**Republic of Yemen**
**Ministry of Higher Education and Scientific Research**
**21 September University of Medical and Applied Sciences**
**Faculty of Laboratory Medicine**

# Antibiotic Consumption in Intensive Care Units In Some Hospitals in Sana'a City

## A Study Research

Research study submitted to Faculty of Laboratory Medicine

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# Dedication

Hearts filled with the light of love and loyalty and covered with the scent of musk, crowned with roses and narcissus, and the contentment of this humble look, To those who planted in our hearts the love of knowledge "Our fathers may God protect them" . To whom to carry us here on weakness "Our dear mothers". To whom we stress our roses and our hearts rejoice in them "Our brothers". To those who helped us acquire knowledge "Our doctors". And to students of knowledge.

# Acknowledgements

It's our pleasure in this respect, after this effort and this hard work, for which we continued night and day, for the sake of which, we thank Allah Almighty for its completion and generosity on us until we completed this work. In recognition of the grace to home it belongs of his family and following his saying, may Allah bless him and grant him peace (who does not thank people will not thank Allah (So, many thanks and appreciation to the distinguished his Excellency the President of the University, **Prof. Dr. Mujahid Maasar** and **Our main supervisor Dr. Ghamdan Altahish**And our co- supervisor **Dr**.**Marwa Al-Radaii** and to everyone who contributed or helped in the completion of this research, and thankfulness for hospitals that help us to collected the data (48 Hospital (48H), AL-Thawra Modern General Hospital (ATH), Al-Jomhori Teaching Hospital (AJH), and Dr. Abdulkader Almutawakel Hospital (AMH).

# Abstract

**Background:** Monitoring antibiotic consumption is crucial to tackling antimicrobial resistance. However, currently there is no system in Sana'a city for recording and reporting on antibiotic consumption. Our study is the first of its kind to look at the antibiotic usage in an ICU in Sana'a, Yemen using DDD and DOT methods.

**Objectives**: to estimate the antimicrobial consumption in hospitals" ICUs at Sana'a city.

**Methods:** A retrospective study on data from the ICU register .The study was carried out on admitted patients of five ICUs of main hospitals at 2020. Antimicrobial consumption data were mostly collected manually. Data were analyzed and presented as defined daily dose (DDD) and days of therapy (DOT) per1000 patient days.

**Results:** A total of 1970 patients were included in this study. In this study we found the total consumption of antibiotics in ICUs were high of by DDD 18017.91 DDD per 1000 patient and by DOT 17448.73 DOT per 1000 patient-days. The study results discovered that ceftriaxone, vancomycin, and meropenem were the most average consumed using both DDD and DOT methods among ICU patients where results by DDDs per 1000 admission were 2479.23, 2124.55 and 1830.54 respectively and by DOTs per1000 patient-days were 2112.69, 2055.33 and 1890.86. Based on therapeutic/pharmacological subgroups in measuring consumption using DDD and DOT, the most consumption were cephalosporins (3882 DDD per 1000 patient and 4227.41DOTs per 1000 patient-days), carbapenems (2987 DDD per 1000 patient and 2888.83DOTs per 1000 patient-days) and quinolones (2900 DDD per 1000 patient per days and2660.41DOTs per 1000 patient-days). The highest amount of antibiotics consumption among WHO AWaRe classification was for "watch" group of 26267.4 DDDs and 14674.5 DDDs per 1000 patient per day.

**Conclusion:** High consumption of antimicrobial agents such as ceftriaxone, vancomycin and meropenem is observed in ICUs of a five hospitals. The findings highlighted the urgent need for an effective antimicrobial stewardship program in these hospitals with focusing on ICUs specific- antimicrobial consumption. The study results can be used as base before designing any intervention aiming to optimize antibiotics utilization in hospitals ICUs. Future studies focusing on concurrent monitoring of antimicrobial resistance with specific prescription patterns may help in improving judicious antimicrobial consumption.

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| Symbol | List of Abbreviation |
|---|---|
| 48MH | 48Modern Hospital |
| AJH | Al-Jomhori Teaching Hospital |
| AMH | Dr.Abdulkader Almutawakel Hospital |
| AMR | Antimicrobial Resistance |
| AR | Antibiotic Resistance |
| ATC | Anatomical Therapeutic Chemical |
| ATH | Al-Thawra Modern General Hospital |
| AWaRe | Access, Watch, Reserve |
| DDD | Defined Daily Dose |
| DOT | Days Of Therapy |
| ESAC | European Surveillance of Antimicrobial Consumption |
| GAP | Global Action Plan |
| GLASS | Global Antimicrobial Resistance and Use Surveillance System |
| ICU | Intensive Care Unit |
| LMICs | Low and Middle Income Countries |
| MDR | Multidrug Resistance |
| PD | Patient Day |
| PDD | Prescribed Daily Dose |
| USTH | University of Science& Technology Hospital |
| WHO | World Health Organization |
| WHOCC | WHO Collaborating Centre for Drug Statistics Methodology |

# Chapter I: Introduction and Literature Review

## 1.1.Introduction

Antimicrobial resistance (AMR) is a major threat to health and human development, affecting the ability to treat a range of infections. When antibiotics stop working against microorganisms, standard antibiotics treatments become ineffective and hence, infections with antibiotic resistant pathogens increase the risk of death, hundreds of thousands of deaths per year are estimated to be attributable to AMR and that number is likely to rise to many millions per year by 2050.(1) The misuse and overuse of antibiotics is a key contributor to this problem. Excessive exposures to antibiotics result in the emergence and spread of antibiotics -resistant bacteria. Higher AMR is associated in countries with higher antimicrobial consumption. The consumption of antibiotics has increased by 67% between 2000 and 2015, and the developing countries are higher antimicrobial consumption.(2)

To monitor the consumption of antimicrobials and promote the prudent use of antibiotics, the WHO developed a methodology for antimicrobial consumption surveillance using a metric, the defined daily dose (DDD), as per the anatomical, therapeutic and chemical classification (ATC) system. The WHO has classified antibiotics into three categories as AWaRe: Access for antibiotics needed for common infections that should be available and accessible, Watch for broad-spectrum antibiotics that should be used with caution because of their high potential to develop resistance and reserve for antibiotics that should be reserved for the treatment of multidrug-resistant infections and used only when other alternatives fail.(3)

The intensive care unit (ICU) is often called the epicenter of infections, due to its extremely vulnerable patients, the wide use of invasive devices and broad spectrum antimicrobials, which favors the emergence of multidrug resistance (MDR).The prognosis of patients who develop hospital-acquired infections (HAI) in the ICU is poor and the mortality rates are higher if it involves an MDR organisms. Inappropriate use of broad-spectrum antimicrobials is frequent, partly because of unwarranted prescriptions of antimicrobials, which may be caused by uncertainty regarding the type of infection, among other possible explanation.(4)

In low income countries like Yemen, in addition to ongoing conflict status, that promote inappropriate and overuse of antimicrobial consumption. The magnitude of antimicrobial consumption in Yemen unknown, because no previous published studies

and reports that addressed this subject, so this study aimed to estimate antibiotic consumption in ICUs of hospitals by using DDD and DOT methods in Sana'a, Yemen. The study results can be used as base before designing any intervention aiming to optimize antibiotics utilization in hospitals ICUs.

## 1.2.Literature review

The discovery of antimicrobial agents is considered to be one of the ten great public health achievements of the twentieth century .(5, 6) These agents have played a pivotal role in the management and control of infectious diseases and in the decrease in infectious disease related mortalities. (5, 7) Initially, antibacterials were seen as truly miraculous drugs and considered the ‘‘panacea’’ of Medicine, but nowadays the evolution of drug- resistant organisms has greatly impaired their therapeutic efficacy.(8) Although antimicrobial resistance has been recognized since the earliest days of antibiotic therapy (it developed rapidly in some bacteria after the first use of penicillin) the process has accelerated and compounded during the last two decades and is now reaching alarming levels in certain pathogens and certain geographical regions, the causes of antimicrobial resistance are complex and multi-factorial in nature. (9, 10) Firstly, antimicrobial resistance is a naturally occurring biological phenomenon driven by Darwinian natural selection

,hence it is an inevitable accompaniment of appropriate antibiotic use.(11) However, accumulated evidence points to misuse of antibacterials having further amplified the emergence and spread of antibacterial resistance.(11, 12) The antimicrobial resistance crisis is heightened by the concomitant downward trend in the intent of pharmaceutical companies to develop novel antimicrobials, as a consequence only a limited number of new antibacterial drugs have been introduced into the market in the last three decades. (13, 14) (Figure 1).

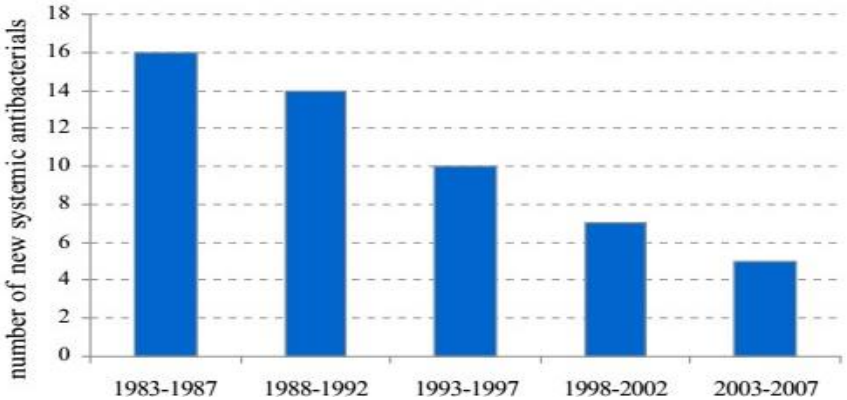


figure (1) systemic antimicrobial

Antibiotics are one of the most commonly used medicines in hospitals and have substantial share from the hospitals’ budget, as their inappropriate use has both medical

(increased risk of side-effects, therapeutic failure), economic (financial burden) and public health consequences (selection of resistance) substantial efforts are needed to rationalize their use. (15)

Before designing any interventions aiming to optimize antibiotic use, data collection and evaluation is needed to identify problematic fields. At international level, the European Surveillance of Antimicrobial Consumption (ESAC) project is tasked with collecting reliable antibiotic use data.

