ANTIBIOTIC USE IN TWO HOSPITALS IN WEST WOLLEGA, ETHIOPIA

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Glory to God!

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ACRONYMS

AB	Antibiotic
AMR	Antimicrobial Resistance
CDC	Center for Disease Control
DACA	Drug Administration and Control Authority of Ethiopia
DDD	Defined Daily Dose
DH	District Hospital
EDL	Essential Drug List
ETB	Ethiopian Birr
FMOH	Federal Ministry of Health, Ethiopia
HC	Health Center
ICD	International Classification of Disease
IP	Inpatient
LDDH	List of Drugs for District Hospital
NGO	Non-governmental Organization
OBD	Occupied Bed Day
OP	Outpatient
PDD	Prescribed Daily Dose
PHARMID	Pharmaceutical Importer and Distributor
PHCU	Primary Health Care Unit
VRE	Vancomycin Resistant Enteroccoci
WHO	World Health Organization

ABSTRACT

In the last decades, there has been an escalating consumption of antibiotics with the number of antibiotic prescriptions increasing worldwide. Overuse or inappropriate use of antibiotics has resulted in a major increase in the development of multi-drug resistant pathogens. Antimicrobial resistance is one of the world's most serious public health problems with great implication in terms of morbidity, mortality, and costs.

To date, there has been no formal antibiotic use study conducted in the West Wollega zone of Ethiopia to assess antibiotic utilization. The objective of this study was to determine the pattern of antibiotic use in two hospitals in the West Wollega zone of Ethiopia, namely Gimbie Adventist Hospital and Nedjo Hospitals, using drug utilization metrics and the costs associated. In addition it was to assess the correlation between diagnosed infectious diseases and antibiotic prescriptions.

This study was a cross-sectional, retrospective, descriptive review of antibiotic usage in the two hospitals in the year 2007. Prescriptions dispensed in the first month of each quarter of 2007 were reviewed. The number of prescriptions screened, antibiotic courses started, antibiotic days by specific agent and overall, the cost of individual and all antibiotics, the number and type of infectious diseases diagnosed were collected from which core drug use indicators were calculated. The correlation between infectious disease diagnosed and the antibiotic days prescribed were analyzed.

A total of 18568 antibiotic and non-antibiotic prescriptions were reviewed retrospectively in the four months of the study period, 47% of which contained at least one antibiotic. The average number of antibiotics per prescription was 1.33 and 1.09 whilst the percentage of injectable antibiotics prescribed was 83.2% and 3.76% to outpatients and inpatients respectively. Antibiotics prescribed from the Essential Drug List (EDL) and List of Drugs for District Hospital (LDDH) were 63.0%, 74.8%, and 90.8% and 76.1% for outpatients and inpatients respectively. 98.6% of outpatient and 97.0% inpatient prescribed antibiotics were actually dispensed. Penicillins and quinolones were the most prescribed antibiotics in both inpatient and outpatient departments constituting 43.46% and 24.08% respectively.

The antibiotic utilization ratio, incidence of outpatient antibiotic use, incidence of inpatient antibiotic use, the number of Defined Daily Doses (DDD)/1000inhabitants/year and DDD/100 Occupied Bed Days (OBD) for the zone was 0.16, 17.25, 23.56, 158.61, and 70 respectively. Antibiotic cost constituted 33.7% of all expenditure on drug, cost of antibiotic per patient care day and cost per antibiotic day was 3.84 Ethiopian Birr (ETB) ($0.40) and 6.29 ETB ($0.66) respectively.

The correlation between infectious diseases diagnosed and antibiotic prescription shows significant variation. At outpatient departments alone an average number of antibiotic courses started was 2.7 at Gimbie Adventist Hospital and 7.6 for Nedjo Hospital. When overall antibiotic days prescribed and required was compared in both hospitals, there were 2.4 and 5 times more antibiotic days prescribed than were required for Gimbie and Nedjo Hospitals respectively. This suggests that the overuse of antibiotic is worse in the government hospital (Nedjo Hospital) than in the mission hospital (Gimbie Adventist Hospital).

This study suggested that there was overuse of antibiotics in the West Wollega hospitals although further investigation is needed to identify its underlying causes and nature. It is recommended that the health personnel, the hospital management, the zonal and regional Health Bureau, the regulatory bodies and Non-Governmental Organizations (NGOs) work hand-in-hand to promote the rational use of antibiotics in this region so that the consequences and financial cost of antimicrobial resistance can be prevented.

CHAPTER 1

1.1 Background

Ethiopia has adopted a federal system of government with nine regional states and two city administrative councils. The nine regional states are further divided into administrative zones, which are further subdivided into districts. The West Wollega is one of the 12 administrative zones of Oromia regional state (the biggest regional state), located in the western part of the country. There are four hospitals in this administrative zone. Two of these hospitals are owned and operated by the government, one by the Seventh Day Adventist Church, and the other by the Lutheran Church.

Health service delivery in Ethiopia is arranged in a four-tier system. The lower level is the primary health care unit (PHCU) which consists of a health center with five satellite health posts, followed by the first referral level, a district hospital, then a zonal hospital and a specialized referral hospital. The District Hospital (DH) is the first referral level for Health centers (HC) within the four-tier health service system. It provides both outpatient and in-patient services with a 50 bed capacity which renders 24-hour-a-day service for a catchment population of 250000. The district hospital provides curative, preventive, promotive and rehabilitative services. The Zonal Hospital is the referral hospital for the district hospital and is staffed with physicians having specialties in four major disciplines of medicine (Internal Medicine, Surgery, Pediatrics and Gynecology and Obstetrics) and three other minor specialties (Psychiatry, Ophthalmology and Dentistry).

All of the hospitals in the West Wollega zone administration are district hospitals but technically three of the hospitals, including Gimbie Adventist Hospital lie between the district and zonal hospital level in terms of the service delivery and staffing. Gimbie Adventist Hospital is a 71-bed hospital, located in Gimbie town (the capital of the administrative zone) 440 km west of Addis Ababa and Nedjo Hospital is a 40-bed government hospital located at a distance of 75 km west of Gimbie and 515 km west of Addis Ababa.

The discovery of antibiotics has brought about a dramatic turning point in the treatment of infectious disease in the 20th century (Katzung, 2001:753). In the last decades there has been an escalating consumption of antibiotics with the number of antibiotic prescriptions increasing worldwide, although recently, some stabilization or decrease in this trend is evident in some countries (Zintzaras & Ionnidis, 2003:1001). This increased consumption of antibiotics has to some extent been related to the development of microbial resistance to many agents. Increased levels of microbial resistance are a global concern and some countries have implemented strategies to decrease unnecessary antibiotic prescribing. Upper respiratory tract infections are one of the conditions in which antibiotics are often inappropriately prescribed. (Carbon & Bax, 1998:663)

According to a study by Bremon and colleagues, focusing on antibiotic utilisation, the development of resistance, antibiotic consumption in hospital and non-hospital settings and the economic impact of antibiotic prescribing in un-indicated conditions appears that the dominant factor underlying the spread of bacterial resistance is the rise in consumption of antibiotics (Bremon, Ruiz-Tovar, Gorricho, Torres & Rodriguez, 2000:395). According to Priest *et. al.,* studies done in this regard give rise to worldwide concern over the development of microbial resistance to antibiotics (Priest, Yudkin, McNulty & Mant, 2001: 1037.).

As microbial resistance is not limited by borders this problem is also the problem of developing countries. Therefore this research focuses on determining the patterns of antibiotic utilisation in two rural hospitals in west Ethiopia, namely Gimbie Adventist Hospital (located in Gimbie) and Nedjo Hospital (located in Nedjo) in the West Wollega Administrative Zone (province).

1.2 Problem Statement

According to Joshi and Miralles infectious diseases are a major cause of morbidity and mortality in Ethiopia, and together with nutritional problems account for 60-80% of the health problems in the country. Joshi and Miralles further suggest that although large scale

studies on the extent of antimicrobial resistance in Ethiopia do not exist, existing reports indicate that it is a growing problem. They further identify the irrational use of antibiotics as one of the major problems contributing to antimicrobial resistance. (Joshi & Miralles, 2006:7)

An assessment of the pharmaceutical sector in Ethiopia by the Federal Ministry of Health (FMOH) in collaboration with World Health Organization (WHO) showed a high rate of antibiotic prescription in that 55.43% of prescriptions contained one or more antibiotics (FMOH and WHO, 2003:24). Another study in health care facilities in North West Ethiopia also demonstrated that antibiotics account for 60% of all prescriptions whilst a study in South West Ethiopia at Jimma University Hospital showed that 25.6% of prescriptions included an antibiotic which is closer to the WHO recommendation of less than 25%. (Desta *et al*, 1997: 760; Wubeante, 2005: 151; WHO, 2004:8).

Observation of prescribing patterns in the West Wollega Province suggests that antibiotics may be inappropriately prescribed and over-utilised. It would appear that there is a trend to give most outpatients and hospitalised patients antibiotics, with general practitioners and other prescribers prescribing antibiotics as an empiric treatment due to limited laboratory facilities.

Observations would also suggest that the number of prescriptions for the previously reserved classes of antibiotics like fluoroquinolones and cephalosporins have recently been increasing. This could either be due to increased availability of these classes of antibiotics or it could suggest increased microbial resistance to other antibiotics. These suspicions are of concern since the misuse and overuse of antibiotics could have significant economic implications and pose a threat of increased antibiotic resistance.

Currently, there is very limited or no formal research conducted in this province to assess antibiotic utilisation, and therefore it is necessary to conduct a baseline study to determine the utilisation of antibiotics in this region, so that evidence based practice in the safe and economical use of antibiotics can be promoted.

1.3 Research Question

What are the prescribing patterns and use of antibiotics and the associated cost implications in two identified hospitals in the West Wollega zone of Ethiopia?

1.4 Objectives

General objectives

The primary aim of this research is to determine the pattern of antibiotic use in two hospitals in the West Wollega zone of Ethiopia.

Specific Objectives

With regards to the use of antibiotics in these two hospitals, the more specific objectives of the study are to:

- Describe the pattern of antibiotic prescribing using pre-defined drug utilisation metrics
- Determine the associated costs of antibiotics prescribed in the two hospitals
- Determine if there is a correlation between antibiotic prescriptions and diagnosed infectious diseases in these hospitals
- Compare antibiotic prescribing patterns between a government and a non-governmental hospital.

CHAPTER 2
LITERATURE REVIEW

2.1 Introduction

An antibiotic can be defined as "a substance produced by or derived from a microorganism that destroys or inhibits the growth of other microorganisms. Antibiotics are used to treat infections caused by organisms that are sensitive to them usually bacteria or fungi." (Concise Color Medical Dictionary, 2002:37).

During the last 60 years, the development of antimicrobial agents is among the most dramatic example of the advances of modern medicine. With a few agents many of the infectious diseases that were once considered incurable and lethal are now curable. The selectivity of the antibacterial agents for highly specific targets that are unique to microorganisms is the reason for their powerful and specific activity. Bacterial or fungal cell wall synthesizing enzyme, the bacterial ribosome, the enzyme required for nucleotide synthesis and DNA replication and the machinery of viral replication are among these targets. (Katzung, 2001: 753).

However, along with the development of chemotherapeutic agents against microbes has been the development of bacterial resistance against chemotherapeutic agents resulting in the emergence of resistance. Overuse or inappropriate use of antibiotics has resulted in a major increase in the development of multi-drug resistant pathogens, leading some to speculate that we are nearing the end of the antibiotic era. In recent times, the development of novel drugs has slowed whilst the need for them has increased. Pending the development of new drugs and targets it is likely that we will have to rely on the currently available classes of drugs. However, considerable effort will be required to maintain the effectiveness of these available agents in the face of continuing development of resistance. (Katzung, 2001: 753; Rang, Dale & Ritter, 1999:657; WHO, 2005:1.)

A brief description of different classes of antibiotics with special emphasis on the mechanisms of antibacterial action and bacterial resistance to the antibiotic class, patterns

of antibiotic use, the relation of antibiotic use and patterns of resistance and strategies to limit antimicrobial resistance is discussed in this chapter.

2.2 Classes of Antibiotics

The development of chemotherapeutic agents which are toxic for the infectious organism but innocuous for the host, are achieved because of the existence of exploitable biochemical differences between the organism and the host (Rang, *et al*., 1999:649). This gives rise to different classes of antibiotics which have activity on different biochemical targets and pathways. These classes of antibiotics are discussed briefly in this section.

2.2.1 β-lactam Antibiotics and other inhibitors of cell wall synthesis

These groups of antibiotics inhibit bacterial growth by interfering with a specific step in the synthesis of bacterial cell wall peptidoglycan. This class of antibiotics includes the penicillins, the cephalosporins, monobactams and vancomycin. (Katzung, 2001: 754)

A. Penicillins

Penicillins are one of the groups of beta lactam antibiotics which include cephalosporins, monobactams and carbapenems. First discovered in 1928, by Alexander Fleming, penicillins are among the most misused and overused antibiotics. (Rang, *et al.,* 1999:690)

Penicillins are classified into three groups based on their pharmacological and antibacterial properties:

i. Narrow spectrum or beta-lactamase sensitive penicillins include benzyl penicillin G, benzathin benzyl penicillin, procaine benzyl penicillin and phenoxymethyl penicillin. These agents are effective against Gram-negative organisms, Gram-negative cocci and non-beta-lactamase producing anaerobes and minimal activity against Gram-negative rods. They are susceptible to hydrolysis by beta-lactamases and are poorly absorbed from gastrointestinal tract.

ii. The second groups of penicillins are beta-lactamase resistant penicillins and include cloxacillin, naficillin, flucloxacillin, dicloxacillin and methicillin. They are active against staphylococci and streptococci but inactive against enterococci, anaerobic bacteria, Gram-negative cocci and rods. (Katzung, 2001: 754; Rang *et al*, 1999:691,693)

iii. Extended-spectrum penicillins which have improved activity against Gram-negative organisms are the third group of penicillins. This class of penicillins can be destroyed by beta-lactamases. These agents include ampicillin, amoxycillin, ticarcillin, piperacillin and azlocillin. (Katzung, 2001: 754, 755).

Some important uses of penicillins include the treatment of bacterial meningitis, bone and joint infections, skin and soft tissue infections, pharyngitis, otitis media, bronchitis in patients with chronic obstructive airway disease, community acquired pneumonia, urinary tract infections, syphilis, and endocarditis in combination with aminoglycosides. (Rang *et al,* 1999:693) *"Penicillin G is the drug of choice for infections caused by streptococci, meningococci, enterococci, penicillin susceptible pneumococci, non-beta-lactamase producing staphylococci, Treponema pallidum and many other spirochetes, Bacillus anthracis, clostridium species, actinomyces, and other Gram-negative rods and non-beta-lactamse producing Gram-negative anaerobic organisms" (*Katzung, 2001: 759).

