 ukagera kuli 5, ku bwawe wavuga ko ikora neza ku ruhe rugero? (5 bivuga ko ikora neza cyane na 1 ikavuga ko idakora na busa)

2. a) Mwaba mwifashisha amabwiriza rusange y'ubuvuzi mwandikira antibiotike abarwayi?

   Yes ☐ Oya ☐

   b) Niba ari oya kuki?

   _____

   _____

   c) Mwigeze mwifuza gutunga amabwiriza rusange mu kuvura? Yego ☐ Oya ☐

   d) Niba ari yego, ni ku kihe kigero mukoresha ayo mabwiriza igihe mwandikira antibiotike abarwayi? (Mwakwifashisha urugero 1-5, aho gatanu bivuga kenshi cyane naho 1 aho mutayikoresha na rimwe)

   _____

3. Mwaba mukeka ko ari ngombwa kuvugurura imikoreshereze ya antibiotike mu bitaro?

   Yego ☐ Oya ☐

   Ntacyo wabivugaho?

Turabashimiye cyane!!!!!

APPENDIX 3: MEDICINE THERAPY ASSESSMENT WORKSHEET

Annex A

Medicine Therapy Assessment Worksheet

Patient number _____

Type of problem	**Criteria**	**Assessment**
Correlation between medicine therapy and medical problem	1. Are there antibiotics without medical indication?	
	2 Are there any untreated medical conditions?	
	3. If 'yes' do they require medicine therapy?	
Antibiotherapy regimen	4. Has the antibiotic regimen been prescribed	
	5. Are the prescribed doses and dosing frequency	
	6. Are doses scheduled to maximize therapeutic	
	7. Is the length or course of antibiotic therapy	
	8. How many antibiotics are prescribed for this	
Therapeutic duplication	9. Is there antibiotic duplication (e.g., combinations of antibiotics that have the same mechanism of	
Interactions	10. Are there medicine–medicine interactions that	
	11. Are there any antibiotics contraindicated given	
Laboratory information	12. Has a specimen been sent to the laboratory?	
	13. Is the antibiotic indicated for the condition or the	

Umugereka A

Ifishi y'isesengura ry'itangwa ry'imiti

Nimero y'umurwayi _

Imiterere y'ikibazo	**Ikigendeweho**	**Isesengura**
Isano hagati y'itangwa ry'imiti n'ikibazo cy'ubuvuzi	1. Haba hari antibiotike zatanzwe atari ngombwa?	
	2. Haba hari ikibazo cy'ubuvuzi kitavuwe?	
	3.Niba gihari, cyaba gikeneye umuti?	
Antibiotike zikoreshwa hamwe	4. Antibiotike ziri gukoreshwa hamwe zaba	
	5. Yaba ingano y'imiti itangwa n'inshuro igomba gufatwa bigenwa neza kandi bigendera ku	
	6. Yaba ingano y'imiti umurwayi yahawe imukiza ku kigero cyo hejuru n' ingaruka mbi zituruka	
	7. Antibiotike zaba zarakoreshwejwe mu gihe	
	8. Uyu murwayi yakoresheje antibiotike zingahe?	
Gukoresha umuti urenze umwe kandi	9. Haba hari imiti yakomatijwe kandi ikora kimwe ?	
Imikoranire y'imiti (Interactions)	10. Haba hari imikoranire y'imiti yigeze igaragara?	
	11. Haba hari antibiotike yatanzwe bidakwiriye	
Amakuru ya laboratwari	12. haba hari amaraso y'umurwayi yoherejwe muli	
	13. Antibiotike yatanzwe yaba ijyanye n'uburwayi	

APPENDIX 4: ETHICAL CLEARANCES