### 1.2.1.The history of drug utilization studies and the Drug Utilization Research Group:

The field of drug utilization research has roots back to the 1960s, when early drug utilization studies were performed in Northern Europe and the United Kingdom. (16) During this early work, international comparisons were impossible, due to the application of different units and methods to measure drug use. To overcome this difficulty, scientists mainly from Northern European countries came together in an informal group and developed a new unit of measurement, initially called the agreed daily dose and later the defined daily dose (DDD). (17) Another important methodological development was the introduction of the uniform Anatomical Therapeutic Chemical (ATC) classification system in the mid-1970s. (18)

The first publication applying the ATC/DDD principles appeared in 1975, while from 1981, the ATC/DDD system was proposed for drug utilization studies. To maintain and develop the ATC/DDD system, the WHO Collaborating Centre for Drug Statistics Methodology was established in 1982 in Oslo. (19, 20) In 1996, the WHO realized that the ATC/DDD system should be implemented and used outside of Europe as well, and the expert panel of WHO International Working Group for Drug Statistics Methodology was founded to facilitate the globalization of the ATC/DDD system.

### 1.2.2.Types of antimicrobials:

Infection is the presence of an organism(s) in body tissue or fluids accompanied by a clinical adverse effect either locally or systemically on the host (21), the causes of antibiotic resistance are complex and include human behavior at many levels of society, the consequences affect everybody in the world. Similarities with climate change are evident. Many efforts have been made to describe the many different facets of antibiotic

resistance and the interventions needed to meet the challenge. However, coordinated action is largely absent, especially at the political level, both nationally and internationally, Antibiotics paved the way for unprecedented medical and societal developments, and are today in dispensable in all health systems. Achievements in modern medicine, such as major surgery, organ transplantation. Treatment of preterm babies, and cancer chemotherapy, antibiotics or antibacterial agent is any compound natural, synthetic or semi-synthetic that is clinically useful in the treatment of bacterial infections (22), all chemically synthesized wholly or partly modified compounds are used to combat bacterial infections (23), such compounds must have minimal toxicity for host and should kill the pathogen. on another hand the host should not become hypersensitive (allergic) to antibiotics (24), specific antimicrobial therapy designates treatment of infections with anti- infective agents directed against the infecting pathogen, one feature follow these pharmaceuticals is selective toxicity which can act upon bacteria at very low concentration levels without causing damage to the host cells(25), there are several classification schemes for antibiotics as the following: First, based on the basis of chemical /biosynthetic origin into biological e.g., Penicillin, semi –synthetic e.g., Penicillin derivatives and synthetic e.g., Chloramphenicol(25), second, are based on their spectrum of activity into Narrow-spectrum against Gram-negative or Gram-positive bacteria, whereas Broad- spectrum antibiotics affect a wide range of bacteria Gram-negative and Gram-positive bacteria(26), third classification, are based on their biological activity into two activity bactericidal and bacteriostatic action. The fourth classification, are based on their route of administration includes of oral, parenteral routes and topical applications (27), fifth classification, are based on their chemical structural class appendix (28), and, sixth classification are based on their mechanism of action including of inhibition the synthesis of the cell wall peptidoglycan or murrain layer, inhibition of cell membrane function, inhibition of protein synthesis, inhibition of nucleic acid synthesis and inhibition of metabolic pathway appendix.(29)

### 1.2.3.Uses of antimicrobial:

of antifungal agents in clinical use are first, polyenes group includes of Natamycin, Rimocidin, Filipin, Nystatin, Amphotericin-B, Candicin and Hamycin (28), second, an azoles group includes of three major groups which are Imidazole's, Triazoles and Thiazoles. Imidazole group includes of Clotrimazole, Miconazole, Ketoconazole ,

Clotrimazole ,Econazole ,Omoconazole, Bifonazole, Butoconazole, Fenticonazole, Isoconazole, Oxiconazole, Sertaconazole, Sulconazole and Tioconazole. While ,Triazoles group includes of Fluconazole, Itraconazole, Isavuconazole and Thiazole includes of third, (30) Allylamine/thiocarbamates includes of Terbinafine, Naftifine and Butenafine all of their antifungal activities to inhibition of synthesis of ergosterol for fungal cell membrane but it does not in animal cells.(31)

### 1.2.3.1.Therapeutic uses:

The best approach would be to rule out a life-threatening infection and if the child is stable ,to wait and watch for the evolution of the illness (32), however, in cases, where it is reasonably certain that there is a possibility of a bacterial infection and waiting is dangerous/detrimental ,initial therapy for infection is often empiric as guided by the clinical presentation, supportive lab evidences and will be modified or stopped as per the reports(33), clinically certain bacterial infection: In certain clear-cut clinical situations, specific microbe-logical tests are not typically performed, and one is justified to start antibiotics at a first stretch. Her, single antimicrobial agents with a narrowest spectrum should be directed at the most likely pathogens for the duration of therapy for clinically certain bacterial infections such as community-acquired pneumonia, otitis media, diphtheria ,bacillary dysentery, acute lymphadenitis, or cellulitis in the ambulatory setting (29), high probability of bacterial infection while waiting for lab results: In stable clinical circumstances, antimicrobial therapy should be deliberately with held until appropriate specimens have been collected and submitted to the microbiology laboratory. Important examples of this principle are suspected of enteric fever, urinary tract infection, infective endocarditis, osteoarticular infections etc. Patients with these infections are frequently ill for a period of several days to weeks ,and in such situations, antibiotic therapy should be delayed until multiple sets of blood cultures have been obtained.(25)

### 1.2.3.2.Prophylactically uses:

When administered during or shortly after surgical treatment, antimicrobial agents prevent infection when effective concentrations are present in the tissues. Since the surgical procedure is usually the time of maximum microbial contamination, it is recommended antimicrobial.

### 1.2.3.3.Surgical application:

Studies have indicated that antimicrobial prophylaxis decreases the frequency of wound infections after head and neck incisions that involve the pharyngeal or oral mucosa some clinicians consider Penicillin-G a better choice against the effective cefazolin because cephalosporin's are not adapted against anaerobic and oral organisms Group-D streptococci, clostridia, and enteric gram-negative bacilli are suspect pathogens in biliary tract surgery . Here ,the cephalosporin should be administered to patients considered to be at high risk, those more than 70 years of age or with acute obstructive jaundice, acute cholecystitis, or common duct stones (34).

Three conditions must be met for an antibiotic to be effective against bacteria:

i) A susceptible antibiotic target must exist in the cell,

ii) The antibiotic must reach the target in sufficient quantity, and

iii) The antibiotic must not be modified

Understanding antibiotic resistance mechanisms requires an understanding of where antibiotics exert their effect. There are five major modes of antibiotic mechanisms of activity and here are some examples(35).

### 1.2.4.Antimicrobial action:

prophylaxis begin just prior to surgery, earlier antimicrobial administration is unnecessary and later administration is usually less effective. A single dose of parenteral antimicrobial given prior to surgery provides adequate tissue level concentration protection throughout the surgical procedure (36).

### 1.2.4.1.Interference with cell wall synthesis:

B-lactam antibiotics such as penicillin's and cephalosporin's interfere with enzymes required for the synthesis of the peptidoglycan layer, Glycopeptide vancomycin, teicoplanin, oritavancin target the bacterial cell wall by binding to the D-alanyl-D-alanine termini of peptidoglycan chain, thereby preventing the cross-linking steps, Telavancin, a novel rapidly bactericidal lipoglycopeptide, inhibits peptidoglycan biosynthesis through preferential targeting of trans glycosylation(22).

### 1.2.4.2.Inhibition of protein synthesis:

Macrolides bind to the 50S ribosomal subunit and interfere with the elongation of nascent polypeptide chains, Aminoglycosides inhibit initiation of protein synthesis and

bind to the 30S ribosomal subunit, Chloramphenicol binds to the 50S ribosomal subunit blocking peptidyl- transferase reaction, Tetracyclines inhibit protein synthesis by binding to 30S subunit of ribosome, thereby weakening the ribosome-tRNA. The semisynthetic tetracycline derivative , colloquially termed the glycylglycines, act at the bacterial ribosome to arrest translation. The glycylglycines bind the ribosome more tightly than previous tetracycline's, so that the TetM resistance factor is unable to displace them from this site, hence TetM is unable to protect the ribosomes from the action of these new drugs. The TetA-mediated efflux system is ineffective against the glycylglycines, as they are not substrates for the transporter, the oxazolidinones , one of the newest classes of antibiotics, interact with the A site of the bacterial ribosome where they should interfere with the placement of the aminoacyl-tRNA(22).

### 1.2.4.3.Interference with nucleic acid synthesis:

Interference with nucleic acid synthesis Rifampicin interferes with a DNA- directed RNA polymerase. Quinolones disrupt DNA synthesis by interference with type II topoisomerases DNA gyrase and to-poisomerase IV during replication and by causing double strand breaks (23).

### 1.2.4.4.Inhibition of a metabolic pathway:

The sulfonamides (e.g. sulfamethoxazole) and trimethoprim each block the key steps in folate synthesis, which is a cofactor in the biosynthesis of nucleotides, the building blocks of DNA and RNA(22).