B. Cephalosporins

Cephalosporins are similar to penicillins with respect to chemical structure and toxicity. They have a broader spectrum of activity than penicillins since they are stable to many bacterial beta-lactamase enzymes.

Cephalosporins are classified into four main groups or generations depending on their spectrum of antibacterial activity. The activity of the first generation agents is predominantly against Gram-positive organisms, whilst the later compounds have improved activity against Gram-negative aerobic organisms. (Katzung, 2001: 762).

i. First generation cephalosporins include cephalexin, cephradine, cefadroxil, cefazolin, cephalothin and cephalosporin. They are effective against Gram-negative organisms including staphylococci, streptococci, pneumococci, *E. coli, Klepsiella pneumoniae,* and *Proteus mirabilis*. They are also active against penicillinase producing *S. aureus,* but not active against methicillin resistant strains of staphylococci. Activity against *H. influenzae*, *P. aeruginosa* indole positive proteus, and enterobacter is limited. There is widespread resistance of Gram-negative organisms to first generation cephalosporins. (Gibbon, 2003: 265; Katzung, 2001: 762).
ii. The second generation agents are cefaclor, cefamandole, cefonicid, cefruoxime, cefroxil, loracarbef and ceforanide. Their activity includes that of the first generation cephalosporins, but they have wider activity against Gram-positive organisms.
iii. Third generation agents includes cefoperazone, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, cefixime, cefpodoxime, ceftibuten and moxalactam. These agents have an extended spectrum of activity with a wider Gram-negative spectrum and are also effective against citrobacter, *Serratia marcescens*, providencia and beta-lactamase producing strains of haemophilus and neisseria. Ceftazidime and cefoperazone are active against *P. aeruginosa.* Some of the third generation cephalosporins can also cross the blood-brain barrier. (Gibbon, 2003: 265; Katzung, 2001: 764).
iv. The fourth generation agents have a similar spectrum of activity to the third generation. However, fourth generation cephalosporins are more resistant to hydrolysis by chromosomal beta-lactamase and some extended-spectrum beta-lactamases that inactivate many of the third generation cephalosporins. Cefepim and cefpirome are examples of this group. They are effective against Gram-positive and Gram-negative organisms including *P. aeruginosa* and are highly active against haemophilus and neisseria. (Gibbon, 2003: 265; Katzung, 2001: 766).

First generation cephalosporins are used clinically for the treatment of urinary tract infection, for minor staphylococcal lesions and for minor polymicrobial infections such as cellulitis or soft tissue abscess, when given orally. Cefazolin is the drug of choice for surgical prophylaxis. (Katzung, 2001: 762).

Second generation agents are used for the treatment of sinusitis, otitis or lower respiratory tract infection caused by susceptible organisms. Cefoxime, cefotetan, or cefmetazole can be used in the treatment of mixed anaerobic infections like peritonitis or diverticulitis. Cefuroxime is used for the treatment of community acquired pneumonia. (Katzung, 2001: 764)

Third generation cephalosporins are used to treat a variety of infections which are caused by organisms resistant to most other drugs. Ceftriaxone and cefixime are the first-line drugs for the treatment of gonorrhea and meningitis. (Katzung, 2001: 766)

C. Carbapenems and monobactams

These are beta-lactum antibiotics developed to deal with beta-lactamase producing gram-negative organisms resistant to broad spectrum and extended spectrum penicillins. However these agents are not active against Gram-positive bacteria or anaerobes. (Rang, *et al.,* 1999: 695; Katzung, 2001: 767)

D. Vancomycin

Vancomycin is a glycopeptide antibiotic which acts by inhibition of cell wall synthesis. It is bactericidal and is effective mainly against Gram-positive bacteria including methicillin resistant staphylococci. Vancomycin is reserved for the treatment of infection due to cloxacillin resistant staphylococci and enterococci. In addition it is used for the treatment of endocarditis and for the treatment of antibiotic associated pseudomembranous colitis produced by *C. difficile*. (Gibon, 2003: 282; Rang, *et al*., 1999:702)

2.2.1.1 Mechanism of action of beta-lactam antibiotics

Beta-lactam antibiotics inhibit bacterial growth by interfering with petidoglycan synthesis during bacterial cell wall synthesis. Peptidoglycan, a complex cross-linked polymer, is a component of the cell wall which consists of polysaccharides and polypeptides. The polysaccharide contains alternating amino sugars, *N*-acetylglucosamine and *N*-acetylmuramic acid and a five-aminoacid peptide is linked to the *N*-acetylmuramic acid

sugar that terminates in D-alanyl-D-alanine (D-Ala-D-Ala). Penicillin-binding proteins (PBPs) catalyze the transpeptidase reaction that removes the terminal alanine to form a crosslink with a nearby peptide, which provides the structural rigidity of cell walls. Beta-lactam antibiotics are structural analogs of the natural D-Ala-D-Ala substrate and they are covalently bound by the PBPs at the active site. The attachment of the penicillins (beta-lactam antibiotics) to PBPs inhibits the transpeptidation reaction which in turn blocks the peptidoglycan synthesis resulting in cell death. (Katzung, 2001: 754, 755). In addition the inactivation of the inhibitor of the autolytic enzymes in the cell wall leads to the lysis of the bacterium (Rang *et al.*, 1999: 691).

2.2.1.2 Microbial resistance to beta-lactam antibiotics

Resistance to penicillin is due to one or more of the following reasons.

i. Inactivation of the antibiotic by beta-lactamases,of which more than a 100 different types have been identified, is the most common mechanism of resistance. Some of the beta-lactamases are narrow in substrate specificity and will hydrolyse penicillins but not cephalosporins. Examples are those produced by Staphylococus aureus, haemophilus species, and *E. coli* (Figure 2.1). Staphylococcal resistance due to production of beta-lactamase has progressively spread. At least 80% of staphylococci in developed countries now produce beta-lactamase. Other beta-lactamases such as those produced by *Pseudomonas aeruginosa* and enterobacter species are broader spectrum and will hydrolyze both penicillins and cephalosporins. (Katzung, 2001: 755,756; Rang *et al*, 1999: 691) The solution for beta-lactamase induced resistance is the use of beta-lactamase inhibitors such as clavulanic acid, sulbactam and tazobactam. Clavulanic acid contains a beta-lactam ring which covalently binds to the enzyme at or near the active site. (Rang *et al*, 1999: 691).

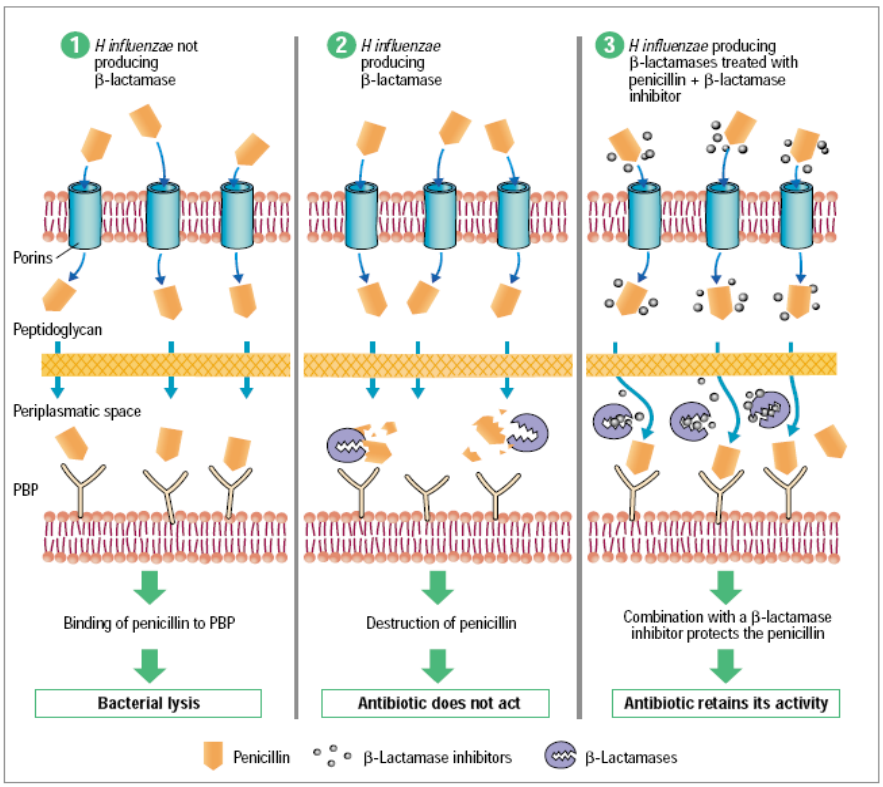

Figure 2.1 Penicillin inactivation by lactamase production by *H. influenzae.* (Source: Pr Michele**,** 8)

ii. Modification of target penicillin binding proteins. Some organisms produce penicillin binding proteins (PBPs) that have a low affinity for binding beta-lactam antibiotics and are only inhibited at relatively higher drug concentrations, which often exceed what is clinically achievable. Methicillin resistance in staphylococci and penicillin resistance in pneumococci, as shown in Figure 2.2, are examples of this (Katzung, 2001: 756; Pr Michele, 10).

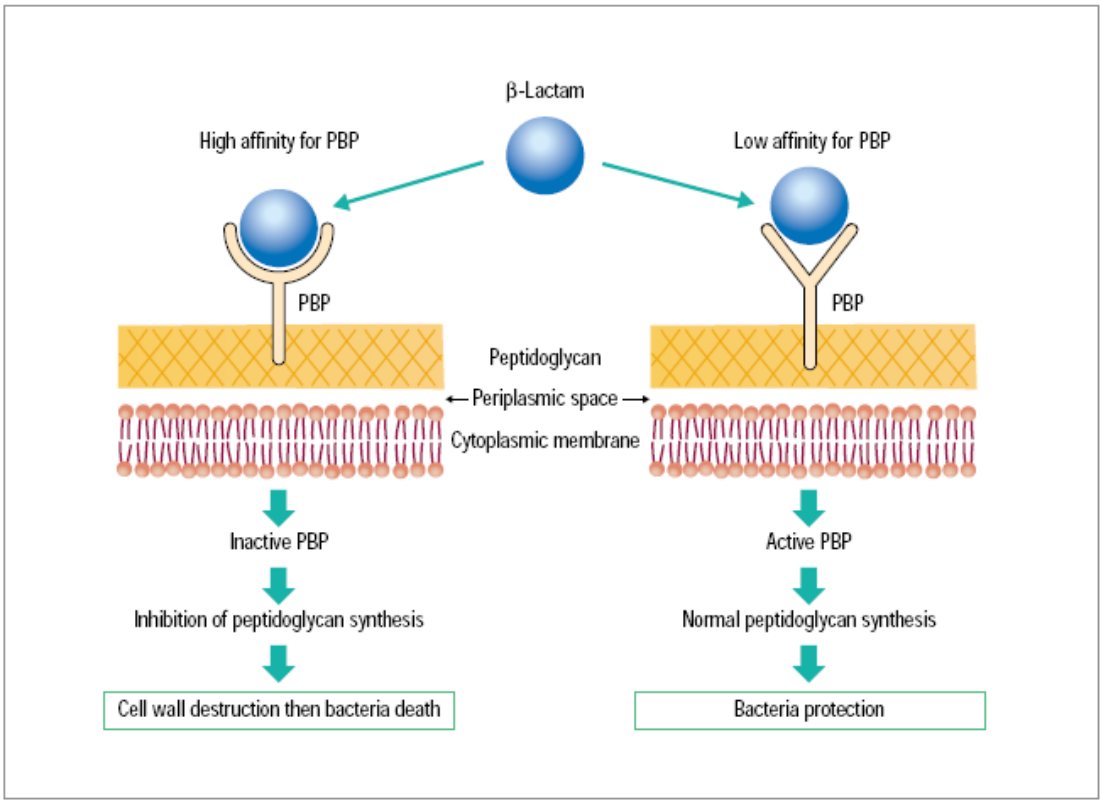

Figure 2.2 *S pneumoniae* resistance to lactams by target alteration. (Source: Pr Michele, 10)

iii. Impaired penetration of drug to target PBPs. This occurs with Gram-negative organisms, which have an outer membrane that limits the penetration of hydrophilic antibiotics. Beta-lactam antibiotics enter Gram-negative organisms by crossing the outer membrane via protein channels (porins). Absence of a proper channel or down regulation of its production can prevent drug entry in to the cell. (Katzung, 2001: 756).

iv. The presence of an efflux pump. An efflux pump, which consists of cytoplasmic and periplasmic protein components, can be produced by Gram-negative organisms. This efflux pump can efficiently transport some beta-lactam antibiotics from the periplasm back across the outer membrane, for example the extrusion of naficillin by *Salmonella typhimurium*. (Katzung, 2001: 755; Rang, *et al.,* 1999:658)

2.2.2 Antibacterial agents affecting bacterial protein synthesis

A. Tetracyclines

Tetracyclines are broad spectrum antibiotics, active against both Gram-positive and Gram-negative bacteria, *Micoplasma, Rickettsia, Chlamydia*, some spirochetes and some protozoa that act by inhibition of protein synthesis (Rang *et al*, 1999:696).

Tetracycline, oxytetracycline, doxycycline, demeclocycline and minocycline are some of the agents in this group. Chlortetracycline was introduced in 1948 isolated from *Streptomyces aureofaciens* while oxytetracycline, obtained from *Streptomyces rimosus,* and tetracycline were identified in 1950 and 1953 respectively. (Katzung 2001: 776,777).

Tetracyclines still remain the treatment of choice for trachoma, psittacosis, urethritis, and lymphogranuloma venereum caused by Chlamydia; for infections caused by rickettsia, brucella, and the spirochetes. They are also used in the treatment of respiratory and genital mycoplasma infection, in acne, in destructive periodontal disease and in exacerbation of chronic bronchitis. (Mehta, 2005:281) They can also be used for the treatment of protozoal infections, e.g. for *Plasmodium falciparum* or *Entaboeba histolytica.*

B. Chloramphenicol

Chloramphenicol is a bacteriostatic broad spectrum antibiotic first isolated in 1947 from *Streptomyces venezuelae* and synthesized commercially in 1949 as the first completely synthesized antibiotic. It is a wide spectrum antibiotic which is active against both aerobic and anaerobic Gram-positive and Gram-negative organisms. It is active against rickettsiae, *Haemophilus influenzae*, *Niesseria meningitides* and some stains of bacteroides. (Katzung, 2001: 774).