### 1.2.4.5.Disorganizing of the cell membrane:

The primary site of action is the cytoplasmic membrane of Gram-positive bacteria, or the inner membrane of Gram-negative bacteria. It is postulated that polymixins exert their inhibitory effects by increasing bacterial membrane permeability, causing leakage of bacterial content, the cyclic lipopeptide daptomycin displays rapid bactericidal activity by binding to the cytoplasmic membrane in a calcium-dependent manner and oligomernezing in the membrane , leading to an efflux of potassium from the bacterial cell and cell death(37).

### 1.2.5.Antimicrobial resistance:

The discovery and production of (synthetic) antibiotics in the first half of the previous century has been one of medicine’s greatest achievements. The use of

antimicrobial agents has reduced morbidity and mortality of humans and contributed substantial human's increased life span. Antibiotics are, either as therapeutic or as prophylactic agents, also widely used in agricultural practices, the first discovered antimicrobial compound was penicillin (38), a β-lactam antibiotic. Soon after this very important discovery, antibiotics were used to treat human infections starting with sulfonamide and followed by the aminoglycoside, streptomycin and streptothricin (39), nowadays numerous different classes of antimicrobial agents are known and they are classified based on their mechanisms of action, antibiotics can for instance inhibit protein synthesis, like aminoglycoside, chloramphenicol, macrolide, streptothricin, and tetracycline or interact with the synthesis of DNA and RNA, such as quinolone and rifampin, other groups inhibit the synthesis of, or damage the bacterial cell wall as β-lactam and glycopeptide do or modify, like sulfon-amide and trimethoprim, the energy metabolism of a microbial cell. Upon the introduction of antibiotics it was assumed that the evolution of antibiotic resistance (AR) was unlikely, this based on the assumption that the frequency of mutations generating resistant bacteria was negligible(39).

The first β-lactamase was identified in *Escherichia coli* prior to the release of penicillin for use in medical practice(40), besides β-lactams, the aminoglycoside–aminocyclitol family was also one of the first groups of antibiotics to encounter the challenges of resistance, over the years it has been shown by numerous ecological studies that ( increased )consumption contributes to the emergence of AR in various bacterial genera (41).

### 1.2.5.1.Mechanisms of resistance:

Bacteria have become resistant to antimicrobials through a number of mechanisms(42) :

i. Permeability changes in the bacterial cell wall which restricts antimicrobial access to target sites,

ii. Active efflux of the antibiotic from the microbial cell,

iii. Enzymatic modification of the antibiotic,

iv. Degradation of the antimicrobial agent,

v. Acquisition of alternative metabolic pathways to those inhibited by the drug,

vi. Modification of antibiotic targets,

vii. Overproduction of the target enzyme.

These AR phenotypes can be achieved in microorganisms by chromosomal DNA mutations, which alter existing bacterial proteins, through transformation which can create mosaic proteins and/or as a result of transfer and acquisition of new genetic material between bacteria of the same or different species or genera(43).

### 1.2.6.Antimicrobial consumption:

In response to the growing threat of antimicrobial resistance (AMR), the World Health Organization (WHO) developed the Global Action Plan (GAP) on AMR, which was adopted by the World Health Assembly in 2015(44), the goal of the GAP on AMR is to ensure continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way and accessible to all who need them. WHO Member States requested the establishment of a global surveillance systems to increase the knowledge base on the spread and drivers of AMR in human health. In 2015, WHO launched the Global Antimicrobial Resistance and Use Surveillance System (GLASS)1 to support the global efforts and development of national surveillance systems. An initial step for GLASS was the surveillance of AMR in bacteria causing common infections in humans. A fundamental component of the new global system is to include surveillance of the main AMR drivers. Antimicrobial use is one of the main drivers of AMR; hence, surveillance and optimal use of antimicrobial medicines are among the key strategies to combat AMR, and are included in the five main objectives of the GAP on AMR. Most antimicrobial consumption occurs in outpatient and community care. However, in the hospital setting, the density of antimicrobial use is much higher, and highly vulnerable patients are in close spatial proximity, contributing to the increased risk of development and spread of resistant microbial pathogens. The prevalence of antimicrobial treatment varies substantially between hospitals and countries, but it is reported that up to 50% of use is inappropriate or unnecessary(45, 46). Antimicrobial stewardship represents a key strategy for promoting responsible antimicrobial use(47), it aims to enhance patient safety and care by improving prescribing practices and providing appropriate antimicrobial treatment. At the public health level, antimicrobial stewardship contributes to minimizing the ecological sequelae of antimicrobial use by reducing the

selection pressure on the microbial population and serves to preserve therapeutic options. The implementation of antimicrobial stewardship programmes is recommended for promoting appropriate antimicrobial use in the hospital sector. Such programmes are based on several core elements that should be implemented in a systematic and coordinated way; these elements are leadership commitment and accountability, and the establishment of supporting structures (e.g. antimicrobial stewardship team) and a bundle of measures and interventions (e.g. clinical audits and education), monitoring of hospital antimicrobial consumption, as an integral part of antimicrobial stewardship programmes, has a central role in guiding antimicrobial stewardship activities; hence, its introduction is an important step towards improving antimicrobial management. As part of the AMR activities, WHO has initiated a global surveillance of the consumption of antimicrobial medicines. A methodology for the surveillance of antimicrobial consumption on a national, regional and global level was developed, and was followed by a period of intensive implementation efforts in low- and middle-income countries(48), areport documenting the results of the first implementation phase (2016–2018) was published in 2018(49), for in-depth assessment of prescribing practices in hospitals, a protocol for the conduct of point prevalence surveys (PPS) on antimicrobial use has been made available (50), with this document, WHO proposes an approach for monitoring antimicrobial consumption in hospitals, based largely on the WHO methodology used for monitoring antimicrobial consumption on a national level (49), one of the main differences between the hospital and GLASS guide for national surveillance systems for monitoring antimicrobial consumption in hospitals national monitoring methodology relates to the use of local hospital activity data instead of population-based data as the reference value (denominator) for antimicrobial consumption.

Consumption was estimated according to the WHO methodology for surveillance of antimicrobial consumption which utilizes (ATC), (DDD) and(DOT), the WHO has classified antibiotics into three categories as AWaRe: Access, Watch and Reserve (2).

### 1.2.6.1.The anatomical therapeutic chemical/defined daily dose system:

The anatomical therapeutic chemical (ATC)/defined daily dose (DDD) system is used as the basis for the classification of medicines and the calculation of medicines consumption estimates. The ATC/DDD system can also be used for antimicrobials. The ATC system represents a hierarchy in which medicinal substances are categorized into different groups according to the organ or system on which they act, and their therapeutic,

pharmacological and chemical properties. The DDD is used to quantify medicines consumption; it is assigned to each medicinal substance, taking into account the route of administration. It represents the average maintenance dose per day of a medicine used for its main indication in adults. The DDD is a purely technical unit; it serves as a standard measure for quantification, but does not necessarily reflect the recommended or actual use of the substance in an individual patient. The ATC/DDD system is maintained by the WHO Collaborating Centre for Drug Statistics Methodology (WHO CC) and is updated at yearly intervals(51), since changes in ATC codes or DDD values are possible, it is important that the ATC/DDD version that has been used for the calculations is noted and reported with the data. In particular, the ATC/DDD version must be taken into consideration when comparing data from different time periods (e.g. for the assessment of trends) and from different hospitals or countries. In addition, the surveillance system should be able to accommodate any changes to the ATC/DDD system; for example, by providing the possibility for recalculation of historical data according to the new DDD version.

### 1.2.6.2.The Anatomical therapeutic chemical (ATC):

In the ATC classification system, drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological, and therapeutic properties. Drugs are classified in groups at five different levels where a seven digit code identifies a unique active agent. The structure of the code is illustrated by the complete classification of levofloxacin:

**The table (1) the anatomical therapeutic chemical (ATC)**

| | |
|---|---|
| **J** | **Antiinefective for systemic use (1st level, anatomical main groug)** |
| **J01** | Antibactirials for systemic use (2nd level, therapeutic subgroup) |
| **J01M** | Quinolone antibacterials (3rd level, pharmacological subgroup) |
| **J01MA** | fluoroquinolones (4th level, pharmacological/chemical subgroup) |
| **J01MA12** | levofloxacin (5th level, chemical substance) |

Medicinal products are classified in the ATC system according to their main therapeutic indication of their main active ingredient. An active ingredient can be classified under more an one ATC code, if it is marketed in different strength and/or formulation with clearly different therapeutic uses (e.g. oral and rectal metronidazole: P01AB01;intravenous metronidazole: J01XD01(52)

### 1.2.6.3.Drug utilization metrics, concept of the defined daily dose (DDD):

The defined daily dose (DDD) is an internationally accepted technical unit in drug utilization studies. It means the assumed average maintenance dose per day for a drug used for its main indication in adults. It should be emphasized that the DDD does not necessarily correspond to the recommended-, or actually prescribed daily dose (RDD and PDD), Drug utilization figures should ideally be standardized. The DDDs per 1,000 inhabitants and per day is the most widely used measurement unit, mainly applied for ambulatory care drug consumption data. When drug use in hospitalized patients is considered, the number of DDDs per 100 patient-days is the WHO recommended technical unit (52), while the number of DDDs per 100 admissions is an optional, complementary unit.

Although the DDD per 100 patient-days is the WHO recommended measure of hospital drug use that allows international comparison(53), its limitations should be emphasized. First, different studies may use different definitions for the length of stay or fail to report the definition which could greatly affect the value of the denominator (i.e. patient-days) and hence the resulting drug consumption value. Due to this, the applied calculation method (e.g. whether days of admission and discharge count together as one or two patient-days) should be clearly stated.(54) Secondly, drug utilization studies rarely assess the precise amount of drug ingested by or administered to the patients .(55) They provide an upper or lower estimation of real drug use, depending on the data source they are derived from (prescribed quantity, distributed quantity, dispensed quantity, reimbursed quantity).

Although the WHO intends to keep the number of alterations to minimum, it is important to be aware that the ATC/DDD index is a dynamic system to which changes are made continually, for enhancing the meaningful comparisons of drug consumption data, the applied version of the ATC/DDD index should be also indicated in the published data. (52)

### 1.2.6.4.Days of therapy (DOT):

were defined as the sum of days (including admission and discharge days) for which any amount of a specific antimicrobial agent was administered to individual patients(3).

### 1.2.6.5.Access, Watch, and Reserve (AWaRe) Categories:

Access, Watch, and Reserve (AWaRe) categories based on the WHO Model List of Essential Medicines were assigned to each antibiotic substance (ATC5) using the latest version, antibiotics substances that are not included in the WHO Model List of Essential Medicines have not yet been categorized, and are reported as “Other” (56).

1- Access (antibiotics needed for common infections that should be available and accessible).

2- Watch (broad-spectrum antibiotics that should be used with caution because of their high potential to develop resistance).

3- Reserve (antibiotics that should be reserved for the treatment of multidrug-resistant infections and used only when other alternatives fail.(2)

# Chapter II: Objectives

# 2.Objectives:

## 2.1.General objective:

Our study aimed to determine the antibiotic consumption in ICUs of hospitals in Sana'a city.

## 2.2.Specific objectives aimed to:

**1-** Assess the antimicrobial consumption patterns in ICUs.

**2-** Assess the antimicrobial consumption according to AWaRe classification.

**3-** Compare the measurement of antimicrobial consumption by defined daily dose (DDD) versus by days of therapy (DOT).

# Chapter III: Materials and Methods

# 3. Materials and Methods

## 3.1. Study design:

A retrospective study of medical records for all admissions to the ICUs. The study was carried out from September 2021 to February 2022.

## 3.2. Study area:

This study was conducted in five main hospitals at Sana'a city – Yemen, three of them were public hospitals and two were private. Public hospitals included Al-Thawra Modern General Hospital (ATH) AL- Jomhori Teaching Hospital (AJH) and 48 Hospital (48H), while private hospitals included Dr.Abdulkader Almutawakel Hospital (AMH) and University and Technology Hospital (USTH).

## 3.3. Study population:

All patient admitted in ICUs of these hospitals at 2020. All the data was collected manually from patient records except data of USTH was electronic.

## 3.4.Sample size:

All adult patient admitted to ICUs with prescribed and received antibiotics of five hospitals during 2020 were included (1970) patients in this study.

## 3.5.Excluded data:

All children admitted to ICUs or patients who lacked data on prescribed and received medications were excluded.

## 3.6.Data collection:

Data of patients in ICUs were extracted from the ICU patient register. using structured questionnaire containing several variables included the age of a patient ,sex , entry day ,discharge day , inpatient days or admission , inpatient days or admission name of antimicrobial with strength, strength antibiotic type ( tab , vial , amp , syr , sus ), antibiotic description (dose No /day /period ), rout of administration (oral , IM , IV ) antibiotic scientific name, antibiotic class, antibiotic subclass. .

## 3.7.Data analysis:

All data were coded and entered into a Microsoft Excel file. The spreadsheet was used for the calculation of DDDs based on the strength of each antibiotic, the number of dose units and the DDD values allocated by the World Health Organization. The statistical

analyses were done using SPSS version 22.0 software package for windows. Measures of relative consumption, expressed as a percentage of total consumption of groups of antibiotics, were derived for each antibiotic and DDD for “Watch” and “Access” category of antibiotics was calculated.

## 3.8.Defined Daily Dose Method (DDD):

To estimated antimicrobial use using the DDD method, the total number of grams of each drug used during the period of study were summed and divided by the WHO-assigned DDD. Dividing total grams of use by the DDD (grams/day) yields an estimate of the number of days of antimicrobial therapy. All DDDs were based on the 2020 version of the ATC classification system. To express aggregate use, total DDDs were normalized per 1000 patient-days.

## 3.9.Days of Therapy Method (DOT):

To estimate antibiotic use using the DOT method, one DOT represented the administration of a single agent on a given day, regardless of the number of doses administered or dosage strength. A single patient receiving two antimicrobial drugs would be recorded as receiving 2 DOTs (1 for each drug administered) and so on according to the number of antimicrobials received daily. To express aggregate use, total DOTs were normalized to 1000 patient-days.

# Chapter IV: Results

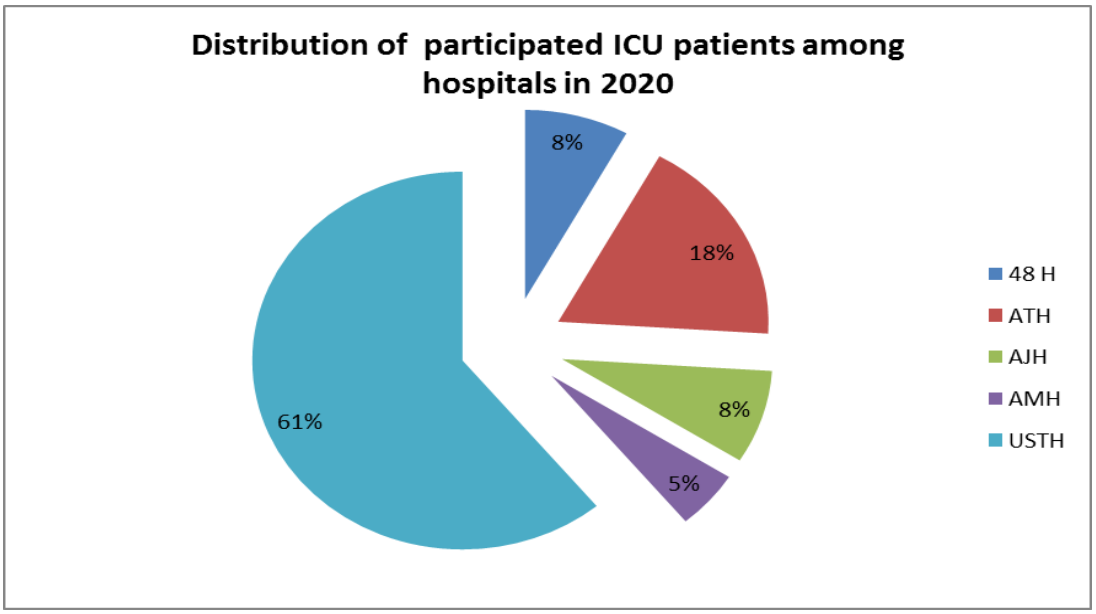
# 4. Results

A total of 1970 patients were included in this study. The data of admitted patients of ICUs hospitals at 2020 was collected from patient recorders of five selected hospitals at Sana'a city. This study was conducted from September 2021 to February 2022 and the following results were found:

## 4.1. Study population and hospital distribution:

A total of 1970 patients their data were collected from University Science and Technology Hospital(USTH), while only 167, 345,156 and 105 were collected from 48 Hospital (48H), AL-Thawra Modern General Hospital (ATH), Al-Jomhori Teaching Hospital (AJH), and Dr. Abdulkader Almutawakel Hospital (AMH), respectively.

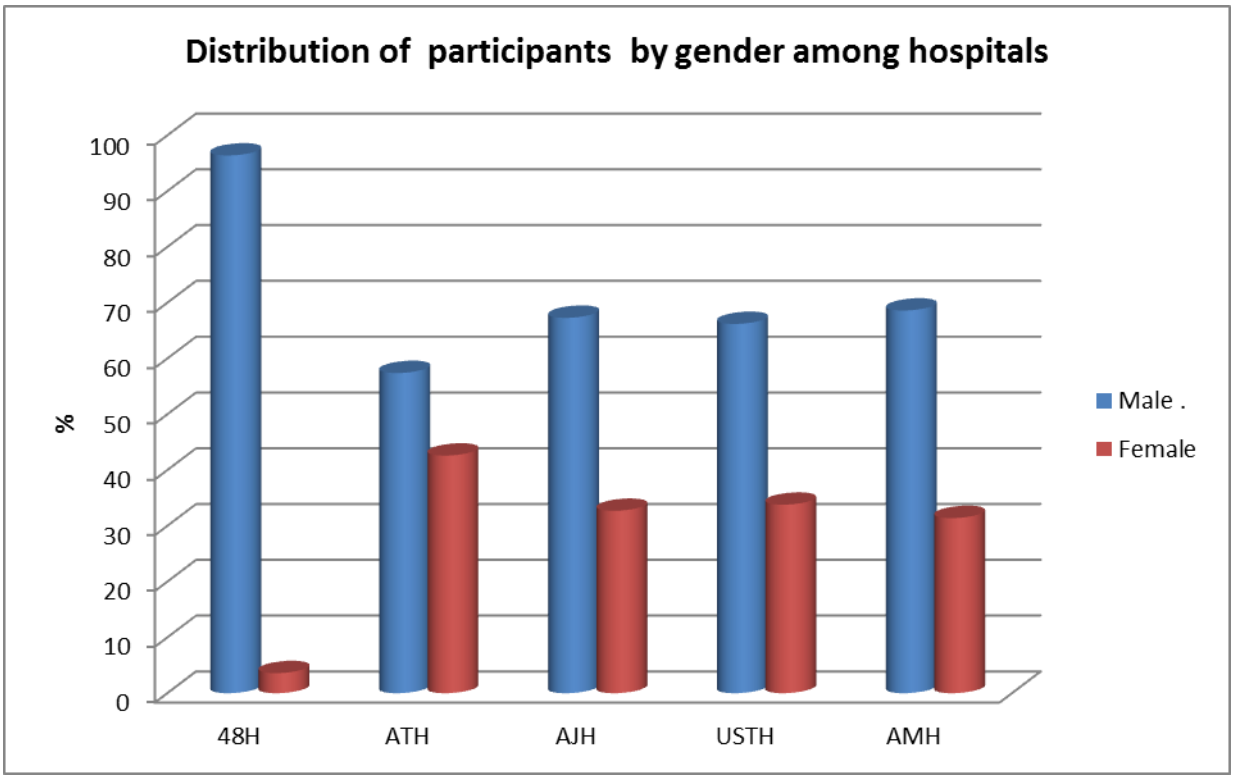
The most participated patients showed that 61% in this study were from USTH while lowest participation from AMH was 5%.