The clinical use of chloramphenicol should be reserved for serious infections in which the benefit out weighs the risk of toxicity. It is used for infections caused by *H.*

influenzae resistant to other drugs, typhoid fever, rikettsial infections (if tetracyclines are contraindicated) and meningitis in patients hypersensitive to penicillins or in penicillin resistant strains of pneumococcus. Chloramphenicol is used for treatment of bacterial meningitis because of its broad spectrum of activity. (Gibbon, 2003: 275; Rang *et al*, 1999: 697).

C. Macrolides

The prototype of this class, erythromycin was first obtained in 1952 from *Streptomyces erythereus*. Clarithromycin and azithromycin are new macrolides, which are synthetic derivatives of erythromycin. Erythromycin has a similar spectrum of activity to that of penicillin and is generally a safe and effective alternative for penicillin-sensitive patients. It is indicated for respiratory infections, whooping cough, legionnaires' disease campylobacter enteritis, chlamydial and mycoplasma infections. (Gibbon, 2003:269; Mehta, 2005:285).

D. Aminoglycosides

Aminoglycosides are a group of antibiotics of complex chemical structure resembling each other in antimicrobial activity. The group includes streptomycin, neomycin, gentamycin, kanamycin, amikacin, netilmycin, tobramycin, and sisomycin. Streptomycin is the oldest aminoglycoside usually reserved for treatment of tuberculosis in combination with other drugs, while gentamycin, tobramycin and amikacin are the most widely used at present. Aminoglycosides are used most widely against Gram-negative enteric bacteria. They are usually used in combination with a beta-lactamase antibiotic because of the synergistic effect and to cover Gram-positive pathogens. (Katzung, 2001:784, 786).

Aminoglycosides act by inhibition of bacterial protein synthesis. Their penetration through the cell membrane of the bacteria depends partly on oxygen dependent active transport and hence they have minimal action against anaerobic organisms.

2.2.2.1 Mechanism of action of protein synthesis inhibitors

Tetracyclines are broad spectrum antibiotics whose value has decreased because of bacterial resistance (Mehta, 2005:281). They are bacteriostatic and function by inhibiting the protein synthesis of Gram-positive and Gram-negative bacteria including anaerobes, rikettsiae, chlamydia, mycoplasma, and some spirochetes. They are also active against some protozoa like amoeba. Antibacterial activity of tetracyclines is similar with the exception of minocycline, which has broader spectrum of activity. (Mehta, 2005:281; Rang *et al*, 1999: 696)

Tetracyclines enter the cell of the bacteria partly by passive diffusion and in part by an energy dependent process of active transport. Tetracyclines bind to the 30S subunit of the bacterial ribosome and block addition of amino acids to the growing peptides in the cell. (Katzung, 2001: 777)

Chloramphenicol binds reversibly to the 50S subunit of the bacterial ribosome and inhibits the peptidyl transferase step of protein synthesis. *"Chloramphenicol blocks the binding of the aminoacyl moiety of the charged tRNA molecule to the acceptor site of the ribosomal mRNA complex. The binding of tRNA to its codon is not affected. Failure of the aminoacyl group to associate properly with the acceptor site prevents the transpeptidation reaction catalyzed by peptidyl tranferase."* (Katzung, 2001: 775). It is bacteriostatic for most organism but exhibits bactericidal property against *Haemophilus influenzae, Neisseria meningitides* and some strains of bacteriodes. (Rang *et al,* 1999: 697).

Macrolides inhibit bacterial protein synthesis by binding to 50S ribosomal subunit. Their action is bacteriostatic at low concentrations but bactericidal at high concentrations (Gibbon, 2003:269). Aminoglycosides bind to the specific 30S subunit ribosomal proteins. They inhibit protein synthesis in at least three ways. They interfere with the initiation complex of peptide formation, induce misreading of mRNA which causes incorporation of incorrect amino acid into the peptide and results in a break up

of polysomes into non-functional monosomes. (Katzung 2001: 284; Rang *et al.*, 1999: 697).

2.2.2.2 Mechanism of bacterial Resistance to Protein synthesis inhibitors

Resistance to tetracyclines occurs via three different mechanisms: (1) decreased intracellular accumulation, which is due to either impaired influx or increased efflux by an active transport protein pump; (2) ribosome production due to production of proteins that interfere with tetracycline binding to the ribosome; (3) enzymatic inactivation of the tetracyclines. (Katzung, 2001: 777)

Resistance to chloramphenicol is mainly due to the production of chloramphenicol acetyl transferase, which is a plasmid encoded enzyme that inactivates the drug. Gram-negative bacilli except *Salmonella typhi* have increasingly developed resistance. (Gibbon, 2003: 274; Rang *et al,* 1999: 697)

Resistance to macrolides is by reduced permeability of the cell membrane or active efflux, production of esterases that hydrolyse macrolides, and modification of the ribosomal binding site by chromosomal mutation or by a macrolide-inducible or a constitutive methylase. Efflux and methylase production accounts for the majority of resistance of Gram-positive organisms. (Katzung, 2001: 779)

Bacterial resistance to aminoglycosides occurs via one of three principal mechanisms namely: (1) production of an enzyme that inactivates the aminoglycosides by adenylation, acetylation, or phosphorylation (2) impaired entry of aminoglycosides into the cell, and (3) the receptor protein on the 30S ribosomal subunit may be deleted or altered as a result of a mutation. (Katzung, 2001: 785)

2.2.3 Antibiotics that interfere with bacterial metabolic pathway

Sulphonamides: are agents that inhibit bacterial growth by reversibly inhibiting folic acid synthesis. Because of increased incidence of resistance to sulphonamides their use

is limited to a combination of trimethoprim-sulfamethoxazole. Bacterial mechanism of resistance is as a result of mutations that cause overproduction of PABA (para amino benzoic acid), production of a folic acid synthesizing enzyme that has a low affinity for sulphonamides, and a loss of permeability to the sulphonamides. (Gibbon, 2003:278; Katzung, 2001: 793)

2.2.4 Antimicrobial agents affecting topoisomerase-II

Fluoroquinolones: are synthetic antibiotics which block bacterial DNA synthesis by inhibiting bacterial topoisomerase-II. They include the broad spectrum agents, ciprofloxacin, ofloxacin, norfloxacin, perfloxacin, gatifloxacin and levofloxacin, and the narrow spectrum cinoxacin and nalidixic acid. (Katzung, 2001: 797, 798)

Nalidixic acid and other older quinolones did not achieve systemic antibacterial levels and were useful only in the treatment of lower urinary tract infections whilst the fluorinated derivatives have greatly improved antibacterial activity. Ciprofloxacin and ofloxacin have potent Gram-negative activity particularly against *Enterobacteriaceae*, *P. aeroginosa*, *Haemophilus*, *Neisseria* and *Legionella* species, but borderline activity against *S. pneumoniae* and other Gram-negative bacteria. Norfloxacin, though structurally related, has a wider spectrum of activity than nalidixic acid and is used in the treatment of urinary tract infections. Mexifloxacin and gatifloxacin have a similar spectrum of activity to other fluoroquinolones but with more activity against Gram-positive organisms including *S. pneumoniae*. (Gibon, 2003:280; Katzung, 2001: 298; Mehta, 2005: 300) Recently the pharmaceutical industry poured considerable resources into producing newer flouroquinolones like sparfloxacin with improved potency and a wider spectrum of activity (Cubbon, & Masterton, 2000: 869).

2.2.4.1 Mechanism of action of agents that affect topoisomerase II

Quinolones block bacterial DNA synthesis by inhibiting DNA gyrase (topoisomerase II) and topoisomerase IV. 'The inhibition of DNA gyrase prevents the relaxation of positively supercoiled DNA, that is required for normal transcription and replication

whilst the inhibition of topoisomerase IV possibly interferes with the separation of replicated chromosomal DNA into the respective daughter cells during cell division. (Katzung, 2001: 797)

2.2.4.2 Mechanism of bacterial resistance to agents that affect topoisomerase II

Resistance to these agents is due to one or more point mutations in the quinolone binding sites of the target enzyme or to a change in the permeability of the organism which could be as a result of the reduction in intrabacterial penetration or active efflux (Figure 2.3). Mutation of genes on the bacterial chromosome results in alteration of the quinolone target with decreased affinity. This is the major mechanism of acquired resistance of *E. coli*, *P. aeruginosa* or *S. aureus* to quinolones by structural alterations of DNA gyrase as shown in Figure 2.4. Cross-resistance to all other members of this class can be conferred if high level resistance to one quinolone occurs. (Katzung, 2001: 797, 798; Pr Michele, 6).

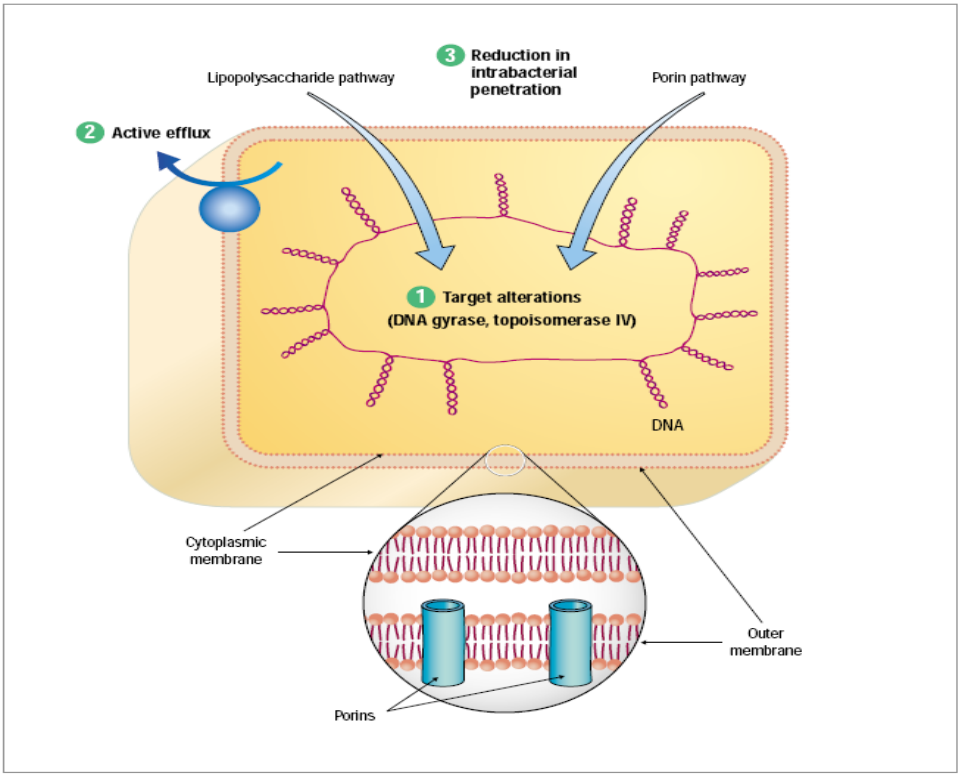

Figure 2.3 The three mechanisms of quinolone resistance in Gram-negative bacteria. (Source: Pr Michele, 7).

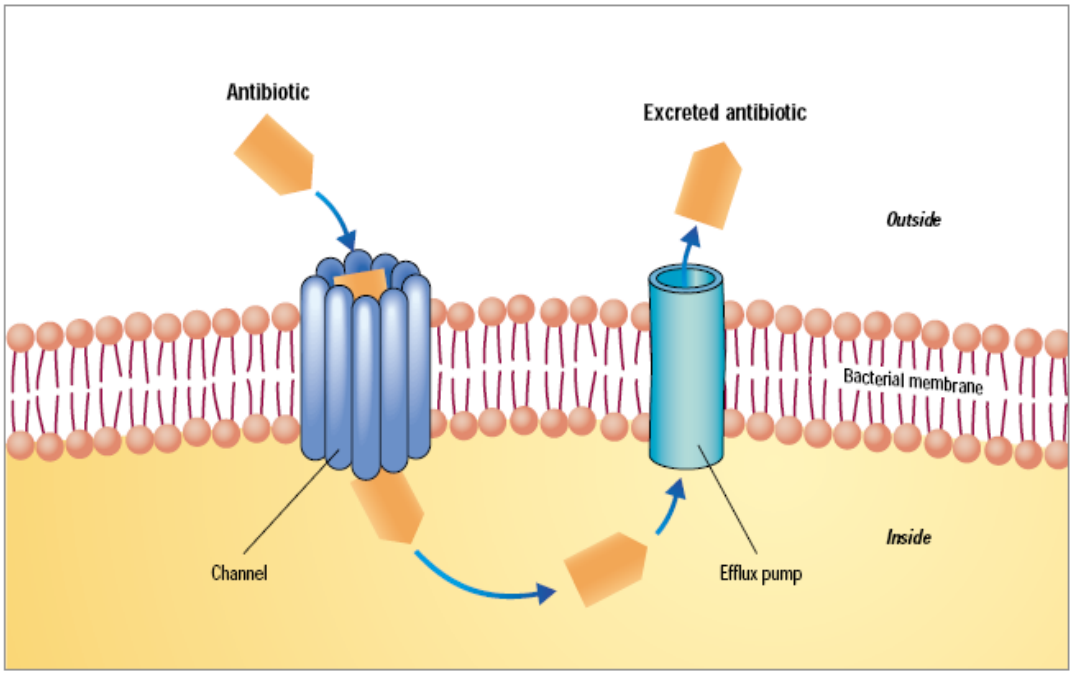

Figure 2.4 Active efflux of antibiotic by enzymatic systems as a mechanism for *E coli* resistance to fluoroquinolones. (Source: Pr Michele, 9)

2.3 Patterns of Antibiotics Use

The world market for antimicrobials, in 1997 was $17 billion. Of this, $12 billion was for the use of antibiotics in the community with approximately 818 billion prescriptions for respiratory tract infections (Carbon & Bax 1998: 663). In Turkey, in 2001 drug consumption was valued at $2,553 million of which 18.2% can be attributed to antibiotics (Aydin, Yaris, Ozcakir, & Agalar, 2005: 169). In 2000, Bremon and colleagues suggested that antibiotic consumption in Spain, amounted to 150 million Euros in hospitals and 559 million Euros in non-hospital settings (Bremon, Ruiz-Tovar, Gorricho, Torres, & Rodriguez, 2000:395). The expenditure on outpatient antibiotics in Greece, from 1990 to 1999, was demonstrated to have increased by 24% (Zintzaras, & Ioannidis, 2003: 1001). A study by Mainous III & Hueston has shown that a substantial proportion of resources in Medicaid in US were being used for non-indicated and ineffective treatment for upper respiratory tract infections (Mainous III, & Hueston, 1998:45).