The figure (2) showed that 61% of data collected was from USTH, while 39% were from other four hospital.

## 4.2. Demographic characteristics of participants:

In figure (3) showed that the ICU patients by gender presented that males (67.4 %, 1328) more than females (33%, 642) among all hospitals. In 48H majority 96.4% of patients were males.




The figure (3) showed that 67.4% of data collected was male, while 32.6% was female.

In figure (3) showed the age categories were distributed from 15 years to more than 60 year, and the highest number of participant belong to the oldest age category was (38.5%) while the lowest number belong to the youngest category was (17.2%).

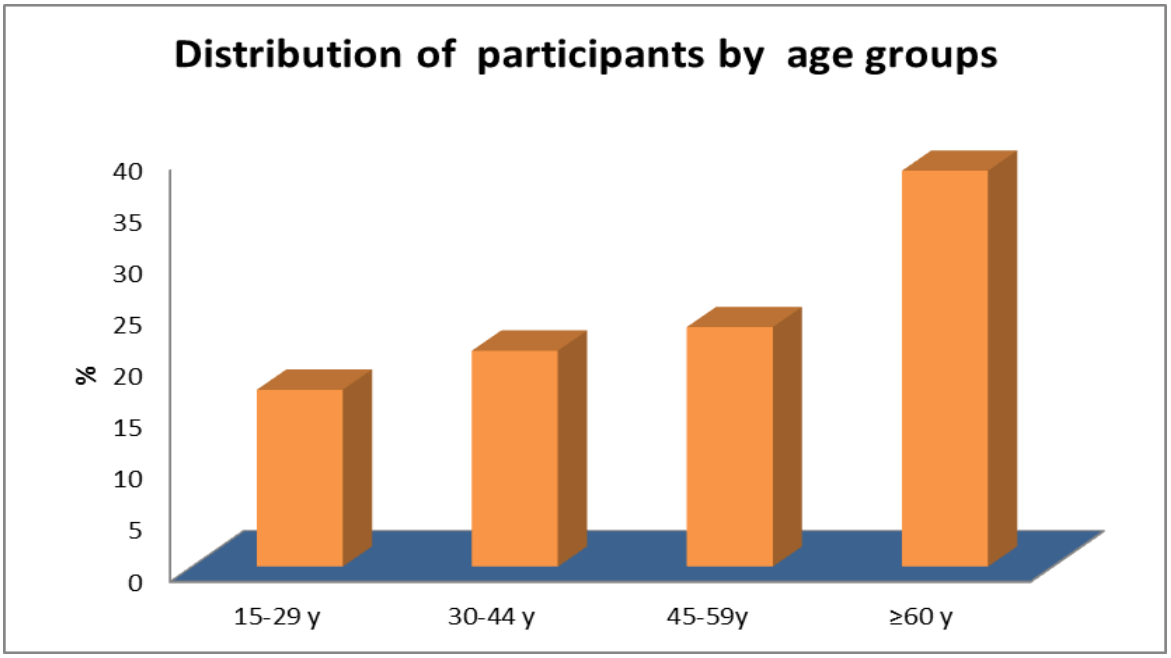



Figure (4) showed the age groups more than 60 year was the highest.

In table (2) showed a total patients day were 13872 days for all ICUs patients and was 7.04 days the average of admission days/patient in this study. It is worth mentioning that USTH reported the highest mean admission days to patient was 8.15 days compare to the other hospitals.

**Table (2) distribution of total patients day and the average for patient among hospitals**

| Hospital | No of ICU patients. | No of ICU beds | Total patients day | Average of admission days/patient |
|---|---|---|---|---|
| 48H | 167 | 23 | 689 | 4.13 |
| ATH | 345 | 45 | 2431 | 7.05 |
| AJH | 156 | 78 | 749 | 4.80 |
| AMH | 105 | 22 | 250 | 2.38 |
| USTH | 1197 | 32 | 9753 | 8.15 |
| Grand total | 1970 | 200 | 13872 | 7.04 |

## 4.3.Antimicrobial prescription

In table (3) we observed that the total number of prescribed antimicrobials for all patients were 5255 and average number. of prescribed antimicrobial /patient was 2.67.

**Table (3) distribution of consumed antimicrobial and the average for patient among hospitals**

| Hospital | No of ICU patients. | No. of consumed Antimicrobial | Average No. of consumed Antimicrobial /patient |
|---|---|---|---|
| 48H | 167 | 402 | 2.41 |
| ATH | 345 | 782 | 2.27 |
| AJH | 156 | 205 | 1.31 |
| AMH | 105 | 171 | 1.63 |
| USTH | 1197 | 3695 | 3.09 |
| Grand total | 1970 | 5255 | 2.67 |

In table (4) a total amount of consumed antimicrobials in gram was (70974.06) and the average of consumption was 8.67 grams per patient. ATH showed the highest average of consumption among hospitals reported 9.78 grams , while the lowest amount in AMH 4.03 grams of antibiotics

| Table (4) distribution of total amount and average of consumed antimicrobial among hospitals | | | |
|---|---|---|---|
| **Hospital** | **No. of ICU patients** | **Total amount of consumed Antimicrobial (grams)** | **Average amount of consumed Antimicrobial/ patient** |
| **48H** | **167** | **3443.79** | **8.57** |
| **ATH** | **345** | **7684.483** | **9.78** |
| **AJH** | **156** | **1566.45** | **7.60** |
| **AMH** | **105** | **692.64** | **4.03** |
| **USTH** | **1197** | **57586.7** | **8.70** |
| **Grand total** | **1970** | **70974.06** | **8.67** |

In table (5) a total days of treatment by antimicrobial was 4.659, and the average of **days of treatment** per patient was 17.45 days. USTH showed the highest average of days of treatment by antimicrobial among hospitals reported 22.51 days , while the lowest amount in AJH 5.90 days of treatment.

| Table (5) distribution of total and average days of treatment among hospitals | | | |
|---|---|---|---|
| **Hospital** | **No of ICU patients.** | **Total days of treatment** | **Average days of treatment/ patient** |
| **48H** | **167** | **1873** | **11.22** |
| **ATH** | **345** | **4204** | **12.19** |
| **AJH** | **156** | **920** | **5.90** |
| **AMH** | **105** | **431** | **4.11** |
| **USTH** | **1197** | **26948** | **22.51** |
| **Grand total** | **1970** | **34376** | **17.45** |

## 4.4.Rout of administration:

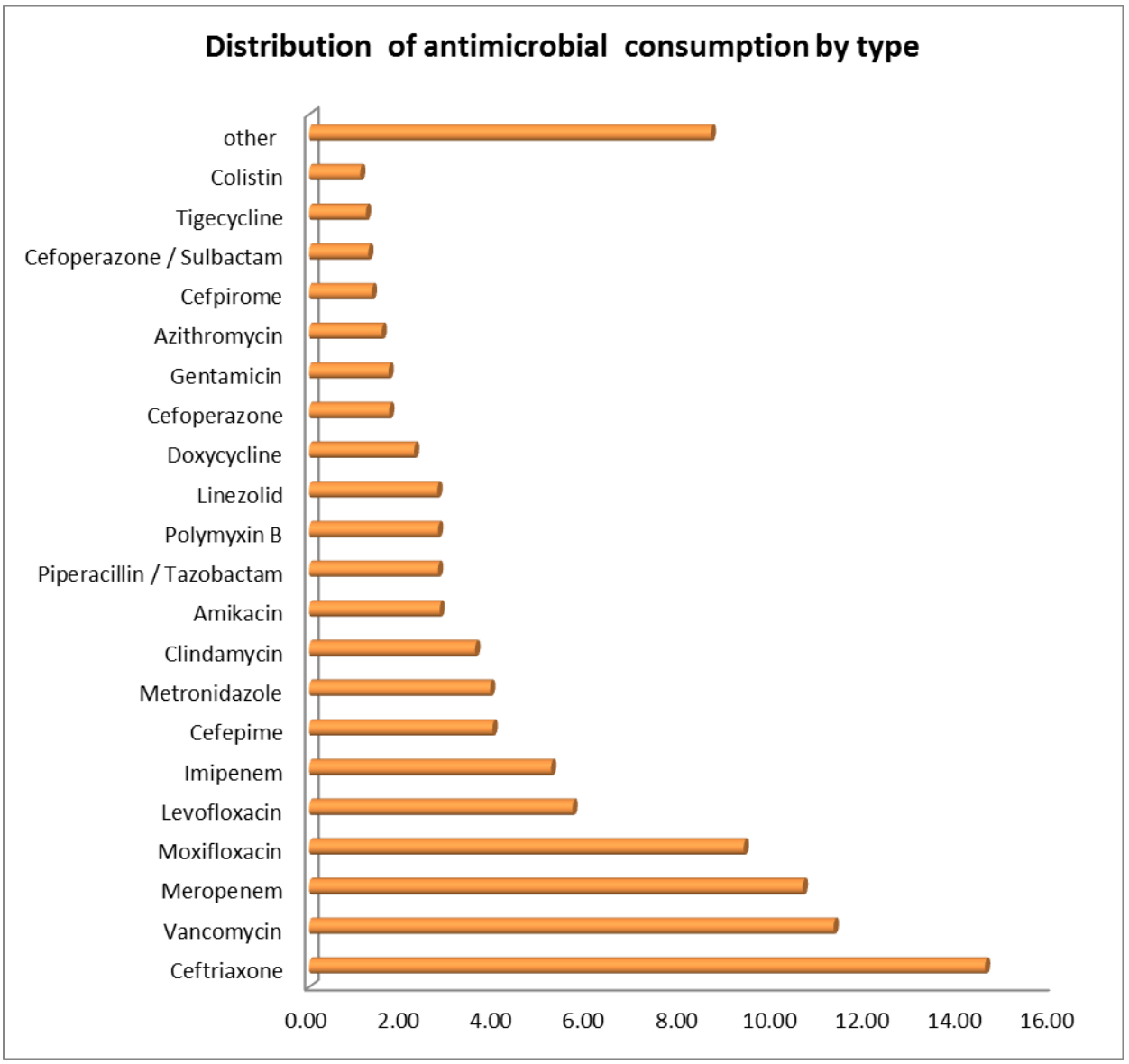
In table (6) the parenteral rout was the most common rout for antibiotics administration of patients in ICU.