A study conducted by Molstad and others, in 13 European countries (including Austria, Belgium, Finland, France, Germany, Greece, Italy, The Netherlands, Portugal, Spain, and

the UK) has shown a marked variation in antibiotic utilization. This difference was shown both in terms of the number of prescriptions per 1000 inhabitants and in the preference for the different antibiotics. In 1997, a beta-lactum antibiotic was the most prescribed antibiotic in all countries, mentioned above, included in the study. (Molstad, Lundborg, Karlsson, & Cars, 2002: 366).

Prescriptions for antibiotics showed a 46% increase in the community in England and Scotland and a 65% increase in France from 1980 to 1991 (Davey, Bax, Reeves, Rutherford, Warren, & Watt, 1996:613).

A base line survey of antibiotic use in many developing countries in Africa suggested that there was overuse of antibiotics. A survey in Nigeria indicated that 59% of patients prescribed antibiotics, and 60% of diarrhea cases and 89% of acute respiratory infections excluding pneumonia were prescribed antibiotics which were inappropriate (FMOH &WHO, 2002: 31, 32). A similar study in Uganda showed that antibiotics were prescribed to 61.9% of patients, and 49.5% of diarrhea cases in children and 88% of non-pneumonia acute respiratory infections were prescribed antibiotics (MOH 2002:8). In Tanzania antibiotics were indiscriminately used for about 44% of diarrhea cases in children and up to 90% of non-pneumonia acute respiratory infections whilst 42% of all patients received antibiotics (MOH & WHO 2002:12, 13).

Similarly studies in Ethiopia showed high percentage of antibiotics use. According to 2002 the national pharmaceutical sector assessment, antibiotics were prescribed for 58% of patients. Antibiotic use in treatment of non-bloody, watery diarrhea and non-pneumonia acute respiratory infection showed significant deviation from Standard Treatment Guideline (STG) in that 49.6% and 60.7% of cases were prescribed antibiotics respectively. (FMOH &WHO, 2002: 24, 32). A study in different parts of the country also suggests similar finding: antibiotics were prescribed for 63.84% of patients in Harari region health facilities (Menassie, 2004: 49); 60% health centers and 65% health stations of North West Ethiopia (Desta *et al.*, 1997: 758) and 25.6% in Jimma Uiversity Hospital in South West Ethiopia (Wubeante, 2005:151).

In 2002 Molstad and colleagues suggested that *"respiratory tract infections were the most common reason for an antibiotic prescription, the majority of which are of viral aetiology*". (Molstad, *et al.*, 2002: 370). Aydin and coworkers investigated common infections and antibiotic prescribing habits of residents in three University hospitals in Turkey and found similarly that upper respiratory tract infections were the most common infection accounting for 54% of outpatient visits to the hospitals (Aydin, *et al.*, 2005: 172). In the United States more than a fifth of all antibiotic prescriptions were for upper respiratory tract infection, however according to the Center for Disease Control (CDC), the antibiotic treatment of adults with nonspecific upper respiratory tract infections, acute bronchitis, or cough does not enhance illness resolution and is not recommended (Priest, *et al.,* 2001:1037).

An increased number of antibiotic prescriptions per 1000 inhabitants was observed in the countries of Southern Europe. In 1997 Greece, Spain and Belgium had the highest number of antibiotic prescriptions per 1000 inhabitants while The Netherlands, Sweden and Austria had the lowest. Between 1994 and 1997, France and Greece had an increase in prescriptions per 1000 inhabitants and Spain, Portugal and Sweden a decrease. Major differences were evident within neighboring countries, for example between The Netherlands and Belgium. These large differences are unlikely to be related to a difference in bacterial infections. The differences in antibiotic prescribing in different countries depends on several factors like differences in health care systems, antibiotic dosage regimens, patient expectations and attitudes towards taking drugs and the information available to and the knowledge of general practitioners. (Molstad, *et al*., 2002: 366, 367).

2.4 Microbial Resistance to Antibiotics

2.4.1 Patterns of Microbial Resistance to Antibiotics

Antibiotic resistance, the insensitivity of bacteria to the antimicrobial actions of a given antibiotic, has increased rapidly and is a worldwide problem being recognized as a major factor contributing to morbidity, mortality and cost. Inappropriate antibiotic use for both humans and animals is a major reason for this increased emergence and spread of resistance. Higher consumption is associated with higher resistance rate. (Aydin, *et al*,

2005: 169; Molstad, *et al.*, 2002: 366; Raymond, Pelletier & Sawyer, 2002: 497; WHO, 2005:1).

From the beginning of the antibiotic era, Alexander Fleming, who discovered penicillin, did not only recognize the benefits of antimicrobials but also the potential risks associated with inappropriate use of them. He was concerned about their indiscriminate prescription by prescribers and that people would be able to purchase them without a doctor's prescription. He wrote the following in 1947:

> *'The greatest possibility of evil in self medication is the use of too small doses, so that instead of clearing up the infection, the microbes are educated to resist penicillin and a host penicillin-fast organisms is bred-out which can be passed on to other individuals and perhaps from there to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save. In such case the thoughtless playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin resistant organism. I hope this evil can be averted.'* (van Bogaert & Ogunbanjo, 2004: 5).

According to the WHO, in some parts of the worlds primary multidrug resistant tuberculosis is as high as 17%; HIV resistance to at least one antiretroviral drug is as high as 25%, penicillin resistance in *Neisseria gonorrhoea* – 98%, penicillin resistance in *Streptococcus pneumoniae* as high as 70%, as many as 90% and 95% shigellosis cases are resistant to ampicillin and cotrimoxazole respectively, and up to 70% of S*taphylococcus aureus* infections are resistant to penicillins and cephalosporins. (WHO, 2005:1).

According to McNulty and others the first strains of penicillin resistant Pneumococci were isolated in the mid 1960s (McNulty, Kane, Foy, Sykes, Suanders, & Cartright, 2000: 493). Similarly, ten years after the discovery of the sulphonamides, 20% of clinical isolates of *Neisseria gonorrhea*e had become resistant to them and as many as 80% of all strains of *Staphylococcus aureus* are resistant to penicillin (Ibezim, 2005:1606).

The rise in consumption of antibiotics is the dominant factor in the spread of bacterial resistance and prior antibiotic administration is an important risk factor for the

development of antibiotic-resistant infection including multidrug-resistant nosocomial pathogens like vancomycin resistant enterococci (Priest, Yudkin, McNulty, & Mant, 2001:1037). The nasopharyngeal carriage of penicillin resistant Pneumococci in children was strongly associated with the use of individual antimicrobial agents and total antimicrobial consumption in a community. Methicillin resistant *Staphylococcus aureus* is also an enormous problem in hospitals and the community. (McNulty, *et al.,* 2000: 493).

In addition the relationship between antibiotic use and resistance in hospital environment is evident. There is a correlation between the level of antibiotic use in the community and the development of resistant respiratory tract bacteria. (Molstad, *et al.,* 2002: 366).

The emergence of vancomycin-resistance enterococci (VRE) has been linked to prior antibiotic use, especially cephalosporins. A study at Cleveland clinic suggested that a change in the prescribing patterns of third generation cephalosporins has resulted in a reduction in resistant enterococcal isolates from 17% in 1999 to 12% in 2000. (Longworth, 2001: 496).

According to a literature review of 18 studies, 15 studies implicated vancomycin use in the emergence of vancomycin-resistant enterococci, four of six studies implicated cephalosporins, four of five studies implicated metronidazole, and five of six studies implicated use of any type of antimicrobial (Patterson, 2001: 427s; Bremon *et al*, 2000: 395). Priest and others demonstrated a positive correlation between resistance of urinary coliform isolates to an antibacterial drug and the prescribing of the drug in the community. In the study the proportion of urinary coliform isolates resistant to the most commonly used antibacterial drug was high – 44% to ampicillin or amoxycillin and 25.4% to trimethoprim. (Priest, *et al.,* 2001:1037).

The Center for Disease Control and Prevention (CDC) reported the development of resistance of *Streptococus pneumonia* isolates from several medical centers. Of 1,600 *S. pneumoniae* isolates, 30% were partially resistant to penicillin and 12% had high level resistance. Four percent of the isolates were resistant to ceftriaxone, 13% to tetracyclines,

and 29% to trimethoprim-sulfamethoxazole. Recently the emergence of quinolone resistant *S. pneumoniae* has been observed. In Canada, the prevalence of strains with reduced susceptibility to ciprofloxacin has risen from zero in 1988 to 1.7% (or 3% among adults) in 1997 with an increase usage of the drug. (Longworth, 2001: 501).

In addition multi-drug resistant strains of *S. pneumoniae* are increasing. The CDC found that among invasive pneumococcal infections in eight US regions, 24% of the isolates in 1998 were penicillin resistant, including 14% that were highly resistant. The penicillin resistant strains were more likely to display high level resistance to other drugs and two thirds of the penicillin-resistant strains were also resistant to all drugs tested. Methicillin resistant coagulase-negative staphylococci are also common. These coagulase negative staphylococci are the leading cause of nosocomal blood stream infections and an important cause of postoperative surgical site infection. (Longworth, 2001: 501). This increased incidence of resistant organisms can be attributed to one or more mechanisms employed by the microbe.

2.4.2 Mechanism of microbial resistance

Bacterial cells may develop resistance to antibiotics either through horizontal transfer, acquisition of already made pre-tested resistant genes from other micro-organisms, or through mutation in different chromosomal loci. Both mutation and horizontal transfer can act synergistically in that horizontal transfer introduces new alleles into a population while mutation produces new variations of these alleles. (Blazquez, 2003: 1201, 1202). Some of the mechanisms by which bacterial resistance develops to an antibiotic are discussed briefly in this section.

A. **Selection**

The destruction of susceptible strains by the antibiotic may allow the naturally resistant organisms to colonize the patient. For example, penicillin therapy destroys much of the normal mouth flora and penicillin-resistant organisms previously present in small numbers can colonize the mouth. (Ibezim, 2005:1608)

B. **Mutation**

"A genetic mutation may occur with drug treatment and becomes apparent when the sensitive organisms are destroyed. Mutation occurs more readily with some antimicrobial agents than with others, and especially with streptomycin, rifampicin, and nalidixic acid." (Ibezim, 2005:1608). Antibiotics as stress producers can increase the mutation rate as demonstrated for fluoroquinolones and aminoglycosides (Blazquez, 2003: 1206).

C. **Phage transduction**

Certain organisms may acquire resistance as a result of the activity of phages (bacterial viruses). These phages incorporate a resistance present in one organism and when released carry the resistance over to an organism which was originally sensitive. (Ibezim, 2005:1608).

D. **Transference**

Resistance may be transferred from one bacterial genus to another as a result of an exchange of extra-chromosomal genetic particles (plasmids) during conjugation. This process occurs in many bacteria including Gram-negative bacilli. Resistance to several antibiotics may be transferred at one time by this mechanism. Resistance to a number of drugs including aminoglycosides, cephalosporins, chloramphenicol, fusidic acid, penicillins, tetracyclines, sulphonamides and trimethoprim can be transmitted in this way. (Ibezim, 2005:1608).

2.4.3 Factors that contribute to microbial resistance

Antibiotic use is the key driver of microbial resistance. A combination of underuse, often for financial reasons, leading to incompletion of treatment courses, overuse particularly for minor infections, and misuse due to lack of access to appropriate treatment of antibiotics have increased the prevalence of multi-drug resistant pathogens leading some to even speculate that we are nearing the end of the antibiotic era (WHO, 2001: 2; Katzung, 2001: 753). This indiscriminate use of antibiotics is promoted by factors such as patient demands, prescribers, drug advertisement, dispensing doctors and the use of antibiotics in agriculture (Ibezim, 2005: 1608).

A. Use of antibiotics in agriculture

The use of antimicrobial agents in animals has become a very important public health issue. Antimicrobials are increasingly used in the prevention and treatment of infectious diseases and are routinely added, at subtherapeutic level, to animal feed for growth promotion in farm animals. This practice can result in the stimulation of microbial resistance to antibiotics with the possible transferance of resistant strains of bacteria from animal to humans through direct contact with the animal or food derived from them. (Al-Mustafa & Al-Ghamdi, 2002:4; Ibezim, 2005: 1610).

A study by Al-Mustafa and colleague showed that 75.9% (22 of 29) antibiotics used in the poultry industry in Saudi Arabia were also used for the treatment of human infections. Among these antimicrobials were tetracyclines (oxytetracycline and doxycycline), penicillins, trimetoprim-sulfamethoxazole, streptomycin and fluoroquinolones. The 29 antimicrobial agents available for poultry were mostly employed for prophylactic or nutritional purposes rather than therapy of infectious diseases. (Al-Mustafa *et al*., 2002:5).

B. **Patients' demands and prescribers**

Doctors and other prescribers are influenced by patients' demands even when they are certain of the diagnosis. This may be due to fear of litigation, to avoid being labeled difficult or not to lose patients. For example in Tanzania, 80% of health workers admit to prescribing inappropriate drugs, especially those demanded by socially influential patients. In India many patients believe in the efficacy of tonics, and if doctors do not prescribe what the patient desires, they do not return to their doctors. For this reason doctors prescribe tonics to patients even when they are ineffective since their livelihood depends on the number of patients that attend to their clinics. On the other hand some prescribers prescribe antibiotics to patients too often and unnecessarily because of a lack of adequate drug knowledge. (Ibezim, 2005: 1608, 1609; van Bogaert *et al.*, 2004: 5).

C. **Drug advertisements**

The pharmaceutical industry can promote bacterial resistance to antibiotics through their, often unethical, practice of drug promotion. Some companies use adverts that do

not clearly explain the use of drugs or provide other needed information. Some doctors totally rely on promotional materials with the biases they contain which may lead to inappropriate use of antibiotics. (Ibezim, 2005: 1609; van Bogaert *et al*., 2004: 5)

D. **Dispensing doctors**

Many doctors who make money from selling drugs prescribe more antibiotics than those who do not. A study in Zimbabwe showed that dispensing doctors prescribed antibiotics to 58% of their patients while the non-dispensing prescribers prescribed the same antibiotics to 48% of their patients. (Ibezim, 2005: 1609).

2.4.4 Impact of microbial resistance

The implication of antimicrobial resistance in terms of morbidity, mortality, and costs is great and is of urgent and global importance, which requires an international effort to control (Cookson, 2000: 66). Antimicrobial resistance (AMR) is one of the world's most serious public health problems. It threatens to undermine the effectiveness of health delivery programs and has been described as a threat to global stability and national security. *"The problem is so serious that unless concerted action is taken worldwide we run the risk of running to the pre-antibiotic era when many more children than now died of infectious diseases and major surgery was impossible due to the risk of infection."* (WHO, 2001: 1; 2005:1)

Antimicrobial resistance results in serious clinical and financial consequences. Mortality and morbidity are increased by delays in administering effective treatment for infections caused by resistant microbes. This can result in costly prolonged illness and hospitalization, and the use of other than first line drugs may increase costs 100-fold making it unaffordable for many governments and patients especially in developing countries. As an example, in the United States, more that half of the 2 million nosocomial infections occurring annually are as a result of antibiotic resistant organisms. This has an estimated impact of more than 70000 lives, $5 to $10 billion dollars annually. (Raymond, *et al,* 2002: 497; WHO, 2005: 1,2)

The presence of antibiotic resistance in bacterial strains is a major factor in increasing mortality rates and places a burden on health care systems. A systematic literature review by Patterson has demonstrated a significantly higher rate of mortality of patients in six hospitals in six continents with extended spectrum β-lactamase producing *K pneumoniae* who received empiric treatment to which these strains were resistant compared with patients who received appropriate antibiotics. In this review was a study result that demonstrated the death of 23 of 43 patients with ceftazidime resistant *K. pneumoniae*. (Patterson, 2001: 427).

Moreover, antibiotic resistance has been found to increase the length of hospital stay of patients. This was demonstrated in a study at Johns Hopkins Hospital, which showed patients with vancomycin resistant enterococci had significantly increased length of stay in the hospital and ICU and higher crude mortality rates (45% vs 27%) compared with patients with vancomycin-susceptible enterococci. Another study at the University of Pittsburgh Medial Center found an association between vancomycin resistant enterococci and mortality among liver transplant patients. 46% of patients with vancomycin resistant enterococci died from enterococcal bacteremia compared with 25% of patients with vancomycin sensitive enterococci. (Patterson, 2001: 427).

Various strategies to limit antimicrobial resistance have evolved some of which are discussed in the next section.

2.4.5 Strategies to limit antimicrobial resistance

Strategies to limit antimicrobial resistance are based on four basic principles, which are containment of resistant species, infection prevention, infection eradication, and optimizing antibiotic utilization (Raymond, *et al*., 2002:1, 2). Optimizing antibiotic utilization is an important and promising means of limiting the spread of antibiotic resistance. As antibiotic utilization is rampant and prior antibiotic administration is an important risk factor for development of antibiotic resistant infections, the most basic goal of antibiotic stewardship is the appropriate utilization of antibiotic. This involves accurately identifying infectious

episodes, obtaining appropriate culture and sensitivity data, applying appropriate treatment modalities, selecting the most appropriate antibiotic for therapy when indicated, and dosing antibiotics appropriately. In addition removal of invasive devises and prosthetic devises, drainage of collections, debridement of devitalized tissue, and avoiding inappropriate antibiotic use such as treatment of bacterial colonization or noninfectious causes of inflammation are important. (Raymond, *et al.,* 2002:1, 2).

The WHO (WHO, 2001: 6) recommends different strategies for the containment of antimicrobial resistance, which are summarized as follows.

1. Education of patients and the general community on the appropriate use of antimicrobials, on the importance of infection prevention measures, on appropriate and informed health care seeking behavior, and on suitable alternatives to the use of antimicrobials for relief of symptoms and the discouragement of patient initiation of self treatment.
2. Prescribers and dispensers education is an important factor for optimizing appropriate antibiotic use. These health care providers needs to be educated on topics such as, the importance of appropriate antimicrobial use and containment of antimicrobial resistance, accurate diagnosis and management of common infections, educating patients on antimicrobial use and the importance of adherence to the prescribed treatments, and factors that influence their prescribing habits such as economic incentives, promotional activities and inducement by the pharmaceutical industry.
3. Guidelines, formularies and regulations. Encourage the development and use of guidelines and treatment algorithms to foster appropriate use of antimicrobials, and empower formulary managers to limit antimicrobial use to the prescription of an appropriate range of selected antimicrobials. Supervision, audit and support of diagnostic, prescribing and dispensing practices to promote appropriate use of antimicrobials is important. Linking professional registrations to requirements for training and continuing education for prescribers and dispensers.
4. At hospital level, establishing infection control programs and therapeutic committees, development of regularly update guidelines for antimicrobial treatment

and prophylaxis, and monitoring antimicrobial use. Ensuring the availability of appropriate diagnostic laboratory services and control and monitoring of pharmaceutical company promotional activities is also one of the strategies to limit microbial resistance.

5. Regulate use of antimicrobials in food-producing animals.
6. National government and health care systems need to play the role of advocacy and take intersectoral action by making the containment of antimicrobial resistance a national priority, developing regulations on registration schemes for dispensing outlets, availability of antimicrobials to prescription only status and ensuring market authorization of antimicrobials of proven safety, efficacy and quality. Establish policies and guidelines and maximize the implementation of such policies and guidelines through education of health care personnel. Surveillance of resistance, antimicrobial usage and disease burden at national level also contribute to the appropriate use of antimicrobials
7. Encourage new drug and vaccine development.

In general, encouraging good practice on the use of antimicrobial agents is of great importance. *"Treatment should be limited to bacterial infections using antibiotics directed against the causative agent, given in optimal dosage, dosage intervals, and length of treatment with steps taken to ensure maximum patient concordance with the treatment regimen, and only when the benefit of the treatment outweighs the individual and global risk."* (Cookson, 2000: 66).

CHAPTER 3
METHODOLOGY

3.1 Study Design

This study was a cross-sectional, retrospective, descriptive review of antibiotic usage in two district hospitals in the West Wollega zone of Ethiopia. The review covers antibiotic prescriptions dispensed over a one-year period, i.e. from January to December 2007. Both hospitals are located in towns in the administrative zone, a distance of 75 km from each other. Nedjo Hospital is owned and operated by the Ethiopian Government while Gimbie Adventist Hospital is owned by the Seventh Day Adventist Church.

This study was designed to retrospectively describe the extent and nature of antibiotic prescribing in the two hospitals identified.

3.2 Study Population

There is no prescription database whereby all the dispensed antibiotic prescriptions are kept centrally or locally. However, all the prescriptions dispensed are kept in each health facility for a minimum period of two years. Therefore, all prescriptions dispensed in the study period were accessed from each hospital. Topical antibiotic preparations and antituberculosis antibiotics, antifungal antibiotics and antiviral were excluded.

The study population included all the dispensed prescriptions in the study period for both in-patients and out-patients and also for patients of all ages.

3.3 Data collection and Management

3.3.1 Sampling

Sampling of hospitals: There are four hospitals in the West Wollega zone. Two of the hospitals are operated by government and the other two are mission hospitals. For

comparative purpose, one of the government and one of the mission hospitals were selected for this study. The two identified hospitals were sampled based on convenience sampling.

Sampling of prescription data: All the dispensed prescriptions for the study period were identified and categorized on a quarterly basis into four periods i.e. - January to March, April to June, July to September and October to December, 2007. Prescriptions dispensed in the first month of each quarter were used for this study. This is to account for and include the different seasons, which may have different patient flows and disease epidemiology and hence should provide for representative results.

3.3.2 Recruitment and training of data collectors

Only pharmacy personnel (pharmacy technicians and pharmacists) were recruited and involved in collecting the data in both hospitals. One pharmacist and three pharmacy technicians were involved in the collection of data with the primary researcher. These pharmacy personnel were selected to increase the reliability of the data collection process as they are more knowledgeable about the antibiotics than other health personnel. Three months data at Gimbie Adventist Hospital and one month prescription data at Nedjo Hospital was collected by the primary researcher. The rest, one month at Gimbie Hospital and three months at Nedjo Hospital was conducted by the selected trained pharmacy personnel.

These data collectors were trained through the provision of a detailed explanation on how to complete the standardized tool. This was done using sample prescriptions which were not included in the study period and sample. In addition the researcher worked closely with these personnel until they were well acquainted with the process.

3.3.3 Pilot

A small scale pilot using prescriptions from ten days in the month of February was conducted. These prescriptions selected from Gimbie Adventist Hospital were used to test

the suitability of the pre-designed data collection tool. Based on this pre-test some adjustments were made to the data collection tool.

3.3.4 Data collection instruments

As this study is a specific drug utilisation review within institutions that have their own specific way of recording data, standard instruments for the capture of prescribing patterns are not sufficiently applicable, and therefore a purpose-designed data collection form was developed and is provided in Appendix I (Smith, 2002:44). A separate purpose designed form (Appendix II) was used for the collection of information on the type and number of infectious diseases diagnosed. These forms were used to collect the required information.

3.3.5 Data collection process

The Administrator of Gimbie Adventist Hospital and the Medical Director of Nedjo Hospital were requested, both in writing and personally by the researcher, for permission to conduct the study. Official letters of permission were granted from both hospitals (Appendix IX & X) after which the pharmacy departments of both hospitals were contacted to carry out the data collection process.

The prescriptions dispensed in both health institutions of the specified year were identified. From these prescriptions, those that were dispensed in the specifically identified study months (January, April, July and October 2000) were separated and sorted, by date, by the researcher.

To avoid bias, antibiotic prescriptions were separated from other prescriptions and counted separately. The numbers of antibiotic and non-antibiotic prescriptions dispensed on each day of the month were recorded by the researcher. It was only then that prescriptions were given to the data collectors to capture the required information on the data collection tool.

These identified antibiotic prescriptions were used to transfer the required information to the data collection tool. Each antibiotic was identified and recorded with its non-proprietary (generic) name, strength and dosage form. Each prescription was coded with a red marker after being recorded to avoid repetition. The coding was done in such a way that explained the month and the day on which the prescription was issued, and the number by which it was recorded on the data collection tool (e.g. Ja1015 indicates that the prescription was issued on the 10th of January and was recorded as number 15 on the data collection tool).

The prescription data capture of three months at Gimbie Adventist Hospital (January, July and October) and one month (January) at Nedjo Hospital was conducted by the researcher whilst one month's conducted by a pharmacist of the hospital. The remainder, two months at Nedjo Hospital and one month of Gimbie Hospital prescriptions were conducted by three pharmacy technicians who were employees in the hospitals.

Furthermore, the following information was collected for each hospital for each of the sample months:

- Number of outpatient antibiotic courses started,
- Number of antibiotic days by specific agent and overall,
- Total number of population in the catchment area,
- Cost of individual antibiotic agents and
- Total cost of all antibiotics.

An antibiotic day is defined as each day a patient is administered a systemic antibiotic. (Mylotte & Keagles, 2005:1118).

In addition, information on the number and type of infectious diseases diagnosed was collected from the statistics departments of both hospitals as there was no diagnosis available on the prescriptions. A separate purpose-designed form was used to gather this information (Appendix II). This information was used to analyze a possible correlation between incidence of antibiotic use and infection rate. The researcher was involved in collecting this information for the sample months under study in both hospitals.

The cost of antibiotics prescribed was calculated for each facility based on the cost from a government owned pharmaceutical importer and distributor company (PHARMID) that supplies hospitals in the country. Invoices of pharmaceuticals purchases made from this company were used to determine the cost of a given antibiotic. In cases where an antibiotic was not commonly supplied by PHARMID other costs from the providing companies were used to calculate the costs.

3.3.6 Monitoring of data collection

To maximize the quality of data collected, the principal researcher did approximately half of the prescription data collection and worked closely with the data collectors for the rest of the data. All the data collected by the data collectors were cross checked with the number of antibiotics recorded at the outset. In addition the researcher closely followed and provided necessary corrections to the data collector at Gimbie Hospital in-person and at Nedjo Hospital, telephonically.

In addition the data collection forms were rechecked by the primary researcher for any missed, incorrect and unreadable information whilst collecting the forms from the data collectors and any necessary corrections were immediately made.

3.3 Data analysis

The total number of each item dispensed was determined for each month included in the study and the total for the four months was calculated. The annual consumption was estimated from these data. The total number of prescriptions, number of antibiotic prescriptions, antibiotic use, and infectious diseases diagnosed, and the cost of antibiotics from each facility, for each month, were captured on an Excel® spreadsheet. The following drug utilization indicators were calculated for out- and in-patients for each facility:

- Percentage of encounters with antibiotic prescribed (is the percentage of patient encounters during which one or more antibiotics are prescribed from the total number of encounters surveyed. (WHO, 1993:14))

- Average number of antibiotics per prescription
- Percentage of encounters with injectable antibiotics
- Percentage of antibiotics prescribed from the Essential Drug List (EDL) and Drug List for District Hospitals
- Percentage of antibiotics actually dispensed
- Number of antibiotic days prescribed by antibiotic class
- Incidence of antibiotic use (number of antibiotic prescriptions per 1000 inhabitants, and number of antibiotic prescriptions per 100 bed per day for inpatients)
- Antibiotic utilisation ratio (ratio of the number of antibiotic days to the number of inhabitants),
- Number of defined daily doses (DDDs) /1000/day and the number of DDD/100 bed days
- Cost of antibiotic
- Cost per antibiotic day for outpatients and cost of antibiotic per patient care day for hospitalized patients
- Percentage of drug budget spent on antibiotics. (Mylotte *et al*, 2005: 1118; Bremon *et al*, 2000: 396; WHO, 2003:22)

The DDD is defined as the "assumed average maintenance dose per day for a drug used for its main indication in adults" (WHO, 2003:38). It is a parameter or unit of measurement used for comparative purposes which does not necessarily correspond directly to the recommended or prescribed daily dose (PDD). It is commonly expressed as the number of DDDs per 1000 inhabitants per day and provides an estimate of the proportion of the study population treated daily with the drug under study. (WHO, 2003:38)

These parameters were estimated for the entire twelve months of the year for outpatients and inpatients of each hospital and were reported.

These drug use indicators were calculated based on the following formulas described in the WHO Manual (WHO, 1993:39-44; 2003: 13-16, 38).

I. Average number of antibiotics per encounter (C): Total number of antibiotics prescribed (B) divided by total number of antibiotic encounters (A).

$$C = B/A$$

II. Percentage of encounters with antibiotics prescribed (D): Total number of prescriptions with one or more antibiotics (A) divided by total number of encounters (F) multiplied by 100.

$$\% \text{ Antibiotic encounters (D)} = (A/F) \times 100$$

III. Percentage of encounters with injectable antibiotics prescribed (G): Total number of patients who received one or more injectable antibiotics (H) divided by total number of encounters with antibiotics (A).

$$\% \text{ Antibiotic injections (G)} = (H/A) \times 100$$

IV. Percentage of antibiotics prescribed from Essential Drug list (I) or List of Drugs for District Hospital (LDDH): Total number of antibiotics prescribed from EDL or LDDH (J) divided by total number of antibiotics prescribed (B) multiplied by 100.

$$I = (J/B) \times 100$$

V. Percent of antibiotics dispensed (K): total number of antibiotics dispensed (N) divided by total number of prescribed antibiotics (B) multiplied by 100.

$$K = N/B \times 100$$

VI. Antibiotic utilization ratio (N): Total number of antibiotic days in the year (O) divided by number of inhabitants (P).

$$N = O/P$$

VII. Incidence of antibiotic use(Q):

Outpatient: total number of outpatient antibiotic prescriptions (R) divided by total number of inhabitants (P) x 1000.