| Table (6) distribution of antimicrobial administration rout among hospitals | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Administration rout** | **48H** | **ATH** | **AJH** | **AMH** | **USTH** | **Total** | **%** |
| **Parenteral** | **400** | **744** | **205** | **167** | **5610** | **7126** | **88.9** |
| **Oral** | **2** | **42** | **1** | **5** | **837** | **887** | **11.1** |
| **Grand Total** | **402** | **786** | **206** | **172** | **6447** | **8013** | **100** |

## 4.5.Prevalence of antibiotics:

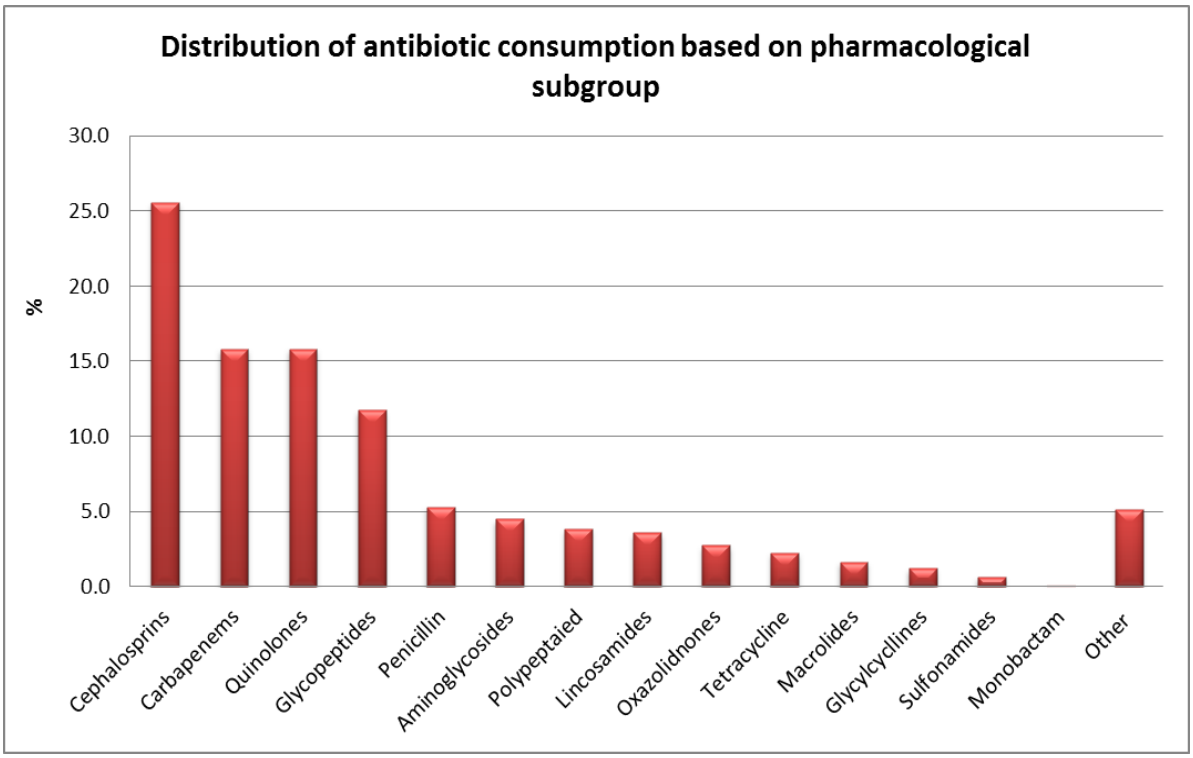
The figure (5) showed the most frequently antimicrobial use were ceftriaxone

(14.5%), vancomycin (11.3%), meropenem (10.6%) and moxifloxacin (9.3%) in all ICUs. Levofloxacin reported (5.7%), imipenem (5.2%) cefepime and metronidazole (3.9%) for each one, while polymyxin B (2.8%), tigecycline (1.2%), and colistin (1.1%).




The figure (5) describe the consumption of antibiotic.

The figure (6) based on pharmacological subgroup of ATC, cephalosporins reported the most consumed group (26%), followed by carbapenems (16%), quinolones (14%) and glycopeptides (12%). Aminoglycosides and penicillins groups reported moderate consumption were (5%) for each one.




The figure (6) describe the consumption of antibiotic.

## 4.6.Consumption of antibiotics by DDDs and DOTs:

In table (7) showed the most average of antimicrobial consumption regarding antimicrobial consumption using DDDs and DOT in ICUs patients were ceftriaxone, vancomycin, and meropenem reported 2479.23, 2124.55 and 1830.54 DDDs per 1000 admissions, respectively. While the average amount of polymyxin B, tigecycline, and colistin were 670.05, 294.42, and 8.68 DDDs per1000 patients, respectively. On the other side, the most average of antimicrobial consumption using DOTs, reported ceftriaxone, vancomycin, and meropenem with 2112.69, 2055.33, and, 1890.86 DOTs per 1000 patient-days, respectively. The same antibiotics were reported by both methods.

**Table (7) Distribution of antimicrobial consumption with DDD and DOT**

| Antimicrobials | Grams (mean ) | DDD(Sum) | DDD (%) | Rate DDD per 1000 patient | DOT(Sum) | DOT (%) | Rate of DOT per 1000 patient-days |
|---|---|---|---|---|---|---|---|
| Amikacin | 3.39 | 762.3 | 2.1% | 386.93 | 1001 | 2.9 | 508.12 |
| Amoxicillin | 1.00 | 0.7 | 0.0% | 0.34 | 1 | 0.0 | 0.51 |
| Amoxicillin /clavulanic acid | 7.21 | 239.7 | 0.7% | 121.69 | 280 | 0.8 | 142.13 |
| Ampicillin | 9.01 | 31.6 | 0.1% | 16.02 | 73 | 0.2 | 37.06 |
| Ampicillin/cloxacillin | 1.32 | | 0.0% | 0.00 | 106 | 0.3 | 53.81 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Azithromycin** | **2.29** | **933.0** | **2.6%** | **473.62** | **547** | **1.6** | **277.66** |
| **Aztreonam** | **4.00** | **2.0** | **0.0%** | **1.02** | **8** | **0.0** | **4.06** |
| **Cefaclor** | **0.13** | | **0.0%** | **0.00** | **1** | **0.0** | **0.51** |
| **Cefadroxil** | **0.50** | **0.8** | **0.0%** | **0.38** | **3** | **0.0** | **1.52** |
| **Cefazolin** | **12.00** | **4.0** | **0.0%** | **2.03** | **3** | **0.0** | **1.52** |
| **Cefepime** | **12.87** | **1016.8** | **2.9%** | **516.12** | **1617** | **4.7** | **820.81** |
| **Cefixime** | **5.26** | **2.0** | **0.0%** | **1.02** | **17** | **0.0** | **8.63** |
| **Cefoperazone** | **11.13** | **384.0** | **1.1%** | **194.92** | **619** | **1.8** | **314.21** |
| **Cefoperazone / sulbactam** | **12.22** | **311.5** | **0.9%** | **158.12** | **505** | **1.5** | **256.35** |
| **Cefotaxim** | **10.13** | **177.3** | **0.5%** | **89.97** | **272** | **0.8** | **138.07** |
| **Cefpirome** | **12.59** | **340.0** | **1.0%** | **172.59** | **537** | **1.6** | **272.59** |
| **Cefpodoxime** | **0.68** | **8.5** | **0.0%** | **4.31** | **11** | **0.0** | **5.58** |
| **Ceftazidime** | **10.74** | **134.3** | **0.4%** | **68.15** | **233** | **0.7** | **118.27** |
| **Ceftriaxon / sulbactam** | **13.39** | **308.0** | **0.9%** | **156.35** | **218** | **0.6** | **110.66** |
| **Ceftriaxone** | **8.38** | **4884.1** | **13.8%** | **2479.23** | **4162** | **12.1** | **2112.69** |
| **Ceftriaxone / tazobactum** | **4.00** | | **0.0%** | **0.00** | **2** | **0.0** | **1.02** |
| **Cefuroxime** | **5.88** | **78.3** | **0.2%** | **39.76** | **128** | **0.4** | **64.97** |
| **Ciprofloxacin** | **2.07** | **153.3** | **0.4%** | **77.79** | **252** | **0.7** | **127.92** |
| **Clarithromycin** | **8.38** | **130.0** | **0.4%** | **65.99** | **60** | **0.2** | **30.46** |
| **Clindamycin** | **7.67** | **1310.0** | **3.7%** | **664.95** | **1216** | **3.5** | **617.26** |
| **Colistin** | **1.75** | **17.1** | **0.0%** | **8.68** | **414** | **1.2** | **210.15** |
| **Doxycycline** | **1.16** | **2104.0** | **5.9%** | **1068.02** | **966** | **2.8** | **490.36** |
| **Gentamicin** | **0.68** | **390.7** | **1.1%** | **198.31** | **468** | **1.4** | **237.56** |
| **Imipenem** | **3.68** | **9.2** | **0.0%** | **4.67** | **19** | **0.1** | **9.64** |
| **Imipenem /cilastatin** | **11.02** | **2270.1** | **6.4%** | **1152.33** | **1947** | **5.7** | **988.32** |
| **Levofloxacin** | **2.35** | **2129.6** | **6.0%** | **1081.02** | **1898** | **5.5** | **963.45** |
| **Lincomycin** | **1.60** | **1.8** | **0.0%** | **0.90** | **2** | **0.0** | **1.02** |
| **Linezolid** | **5.96** | **1098.5** | **3.1%** | **557.62** | **1025** | **3.0** | **520.30** |
| **Meropenem** | **12.71** | **3606.2** | **10.2%** | **1830.54** | **3725** | **10.8** | **1890.86** |
| **Metronidazole** | **5.81** | **1209.4** | **3.4%** | **613.91** | **1487** | **4.3** | **754.82** |
| **Moxifloxacin** | **1.83** | **3429.0** | **9.7%** | **1740.61** | **3086** | **9.0** | **1566.50** |
| **Nitrofurantoin** | **1.60** | | **0.0%** | **0.00** | **8** | **0.0** | **4.06** |
| **Norfloxacin** | **0.05** | | **0.0%** | **0.00** | **3** | **0.0** | **1.52** |
| **Ofloxacin** | **0.80** | **2.0** | **0.0%** | **1.02** | **2** | **0.0** | **1.02** |
| **Penicillin G** | **2.65** | **2.9** | **0.0%** | **1.49** | **11** | **0.0** | **5.58** |
| **Piperacillin** | **8.70** | **13.7** | **0.0%** | **6.94** | **106** | **0.3** | **53.81** |
| **Piperacillin / Tazobactam** | **61.86** | **981.0** | **2.8%** | **497.94** | **1002** | **2.9** | **508.63** |
| **Polymyxin B** | **0.89** | **1320.0** | **3.7%** | **670.05** | **1011** | **2.9** | **513.20** |
| **Rifaximin** | **4.23** | **586.0** | **1.7%** | **297.46** | **356** | **1.0** | **180.71** |
| **Sodium fusidate** | **0.75** | | **0.0%** | **0.00** | **15** | **0.0** | **7.61** |
| **Sulfamethoxazole/ trimethoprim** | **8.54** | | **0.0%** | **0.00** | **267** | **0.8** | **135.53** |
| **Tazobactam** | **135.00** | | **0.0%** | **0.00** | **10** | **0.0** | **5.08** |
| **Teicoplanin** | **3.41** | **307.0** | **0.9%** | **155.84** | **171** | **0.5** | **86.80** |
| **Tetracycline** | **4.00** | **40.0** | **0.1%** | **20.30** | **2** | **0.0** | **1.02** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Tigecycline** | **0.59** | **580.0** | **1.6%** | **294.42** | **452** | **1.3** | **229.44** |
| **Vancomycin** | **9.26** | **4185.4** | **11.8%** | **2124.55** | **4049** | **11.8** | **2055.33** |
| **Total** | | **35495.3** | **100.0%** | **18017.91** | **34374** | **100.0** | **17448.73** |