Inpatients: total number of inpatient antibiotic prescriptions (S) divided by number of bed days in a year (T) multiplied by 100.

$$Q\ outp. = (R/P) \times 1000, \quad Q\ inp. = (S/T) \times 100$$

VIII. Number of patient (bed) days (U): Total number of beds (V) x Occupancy (W) x number of days in the study period (X), which is 365.

$$U = V \times W \times X$$

IX. Number of DDD

a. Total number of Defined daily doses (DDD) of a given antibiotic (Y): total amount of the antibiotic dispensed (Z) multiplied by Strength in grams (a) divided by its DDD. For antibiotics with more than one strengths, the sum of the products of the strength and amount dispensed were used.

$$\text{Total DDD} = Y = (Z \times a)/\text{DDD of the antibiotic},$$

$$Y = (Z1 \times a1) + (Z2 \times a2) + (Z3 \times a3)/\text{DDD of the antibiotic}$$

b. DDD per 1000 inhabitants days =
(Total no. of DDD/ total no. of inhabitants x 365) x 1000

c. DDD per 100 bed days =
(Total no of DDD in the year/total no of beds x occupancy rate x 365) x 100

CHAPTER 4
RESULTS

4.1 Prescribing Indicators

4.1.1 Percentage of Prescriptions with Antibiotics

A total of 18568 antibiotic and non-antibiotic prescriptions were reviewed retrospectively in the four months of the study period at both Gimbie and Nedjo Hospitals. 7315(39%) of prescriptions were from Nedjo Hospital and 11253 (61%) from Gimbie Adventist Hospital. Prescriptions containing one or more systemic antibiotics at Gimbie Adventist Hospital were 5342 (47.47%) and at Nedjo Hospital were 3393 (46.38%). The average antibiotic prescribing encounters for the West Wollega was 47%. This is shown in Figure 4.1 and Figure 4.2.

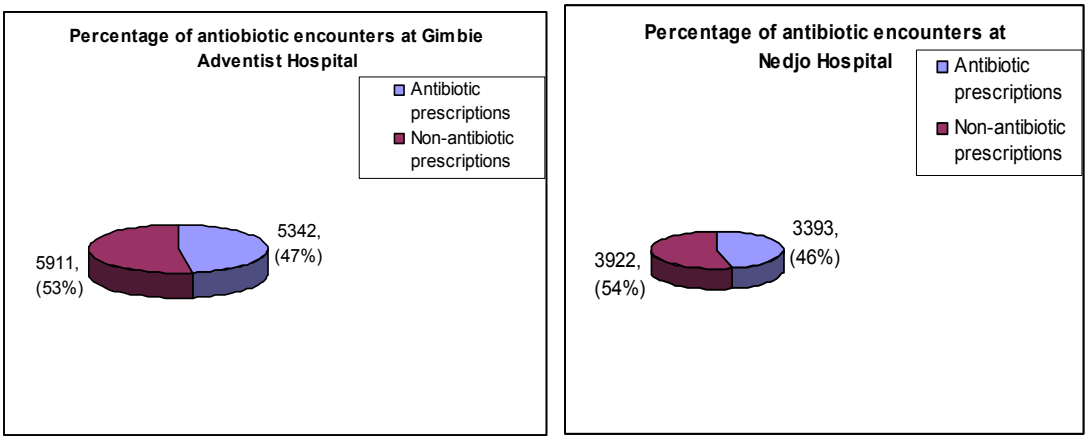

Figure 4.1 Percentage of antibiotic prescriptions encountered at Gimbie Adventist and Nedjo Hospitals, 2007

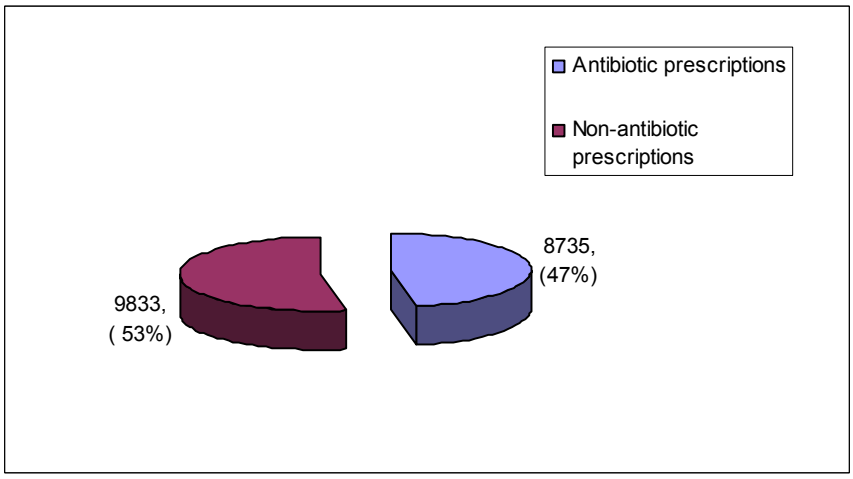

Figure 4.2 Antibiotic and non-antibiotic prescription encounters in two hospitals in the West Wollega zone, 2007.

Of all the antibiotic prescriptions reviewed in the West Wollega 61% were from Gimbie Adventist Hospital and 39% were from Nedjo Hospital as shown in Figure 4.3.

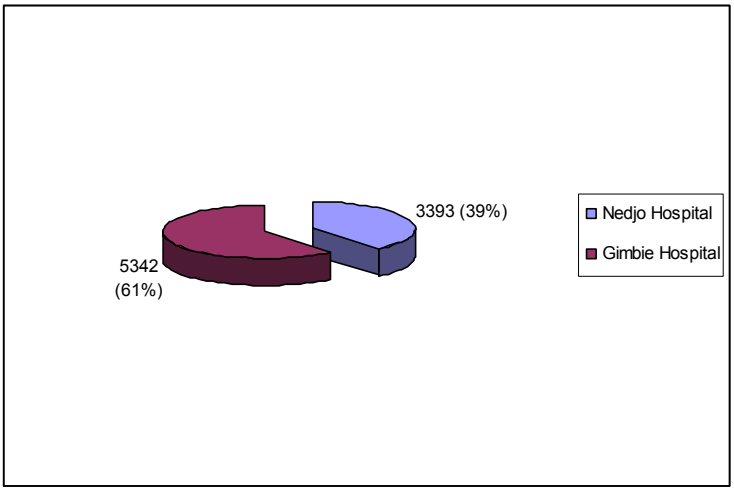

Figure 4.3 Distribution of antibiotic encounters by hospitals in West Wollega zone, 2007

Of all antibiotic prescriptions reviewed, the number of outpatient antibiotic prescriptions were 6145 (70.0%) whilst inpatient prescriptions were 2590 (30.0%). The breakdown of prescriptions reviewed by each hospital was 2043 (78.9%) inpatient and 3299 (53.7%) outpatient prescriptions at Gimbie Adventist Hospital and 547 (21.1%) inpatient and 2846 (46.3%) outpatient at Nedjo Hospital.

4.1.2 Antibiotic prescriptions by age group and gender

4.1.2.1 Distribution by age group

Distributions of antibiotic prescriptions were determined for different age groups. The majority (70%) of outpatient and inpatient antibiotic prescriptions at both Hospitals were issued to patients of 15-49 years of age whilst the least (3.3%) number of prescriptions were for those under the age of one year. About 4.5% of the antibiotic prescriptions were issued to geriatrics (65 years and above). Table 4.8 summarizes overall antibiotic prescriptions by age group and gender for both Hospitals.

Table 4.1 Antibiotic encounters by gender and Age group in the West Wollega zone of Ethiopia, 2007

Age group (Years)		Gimbie Adventist Hospital				Nedjo Hospital				West Wollega			
		Male		Female		Male		Female		Male		Female	
		No	%	No	%	No	%	No.	%	No	%	No	%
Under 1	OP	35	66.0	18	34.0	66	58.4	47	41.6	101	60.8	65	39.2
	IP	41	60.3	27	39.7	33	58.9	23	41.1	74	59.7	50	40.3
1-4 yrs	OP	103	58.2	74	41.8	129	50.8	125	49.2	232	53.8	199	46.2
	IP	60	67.4	29	32.6	46	66.7	23	33.3	106	67.1	52	32.9
5-14 yrs	OP	90	47.1	101	52.9	99	48.8	104	51.2	189	48.0	205	52.0
	IP	45	42.5	61	57.5	22	56.4	17	43.6	67	46.2	78	53.8
15-49 yrs	OP	872	44.2	1100	55.8	980	50.2	974	49.8	1852	47.2	2074	52.8
	IP	725	39.9	1092	60.1	131	35.2	241	64.8	856	39.1	1333	60.9
50-64 yrs	OP	174	46.3	202	53.7	104	52.3	95	47.7	278	48.3	297	51.7
	IP	78	38.8	123	61.2	16	44.4	20	55.6	94	39.7	143	60.3
≥ 65 yrs	OP	97	63.4	56	36.6	44	60.3	29	39.7	141	62.4	85	37.6
	IP	98	70.5	41	29.5	11	44.0	14	56.0	109	66.5	55	33.5
Total		2418	45.3	2924	54.7	1681	49.5	1712	50.5	4099	46.9	4636	53.1

4.1.2.2. Distribution of Antibiotic encounters by gender

Of the antibiotics prescribed 54% were for females whilst the remainder - 46% were for males in the West Wollega zone. Females were prescribed more antibiotics than the male counterparts at Gimbie Adventist Hospital (54.74%) and about the same at Nedjo Hospital (50.46%).

4.1.3 Average number of antibiotics per prescription

The average number of antibiotics per encounter was identified for both inpatient and outpatient prescriptions. According to this the average number of antibiotics per encounter for outpatients was 1.63 at Nedjo and 1.25 at Gimbie Hospital. For inpatients it was 1.04 and 1.13 for Nedjo and Gimbie Hospitals respectively. This is shown in Figure 4.4.

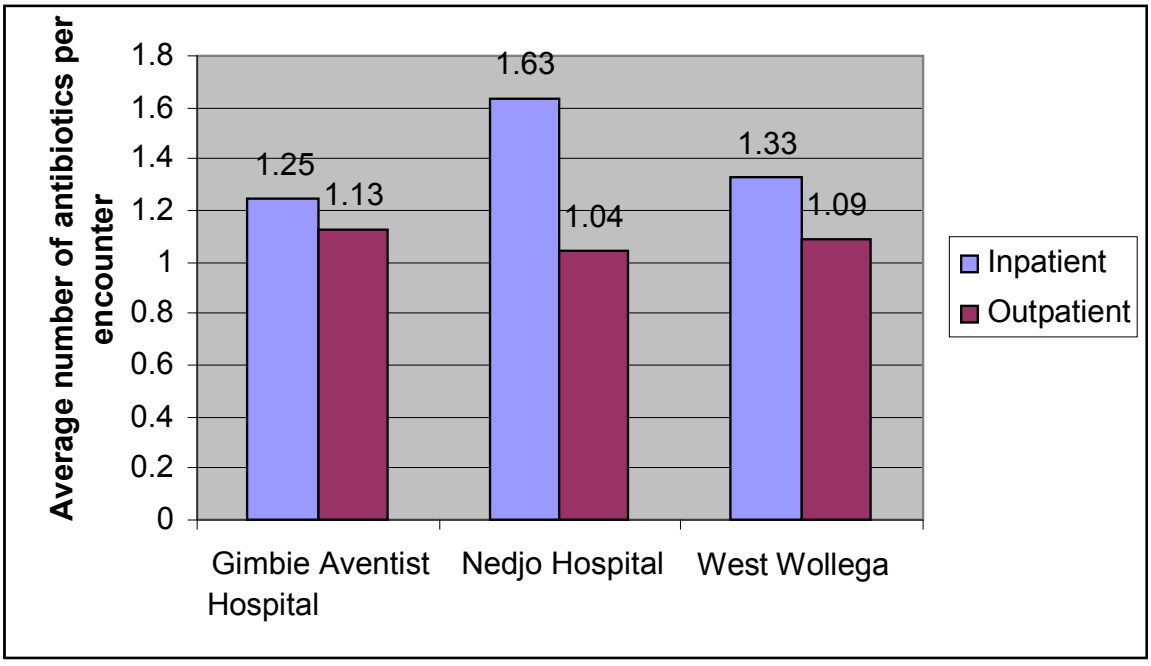

Figure 4.4 Average numbers of antibiotics per encounter for two hospitals in West Wollega, 2007

4.1.4 Percent of Encounters with Injectable antibiotics

The number of encounters that contained one or more injectable antibiotics was determined for both hospitals. At Nedjo Hospital, 95.25% of inpatient antibiotic encounters involved an injectable antibiotic whilst it was only 79.98% of the antibiotic encounters at Gimbie Hospital that included injectable antibiotics. Figure 4.5 shows the percentage of one or more injectable antibiotic encounters for both hospitals and the West Wollega zone.

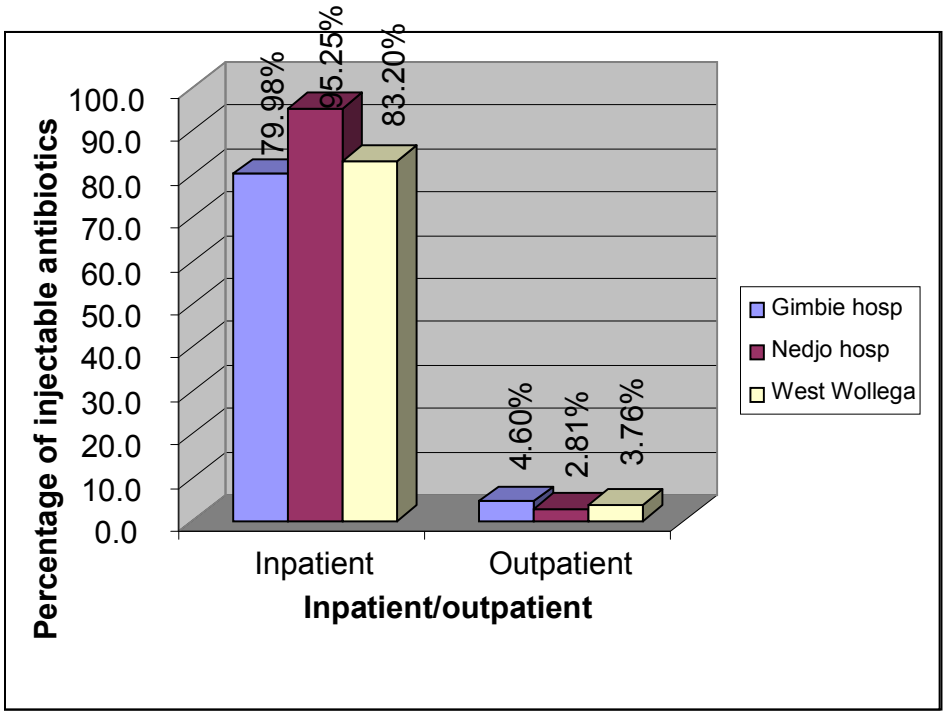

Figure 4.5 Percentage of encounters with one or more injectable antibiotics at Nedjo and Gimbie Hospital, 2007

4.1.5 Percentage antibiotics prescribed from the Essential Drug List and List of Drug for District Hospitals

The percentage of antibiotics prescribed from the Essential Drug List (EDL) of Ethiopia and the List of Drugs for District Hospitals was analyzed. This was calculated based on the EDL and list of drugs for different levels of health institutions as developed by the Drug Administrations and Control Authority of Ethiopia (DACA).

Percentage prescribed from the EDL of Ethiopia. The percentage prescribed from the EDL was calculated for both inpatient and outpatient departments of both hospitals. From the total of antibiotics prescribed to outpatients (2959), the percentage prescribed from the EDL at Nedjo Hospital was 2023 (68.4%) whilst that of inpatients was 859 of 893 antibiotics prescribed (96.2%). For both departments 74.8% of prescribed antibiotics were from the EDL whilst the remaining 25.2% were not.
At Gimbie Adventist Hospital the total number of antibiotics prescribed was 3733 to outpatients and 2552 to inpatients. Of this, the percentage of EDL antibiotics prescribed was 2190 (58.7%) and 1717 (67.3%) to outpatients and inpatients respectively. The overall inpatient and outpatient antibiotics prescribed from the EDL were 62.2%.

The average percentage of antibiotics prescribed from the EDL for the West Wollega was 63.0% and 74.8% for outpatients and inpatients respectively.

Percentage prescribed from the List of Drugs for District Hospitals (LDDH). Both hospitals do not have a formulary specific to their hospital and therefore the LDDH, as developed by the DACA was used. According to this, at Nedjo Hospital the percentage of antibiotics prescribed from the LDDH was 99.3% 2959 outpatient encounters and 97.0% of 893 inpatient encounters. The average antibiotic prescribing in accordance with the LDDH was 98.8%.

The percentage of antibiotics prescribed from the LDDH at Gimbie Adventist Hospital was 85.4% for 3733 outpatient encounters and 68.8% of 2552 inpatient encounters. The average antibiotic prescriptions for the whole hospital in accordance with the LDDH was 78. 6%.

The average percentage of antibiotics prescribed in accordance with the LDDH for the West Wollega was 90.8% and 76.1% for outpatients and inpatients respectively.

4.2 Patient Care Indicators

4.2.1 Percentage of antibiotics actually dispensed

The percentage of prescribed antibiotics that were actually dispensed in both hospitals for outpatients and inpatients was 98.6% and 97.0% respectively. Almost all of the antibiotics prescribed were dispensed at both inpatients and outpatient pharmacies of Gimbie Adventist Hospital with a few exceptions. These exceptions include cloxacillin injection (penicillin), and chloramphenicol injection prescribed to inpatients. Of the antibiotics prescribed to outpatients 3721 (99.8%) of 3733 antibiotics prescribed were dispensed whilst 2455 (96.2%) of the 2551 antibiotics prescribed to inpatients were dispensed. The overall percentage of antibiotics prescribed at Gimbie Adventist Hospital that were actually dispensed was 98.3%.

At Nedjo Hospital the total number of prescribed antibiotics that were not dispensed was 82 to outpatients and 8 to inpatients suggesting that 97.2% and 99.1% of prescribed antibiotics were dispensed to outpatients and inpatients respectively. The average percentage of prescribed antibiotics that were actually dispensed at this hospital was 97.7%. Table 4.2 illustrates the summary of prescribing and patient care indicators at both hospitals.

Table 4.2 Summary of prescribing & patient care indicators in the West Wollega zone hospital, 2007

	Gimbie hospital		Nedjo hospital		west Wollega	
	OP	IP	OP	IP	OP	IP
Average no. of antibiotics per encounter	1.13	1.25	1.04	1.63	1.09	1.33
% of injectable antibiotics prescribed	4.6	80.0	2.8	95.3	3.8	83.2
% prescribed from EDL	58.7	67.3	68.4	96.2	63.0	74.8
% prescribed from LDDH	85.4	68.8	99.3	97.0	90.8	76.1
% of antibiotics actually dispensed	99.8	96.2	97.2	99.1	98.6	97.0
% of antibiotic encounters (OP & IP)	47.0		46.4		47	

4.3 Aggregate antibiotic use Indicators

4.3.1 Antibiotic days prescribed by Antibiotic class

A total of 32990 antibiotic days was prescribed in the four months study period at Gimbie Adventist Hospital. Outpatients accounted for most (85%) of the antibiotic days prescribed when compared with the inpatients (15%).

Penicillins were the most prescribed antibiotic class constituting 36.7% and 51.6% of the total antibiotic days prescribed to inpatients and outpatients respectively at Gimbie Adventist Hospital (Table 4.3). Quinolones accounted for the second most antibiotic days prescribed to outpatients (25.16%) whilst cephalosporins were second when considering inpatients (18.85%).

Table 4.3 Number and percentage of antibiotic days prescribed by antibiotic class at Gimbie Adventist hospital, 2007

	Outpatient		Inpatient		Total	
Antibiotic Class	Antibiotic days	%	Antibiotic days	%	Antibiotic days	%
Penicillins	10233	36.5	2543	51.57	12776.00	38.73
Quinolones	7061	25.2	275	5.58	7336.00	22.24
Macrolides	3718	13.3	24	0.49	3742.00	11.34
Cephalosporins	2028	7.2	929.5	18.85	2957.50	8.96
Sulfamethoxazole + trimethoprim	1893	6.7	201	4.08	2094.00	6.35
Amoxycillin + Clavulanic acid	1146	4.1	49	0.99	1195.00	3.62
Chloramphenicol	999	3.6	558	11.33	1557	4.72
Tetracyclines	924	3.3	48	0.97	972.00	2.95
Aminoglycosides	57	0.2	303.5	6.15	360.50	1.09
Total	28059	100	4931	100	32990	100

At Nedjo Hospital outpatient antibiotic days were the highest, contributing 92,0% when compared to inpatients which accounted for only 8.0%. At Nedjo Hospital, as illustrated in Table 4.4, penicillins accounted for 50.0% of all antibiotic days prescribed to outpatients and 54.0% of inpatients. Chloramphenicol was the second most prescribed antibiotic to inpatients (21.86%) whilst quinolones was the second most prescribed with respect to outpatients (28.75%).

Table 4.4 Percentage of antibiotic class prescribed by antibiotic days at Nedjo Hospital, 2007

	Outpatient		Inpatient		Total	
Antibiotic Class	**Antibiotic days**	**%**	**Antibiotic days**	**%**	**Antibiotic days**	**%**
Penicillins	10660	50.00	867	53.99	11527	50.28
Quinolones	6129	28.75	0	0.00	6129	26.73
Macrolides	1628	7.64	7	0.44	1635	7.13
Cephalosporins	1073	5.03	14	0.87	1087	4.74
Sulfamethoxazole + trimethoprim	894	4.19	0	0.00	894	3.90
Amoxycillin+Clavulanic acid	459	2.15	0	0.00	459	2.00
Chloramphenicol	237	1.10	351	21.86	588	2.56
Tetracyclines	191	0.90	25	1.56	216	0.94
Aminoglycosides	49	0.23	342	21.30	391	1.71
Total	21320	100.00	1606	100.00	22926	100.00

The distribution of antibiotic days for both hospitals is presented in Table 4.5. Penicillins were the leading antibiotic class that was prescribed to both inpatients and outpatients constituting 43.46% of all antibiotic days. Quinolones were the second most prescribed to outpatients (26.71%) and overall (24.08%) whilst cephalosporins were second with respect to inpatients (14.43%).

Table 4.5 Antibiotic days prescribed by antibiotic class in two hospitals in West Wollega, 2007

	Outpatient		Inpatient		Total	
Antibiotic Class	**No. of days**	**%**	**No. of days**	**%**	**No. of days**	**%**
Penicillins	20893	42.31	3410	52.16	24303	43.46
Quinolones	13190	26.71	275	4.21	13465	24.08
Macrolides	5346	10.83	31	0.48	5377	9.62
Cephalosporins	3101	6.28	943.5	14.43	4044.5	7.23
Sulfamethoxazole + trimethoprim	2787	5.64	201	3.07	2988	5.34
Amoxycillin + clavulanic acid	1605	3.25	49	0.75	1654	2.96
Chloramphenicol	1236	2.5	909	13.91	2145	3.84
Tetracyclines	1115	2.26	73	1.12	1188	2.13
Aminoglycosides	106	0.22	645.5	9.87	751.5	1.34
Total	49379	100.00	6537	100.00	55916	100.00

4.3.2 Antibiotic days prescribed by dosage form

The oral solid formulations were the most frequently prescribed antibiotic dosage form in both Gimbie and Nedjo Hospitals accounting for 84% and 83% respectively. Oral liquid dosage forms were the least (7%) prescribed antibiotic dosage form at Gimbie Hospital followed by parental preparations (9%). Oral liquid and parental antibiotic formulations prescribed at Nedjo Hospital were 9% and 8% respectively.

The average distribution of antibiotic days prescribed by dosage form for West Wollega is illustrated in Figure 4.6.

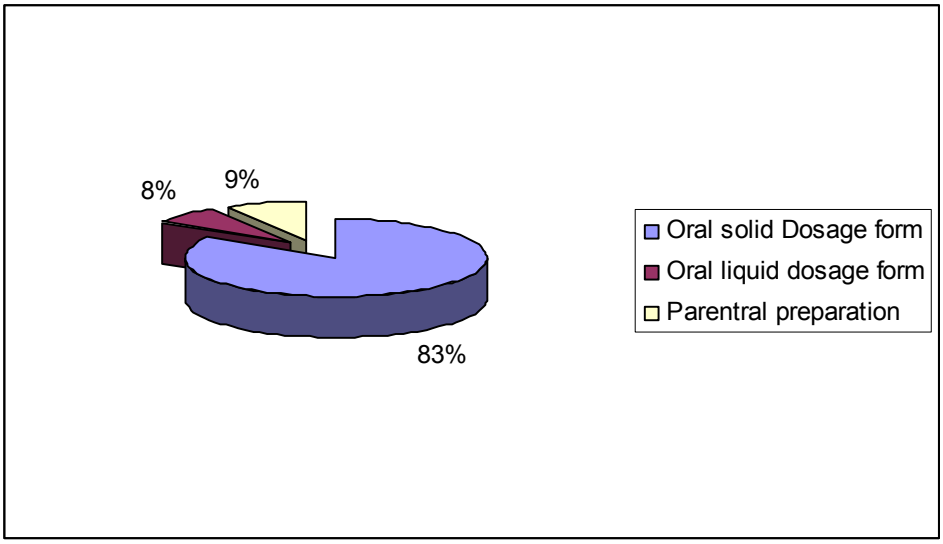

Figure 4.6 Percentage distributions of antibiotic dosage forms prescribed in two hospitals in West Wollega, 2007

4.3.3 Antibiotic Utilization Ratio

The antibiotic utilization ratio is the ratio of the number of antibiotic days to the number of inhabitants. At Gimbie Adventist Hospital the number of antibiotic days for the four months study period for both inpatients and outpatients was 32990 (which suggests 98970 antibiotic days for the year). The target population that is being served by the hospital is 524097. Therefore, the antibiotic utilization ratio for the year was 0.1888 (0.188 antibiotic days per person per year). The antibiotic utilization ratio for Nedjo Hospital was calculated using the catchment population served, which is 544332. The antibiotic utilization ratio, therefore, was 0.042. The average antibiotic utilization ratio for the West Wollega zone was 0.16.

4.3.4 Incidence of Antibiotic Use

The incidence of antibiotic use, the number of antibiotic prescriptions per 1000 inhabitants, for the hospitals was aggregated based on the number of inhabitants and prescriptions encountered in the study period.

The number of antibiotic prescriptions encountered at Gimbie Adventist Hospital was 3299 for outpatients and 2043 for inpatients. At Nedjo Hospital the figure was 2846 and 547 for outpatients and inpatients respectively. This made the annual number of outpatient antibiotic prescriptions 9897 and 8538 at Gimbie and Nedjo Hospitals respectively. The annual number of inpatient prescriptions was 6129 at Gimbie and 1641 at Nedjo. Based on this the incidence of antibiotic use for outpatients was 18.88 (18.88 antibiotic prescriptions per 1000 inhabitants per year) for Gimbie Hospital and 15.67 for Nedjo Hospital.

The incidence of antibiotic use for inpatients was calculated i.e. the number of antibiotic prescriptions per 100beds/ day. The number of hospital beds and the occupancy rate was taken into account. The inpatient incidence of antibiotic use was 28 antibiotic prescriptions per 100 beds per day at Gimbie Hospital and 15 at Nedjo Hospital. The incidence of hospital outpatient antibiotic use for the region was 17.25 whilst the incidence of inpatient use was 23.56.

4.3.5 Antibiotic use in Number of Defined Daily Doses (DDD)

The total number of DDDs were calculated by using DDDs of each antibiotic as set by WHO Collaborating Centre for Drug Statistics Methodology (WHO, 2008). Based on this the total number of DDDs calculated at Gimbie Adventist Hospital was 106055.2 and 14557.35 for outpatients and inpatients departments respectively as shown in Table 4.6.