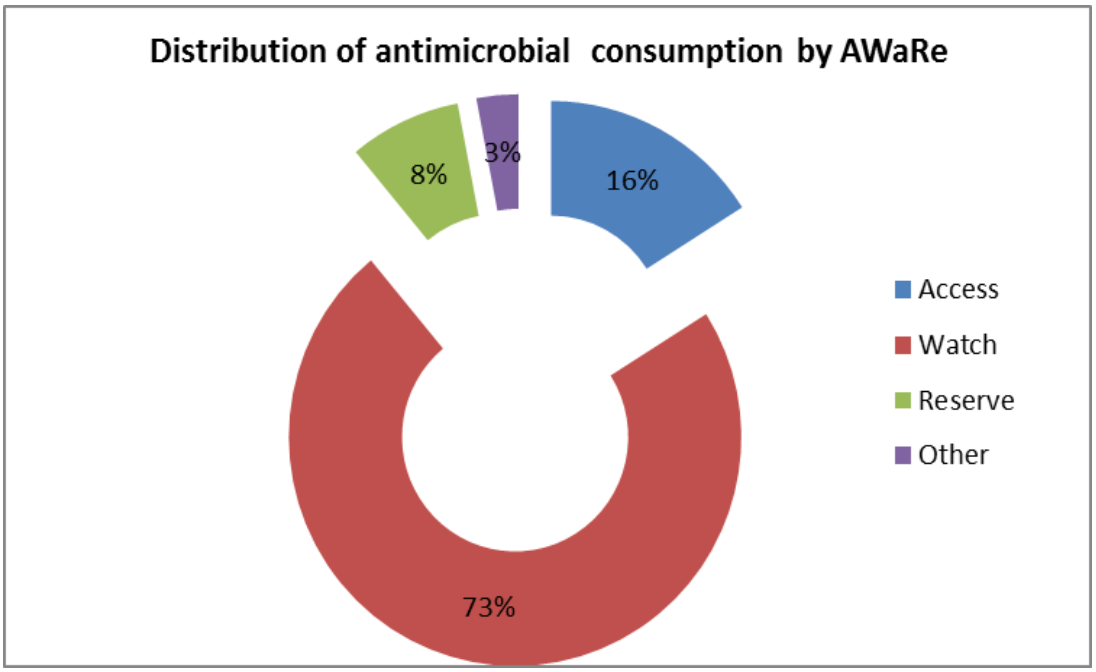
The table (8) showed a total consumption of antibiotic for systemic use was 18017 DDD per 1000 patient . The vast majority of consumption among therapeutic/Pharmacological subgroups consisted of cephalosporins (3882 DDD per 1000 patient), while carbapenems (2987 DDD per 1000 patient) and quinolones (2900 DDD per 1000 patient per days). The rate of DOTs per 1000 patient-days were cephalosporins was 4227.41DOTs per 1000 patient-days, while carbapenems was 2888.83DOTs per 1000 patient-days, and quinolones was 2660.41DOTs per 1000 patient-days.

**Table (8) Distribution of therapeutic/Pharmacological subgroup of antimicrobial with DDD and DOT**

| Therapeutic/Pharmacological Subgroup (ATC) | Number of DDDs | Rates DDD per 1000 patient | Number of DOTs | Rates DOT per 1000 patient days |
|---|---|---|---|---|
| **Aminoglycosides** | **1152.9** | **585.24** | **1469** | **745.69** |
| **Carbapenems** | **5885.5** | **2987.54** | **5691** | **2888.83** |
| **Cephalosprins** | **7649.4** | **3882.95** | **8328** | **4227.41** |
| **Glycopeptides** | **4492.4** | **2280.38** | **4220** | **2142.13** |
| **Glycylcycllines** | **580.0** | **294.42** | **452** | **229.44** |
| **Lincosamides** | **1311.7** | **665.86** | **1218** | **618.27** |
| **Macrolides** | **1063.0** | **539.61** | **607** | **308.12** |
| **Monobactam** | **2.0** | **1.02** | **8** | **4.06** |
| **Oxazolidnones** | **1098.5** | **557.62** | **1025** | **520.30** |
| **Penicillins** | **1269.5** | **644.43** | **1589** | **806.60** |
| **Polypeptaied** | **1337.1** | **678.73** | **1425** | **723.35** |
| **Quinolones** | **5713.9** | **2900.43** | **5241** | **2660.41** |
| **Sulfonamides** | | **0.00** | **267** | **135.53** |
| **Tetracycline** | **2144.0** | **1088.32** | **968** | **491.37** |
| **Other** | 1795.4 | 911.37 | 1866 | 947.2 |
| **Total** | **35495.3** | **18017.91** | **34374** | **17448.73** |

## 4.7AWaRe categories :

In figure (7) showed the most commonly used antibiotics by AWaRe category were those from the Watch category 73%, followed by the Access category 16%.




The figure (7) shows that 73% of antibiotics was watch, and 27% was the other classification.

In table (9) the highest amount of antibiotics consumption among WHO AWaRe classification was for "watch" group of 26267.4 DDDs and 14674.5 DDDs per 1000 patient per day.

**Total (9) Distribution of antibiotics consumption by DDD per 1000 Patient per day by WHO AWaRe system**

| WHO AWaRe Category | Number of DDDs | Rates DDD per 1000 patient |
|---|---|---|
| **Access** | 6121.2 | 3419.7 |
| **Watch** | 26267.4 | 14674.5 |
| **Reserve** | 1804.6 | 1008.2 |
| **Other** | 5347.0 | 2987.2 |
| **Total** | **34836.7** | 19461.9 |

# Chapter V: Discussion

## 5.Discussion:

This is the first study to report on antibiotic consumption in Yemen. The findings of this study are important as they serve as a baseline for future monitoring of antibiotic consumption in the country.

In this report using multiple metrics; including DDD, DOT, and the frequency of daily consumption. The calculation of different metrics was essential to improve the clinical and benchmarking usability of this data. For example, it has been shown that the choice of indicator for the surveillance of antimicrobial consumption is critical to evaluate the impact of any stewardship program and to enhance the ability to predict future antimicrobial resistance AMR. Additionally, complementary and sometimes conflicting findings of the impact of antimicrobial stewardship have been reported based on whether DDDs versus DOTs are calculated. This is further complicated by the main stewardship target; the length of stay, number of patients receiving treatment, or duration of treatment. Moreover, DDDs and DOTs are theoretically reflecting different aspects of antimicrobial consumption.(58 )

The main advantages of the DDD method are that it enables antimicrobial use to be compared using standardized methods across a wide number of healthcare settings and countries, because it can be used with relative ease where administrative records are less developed and where it is more feasible to count packages and vials that have been purchased or dispensed than to measure the number of days of antimicrobial therapy. The most important limitation of DDD methods is discrepancies between administered daily doses and the WHO-assigned DDD. The main advantages of the DOT method are that it is not influenced by changes in the DDD or by discrepancies between the administered daily doses and DDD. The most important limitation of DOT methods results is the difficulty of measurement when computerized pharmacy records are not available.

The main finding of this study was the high consumption of broad-spectrum antimicrobial agents, specifically ceftriaxone, meropenem, and vancomycin irrespective of the metrics used. On the other hand, the majority of international studies show that penicillin's or cephalosporin's are the most frequently consumed antimicrobials in adult ICUs. Unfortunately, this study cannot determine the magnitude of inappropriate consumption in the above broad-spectrum antimicrobials.

Comparison of the consumption rates from this study with local data is impossible because no previous published studies addressed this subject. On the other hand, the consumption of cephalosporin's in this study was considerably higher than the rates reported by several reports around the world.(3) For example, it was 3882.95 DDDs per 1000 patient-days in current ICUs compared with 47.6 in Saudi Arabia, 264.19 in the Romania, and higher than Nepal, Spain, and Sierra Leone.

The consumption of carbapenems in this study was higher than rates reported by above international reports. For example, the consumption of carbapenems in this study was 2987.54 DDDs per 1000 patient which was higher than Saudi Arabia ICUs 255.9, Romania 224.59, and more than Spain and Nepal. The consumption of vancomycin in our study was 2124.55 DDDs per 1000 patient was higher than above international reports. (2,58)

As most of the DOT-based international reports of antimicrobial consumption were derived from whole hospital data populations comparing the current ICU-specific DOT rates is challenging. Nevertheless, this study had slightly higher.

The findings of this study can be used as a starting point in the implementation and strengthening of Antimicrobial Stewardship Programs (DDD and DOT) and encourage other hospitals throughout the country to measure their antibiotic consumption rates. Antibiotic consumption measurement and reporting are an important part of DDD. Many studies recommend implementation of DDD in hospitals to combat antimicrobial resistance due to over-consumption of antibiotics, since implementation of DDD is shown to reduce antibiotic consumption rates. The government should encourage the establishment of a sustainable antibiotic surveillance reporting framework. (3,57,58)

This study used the amount of antibiotics dispensed in ICU to estimate the consumption rates of antibiotics and this might not always reflect the actual amount “consumed” by patients. However, even with this inherent limitation of the study, we believe the methodology adopted would be more than adequate to give a clue to the antibiotic consumption rate using a standardized metric. Future studies should focus on computing antibiotic consumption from all wards and use days-of-therapy to calculate antibiotic consumptions.

The most frequently consumed antibiotics according to therapeutic/pharmacological subgroup were cephalosporin's, carbapenem, vancomycin and other antibiotics, consisting

mainly of Parenteral. Antibiotics were consumed orally and parenterally at different rates, the total intravenous antibiotic use was 8460 while the total oral dose was 885. Of the total DDD per 1000 admission per day. Unlike Sierra Leone was parenteral antibiotic consumption representing less than 2% of total DDD per 1000 inhabitants per day. (3)

According to the WHO AWaRe classification, the watch is highest antibiotic consumption in our study was between (73%, 5836), followed by access (16%, 1305), while reserve was (8%, 631) Comparing with Sierra Leone was AWaRe categories, the highest consumption was found among Access antibiotics 64% ,followed by Watch antibiotics 30%, with no consumption at all of Reserve antibiotic. (57)

A major limitation of this study was the inability to access to all admitted patients data in most of hospitals because of administrated constrains and unavailable of electronic system for data patients that facilities getting data instead of manually collection from ICU register. The target population was patients in ICU only therefore, interpretation and comparisons of the current findings should be done accordingly. Finally, the study was not designed to take in consider action variations among ICUs in patient mix or predominant bacterial pathogens and their susceptibility patterns. Nevertheless, using the current data to monitor the long term impacts of different interventions of an antimicrobial stewardship program can potentially help to improve the current prescription practices, reduce cost, and avoid side effect.

# Chapter IV: Conclusions & Recommendations

## 6.1.Conclusions:

Current results show a high consumption of broad spectrum antimicrobial agents such as cephalosporin and carbapenem in addition to vancomycin by patients of intensive care units of 48H, ATH, AJH ,AMH and USTH. The consumption of ceftriaxone, vancomycin, and meropenem were the highest using both DDD and DOT methods among ICU patients.

The findings highlight the urgent need for an effective antimicrobial stewardship program in these hospitals with focusing on ICUs specific antimicrobial consumption. The study results can be used as base before designing any intervention aiming to optimize antibiotics utilization in hospitals ICUs. Antimicrobial resistance is seen as a major threat, and this study represents effort proposed to help mitigate the emergence of antimicrobial resistance in the Sana'a hospitals.

## 6.2.Recommendations:

At the end of this study, to reduce the amount of antimicrobial consumption we recommend :

- Guiding antimicrobial stewardship programs in hospitals for contentiously monitoring and measuring antimicrobial consumption.
- Promoting rational use of antibiotics in hospitals
- Increasing the awareness about over-consumption of antibiotics and its effects on microbial resistance.
- Using DDD and DOT methods as standardized metrics to measure and compare antibiotic consumption rates.
- Encourage decision makers and stakeholders to establish a local and national sustainable antibiotic surveillance reporting framework
- Future studies should focus on computing antibiotic consumption from all wards.

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# Chapter VIII: Reference

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# الملخص

**الخلفية:**

مراقبة استهلاك المضادات الحيوية أمر بالغ الأهمية لمعالجة مقاومة مضادات الميكروبات. ومع ذلك ، لا يوجد حاليًا نظام في مدينة صنعاء للتسجيل والإبلاغ عن استهلاك المضادات الحيوية. دراستنا هي الأولى من نوعها للنظر في استخدام المضادات الحيوية في وحدة العناية المركزة في صنعاء ، اليمن باستخدام طرق DDD و DOT.

**الأهداف:** تقدير استهلاك مضادات الميكروبات في المستشفيات "وحدات العناية المركزة في مدينة صنعاء.

**الطريقة:** دراسة بأثر رجعي على البيانات من سجل وحدة العناية المركزة. أجريت الدراسة على المرضى المقبولين في خمس وحدات العناية المركزة في المستشفيات الرئيسية في عام ٢٠٢٠. تم جمع بيانات استهلاك مضادات الميكروبات يدويًا في الغالب. تم تحليل البيانات وتقديمها كجرعة يومية محددة (DDD) وأيام العلاج (DOT) لكل ١٠٠٠ يوم مريض.

**النتائج:** تم تضمين ما مجموعه ١٩٧٠ مريضا في هذه الدراسة. في هذه الدراسة وجدنا أن الاستهلاك الإجمالي للمضادات الحيوية في وحدات العناية المركزة كان مرتفعًا بمقدار DDD 18017.91 DDD لكل ١٠٠٠ مريض وبواسطة DOT 17448.73 DOT لكل ١٠٠٠ مريض–يوم. اكتشفت نتائج الدراسة أن سيفترياكسون وفانكومايسين وميروبينيم كانت الأكثر استهلاكًا باستخدام طرق DDD و DOT بين مرضى وحدة العناية المركزة حيث كانت نتائج DDDs لكل ١٠٠٠ إدخال ٢٤٧٩.٢٣ و ٢١٢٤.٥٥ و ١٨٣٠.٥٤ على التوالي و DOTs لكل ١٠٠٠ مريض – يوم كانت ٢١١٢.٦٩ ، ٢٠٥٥.٣٣ و ١٨٩٠.٨٦. بناءً على المجموعات الفرعية العلاجية / الدوائية في قياس الاستهلاك باستخدام DDD و DOT ، كان أكثر استهلاك هو السيفالوسبورين (٣٨٨٢ DDD لكل ١٠٠٠ مريض و ٤٢٢٧.٤١DOT لكل ١٠٠٠ مريض – يوم) ، carbapenems (2987 DDD لكل ١٠٠٠ مريض و ٢٨٨٨.٨٣ DOT لكل ١٠٠٠ مريض – يوم) ) والكينولونات (٢٩٠٠ DDD لكل ١٠٠٠ مريض في اليوم و ٢٦٦٠.٤١ DOT لكل ١٠٠٠ مريض – يوم). كان أكبر قدر من استهلاك المضادات الحيوية بين تصنيف منظمة الصحة العالمية AWaRe لمجموعة "المراقبة" من ٢٦٢٦٧.٤ DDDs و ١٤٦٧٤.٥ DDDs لكل ١٠٠٠ مريض في اليوم.

**التوصيات:** لوحظ ارتفاع استهلاك العوامل المضادة للميكروبات مثل سيفترياكسون وفانكومايسين وميروبينيم في وحدات العناية المركزة في خمسة مستشفيات. أبرزت النتائج الحاجة الملحة لبرنامج إشراف فعال على مضادات الميكروبات في هذه المستشفيات مع التركيز على استهلاك مضادات الميكروبات في وحدات العناية المركزة. يمكن استخدام نتائج الدراسة كأساس قبل تصميم أي تدخل يهدف إلى تحسين استخدام المضادات الحيوية في وحدات العناية المركزة بالمستشفيات. قد تساعد الدراسات المستقبلية التي تركز على المراقبة المتزامنة لمقاومة مضادات الميكروبات بأنماط وصفة طبية محددة في تحسين الاستهلاك الحكيم لمضادات الميكروبات.

الجمهورية اليمنية
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كلية الطب المخبري

# استهلاك المضادات الحيوية في أقسام العناية المركزة في مستشفيات العاصمة صنعاء

**بحث تخرج**

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**مروى الرداعي**
معيد في قسم الاحياء الدقيقة

**٢٠٢١م –**
**١٤٤٢هـ**