Table 4.6 Antibiotics dispensed in number of defined daily doses at Gimbie Adventist Hospital, 2007

Antibiotic Name	DDD (g)	Number of DDD	
		outpatient	Inpatient
Clarithromycin, oral	0.50	18762	84
Amoxycillin, oral	1	40628.25	2969.25
Cephalexin, oral	2	5820.75	366.75
Amoxycillin + Clavulanic acid, oral	1	3240.75	108
Ciprofloxacin, oral	1	11431.5	73.8
Erythromycin, oral	2	1762.5	30
Cloxacillin, oral	2	3057	874.5
Norfloxacin, oral	0.80	9462	456
Chloramphenicol, oral	3	1790	283
Ceftriaxone, parentral	2	255	2208.75
Cotrimoxazole, oral	2	3081	320.4
Ampicillin, oral	2	701.25	1338.75
Doxycycline, oral	0.10	5544	210
Benzathine benzyl penicillin, parentral	3.60	232.2	8.4
Gentamycin, parentral	0.24	140	812
Procain penicillin fortified, parentral	0.60	132	0
Penicillin V, oral	2	15	0
Ampicillin, parentral	2	0	1740.75
Crystalline benzyl penicillin G, parentral	3.60	0	1889
Chloramphenicol, parentral	3	0	784
Total		**106055.2**	**14557.35**

The number of DDD/1000 inhabitants/day for Gimbie Adventist Hospital was calculated. The number of inhabitants is 524097, thus the number of inhabitant days in a year would be 191295405. The DDD per 1000 inhabitants per day was 0.55. In other words the DDD/1000 inhabitants per year was 200.75.

The number of DDDs for inpatients was calculated. Gimbie Adventist Hospital has 71 beds and the bed occupancy rate in the study period was estimated to be 85%. From this the number of bed days in the year was 22027.75 (number of beds X occupancy X 365 days). Therefore, the number of DDD per 100 beds per day was 66.09 (DDD/no. of bed days X 100), i.e. 66 defined daily doses of antibiotics per 100 beds per day.

At Nedjo Hospital the number of DDDs for outpatients was 63417.63 and for inpatients was 8441.5 (Table 4.7). The number of inhabitants in the catchment area is 544332 and hence the number of inhabitant days was 198681180. The DDD per 1000 inhabitant days was 0.32. As Nedjo hospital has 40 beds and the occupancy rate was estimated to be 75% during the study period, the DDDs per 100 bed days was 77.09.

The number of DDDs per 1000 inhabitants per day in the outpatient department in the West Wollega zone was therefore 0.4346, which is 158.61 DDDs /1000/ year. For inpatients the number of DDDs/100bed/day was 70.0. i.e. 70 defined daily doses of antibiotics were dispensed per 100 patients per day.

Table 4.7 Antibiotics dispensed in number of defined daily doses at Nedjo Hospital, 2007

Antibiotic Name	DDD (g)	Number of DDD	
		outpatient	Inpatient
Clarithromycin, oral	0.5	42	0
Amoxycillin, oral	1	29437.5	484.5
Cephalexin, oral	2	522	0
Amoxycillin + Clavulanic acid, oral	1	513.75	0
Ciprofloxacin, oral	1	15504	0
Erythromycin, oral	2	3234.75	63
Cloxacillin, oral	2	1108.5	27.75
Norfloxacin, oral	0.80	2568	0
Chloramphenicol, oral	3	696.5	0
Ceftriaxone, parentral	2	72	129
Cotrimoxazole, oral	2	2599.2	0
Ampicillin, oral	2	805.13	3
Doxycycline, oral	0.10	5322	0
Benzathine benzyl penicillin, parentral	3.6	19.8	0
Gentamycin, parentral	0.24	65	837
Procain penicillin fortified, parentral	0.6	864	36
Ampicillin, parentral	2	0	4355.25
Crystalline benzyl penicillin G, parentral	3.6	0	1530.5
Chloramphenicol, parentral	3	0	860
Tetracycline, oral	1	22.5	0
Cloxacillin, parentral	2	0	115.5
Spectinomycin, parentral	2	21	0
Total		**63417.63**	**8441.5**

4.4 Hospital Indicators

4.4.1 Cost of antibiotics

A total of 1042701.90 Ethiopian Birr (ETB) which is equivalent to 109758.09USD ($) was spent on the purchase of pharmaceuticals in the two hospitals in West Wollega. Of this

antibiotic expenditure alone was 351485.04 ETB ($36998.43) which constituted 33.7% of all drug expenditure.

The total money spent on the purchase of drugs in 2007 at Gimbie Adventist Hospital was 708500.00 ETB ($74578.95 USD) of which 240597.20 ETB (25326.02 USD) was spent on antibiotic purchase. This means that the expenditure on antibiotics accounts for 34% of total medicine expenses. This is shown in Figure 4.7.

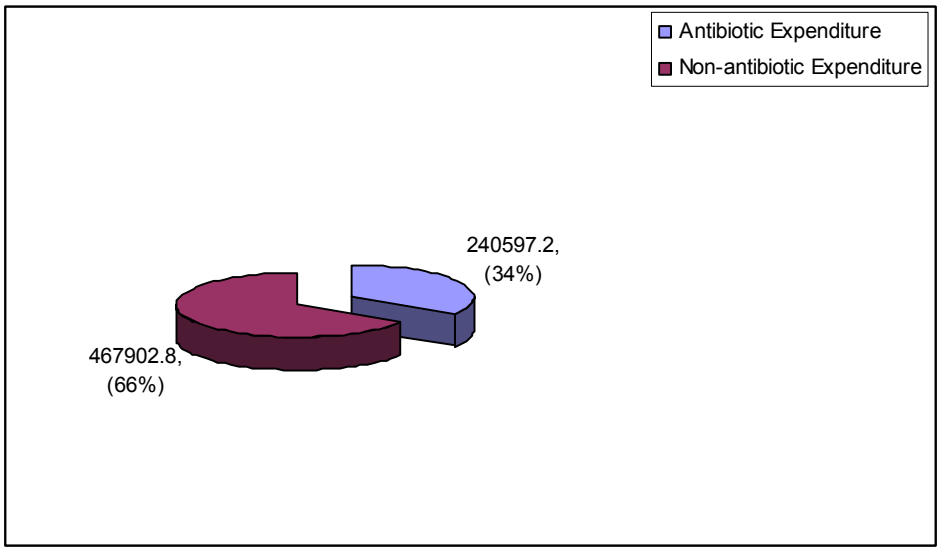

Figure 4.7 Percentage of drug budget spent on antibiotics at Gimbie Adventist Hospital, 2007

Of the antibiotic expenditure 166430.65 ETB ($17519.02) (69%) was spent on antibiotics dispensed to outpatients while the balance, 74166.50 ETB ($7807) (31%), was on inpatients.

The expenditure on clarithromycin alone was 62852.20 ETB ($6616.02), which accounted for 37.77% of all antibiotic expenditure, indicating that clarithromycin was the most expensive antibiotic dispensed in the year. Amoxicillin was the second followed by cephalexin, clarithromycin, amoxicillin, cephalexin, amoxicillin + clavulanic acid and ciprofloxacin. These agents accounted for 80% of all the costs of antibiotics dispensed in the study period. This and all other antibiotics dispensed to outpatients is illustrated in Appendix V.

The cost of ceftriaxone alone accounts for about 41% of all inpatient antibiotic expenditures followed by crystalline penicillin. About 82% of the total inpatient antibiotic expenditure was on ceftriaxone, crystalline penicillin G and ampicillin injections alone (Appendix VI).

When the overall inpatient and outpatient antibiotic costs were considered, clarithromycin constituted 26.24% whilst amoxicillin was second accounting for 12.17% (Table 4.8). Clarithromycin was the most expensive antibiotic dispensed whilst amoxicillin, although a cheaper antibiotic, was dispensed in the highest quantity, making it the second highest in terms of cost.

Table 4.8 Cost of antibiotics dispensed to both inpatients and outpatients at Gimbie Adventist Hospital, 2007

Antibiotic Class/specific agent	Unit	Year total	Unit cost (ETB)	Total cost (ETB)	%	Cumm. %
Clarithromycin 500mg tabs	Tablets	18846	3.35	63134.10	26.24	26.24
Amoxycillin 500 mg capsule	Capsules	82035	0.35706	29291.42	12.17	38.41
Ceftriaxone 1g injection	Vials	3993	6.727	26860.91	11.16	49.58
Crytalline penicillin G injection 1mil unit vial	Vials	11334	1.7588	19934.24	8.29	57.86
Cephalexin 500 mg caps	Capsules	24615	0.63	15507.45	6.45	64.31
Amoxyclav 625 mg tablets	Tablets	3339	3.6	12020.40	5.00	69.31
AmoxyClav 375 mg tablets	Tablets	4947	1.977	9780.22	4.06	73.37
Ciprofloxacin 500 mg tablets	Tablets	23601	0.3071	7247.87	3.01	76.38
Ampicillin injection 500mg vial	Vials	4563	1.58	7209.54	3.00	79.38
Ceftriaxone 500 mg injection	Vials	1869	3.61	6747.09	2.80	82.18
Ampicillin injection, 1g vial	Vials	1200	3.16	3792.00	1.58	83.76
Chloramphenicol 1g injection	Vials	2352	2.2462	5283.06	2.20	85.96
Cloxacillin 500mg caps	Capsules	15330	0.3375	5173.88	2.15	88.11
Erythromycin 500 mg tablets	Tablets	7080	0.73	5168.40	2.15	90.25
Chloramphenicol 250 mg capsule	Capsules	24516	0.15415	3779.14	1.57	91.82
Norfloxacin 400 mg tablets	Tablets	19836	0.173	3431.63	1.43	93.25
Ampicillin 500mg caps	Capsules	7950	0.36	2862.00	1.19	94.44
Cotrimoxazole 240 mg/5ml suspension, 100ml	bottles	549	4.61	2530.89	1.05	95.49
AmoxyClavul 325mg/5ml suspension, 100ml	bottles	57	31.15	1775.55	0.74	96.23
Amoxycillin 125 mg/5ml suspension, 100ml	bottles	186	6.25	1162.50	0.48	96.71
AmoxClavula 156mg/5ml suspension, 100ml	bottles	63	18.18	1145.34	0.48	97.19
Cotrimoxazole 480 mg tablets	Tablets	10419	0.10687	1113.48	0.46	97.65
Amoxycillin 250 mg capsule	Capsules	7140	0.1512	1079.57	0.45	98.10
Doxycycline 100 mg caps	Capsules	5754	0.16375	942.22	0.39	98.49
Gentamycin 80 mg/2ml injection	Ampoules	2856	0.3238	924.77	0.38	98.88
Benzathine pencillin 2.4 mil units inj	Vials	477	1.63	777.51	0.32	99.20
Amoxycillin 250mg/5ml suspension, 100ml	bottles	66	7.85	518.10	0.22	99.42
Benzathin penicillin 1.2 Million units inj	Vials	249	1.661	413.59	0.17	99.59
Chloramphenicol 125 mg/5ml suspension, 100ml	bottles	36	7	252.00	0.10	99.69
Ampicillin 125mg/5ml suspension, 100ml	bottles	36	6.25	225.00	0.09	99.79
Cloxacillin 250 mg caps	Capsules	792	0.2104	166.64	0.07	99.86
Cephalexin 125 mg/5ml suspension, 100ml bottle	bottles	15	5.39	80.85	0.03	99.89
Cephalexin 250 mg/5ml suspension, 100ml bottle	bottles	6	13.15	78.90	0.03	99.92
Procain penicillin fortified 4 mil units inj.	Vials	33	2.294	75.70	0.03	99.95
Erythromycin 200 mg/5ml suspension, 100ml	bottles	6	8	48.00	0.02	99.97
Erythromycin 250 mg tabs	Tablets	84	0.365	30.66	0.01	99.99
Ampicillin 250mg/5ml suspension, 100ml bottle	bottles	3	7.85	23.55	0.01	100.00
Penicillin V 500 mg tabs	Tablets	60	0.15	9.00	0.00	100.00
				240597.2	100.00	

At Nedjo Hospital antibiotic costs accounted for 33% of the total drug budget in the year 2007 (Figure 4.8). The actual cost of the dispensed antibiotics to both inpatients and outpatient was 110887.84 ETB. Outpatient antibiotic expenditure was 53% of the total antibiotic expenditure.

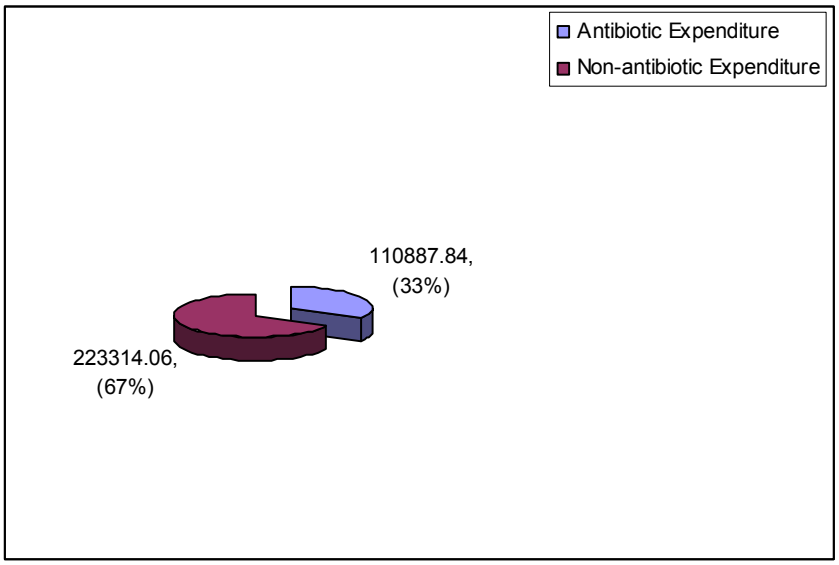

Figure 4.8 Percent antibiotic expenditure at Nedjo hospital, 2007

Amoxycillin was the most dispensed antibiotic in quantity and also accounted for 31.47% of the outpatient antibiotic expenditure followed by ciprofloxacin (16.25%) and erythromycin (15.90%) (Appendix-VII).

On the other hand amoxicillin was among the least prescribed antibiotic to inpatients accounting for less than 1% of the total antibiotic costs. Ampicillin injections accounted for the highest percentage (43.59%) of all antibiotic costs prescribed to inpatients. Ampicillin injections together with crystalline penicillin and chloramphenicol injection constituted more than 85% of all inpatient antibiotic costs.

Penicillins (ampicillin injections, amoxicillin capsule and crystalline penicillin G) constituted the highest percentage of all antibiotic expenditure at Nedjo Hospital followed by ciprofloxacin. All other antibiotic expenditure by specific agent is shown Table 4.9.

Table 4.9 Antibiotics dispensed to outpatients and inpatients and their cost at Nedjo hospital, 2007

Antibiotic Class/specific agent	Unit	Qty dispensed (yr)	Unit cost (ETB)	Total cost (ETB)	%	Cumm. %
Ampicillin injection, 1g vial	Vials	7212	3.16	22789.92	20.55	20.55
Amoxycillin 500 mg capsule	Capsules	52569	0.35706	18770.29	16.93	37.48
Crytalline penicillin G injection 1mil unit vial	Vials	9183	1.7588	16151.06	14.57	52.04
Ciprofloxacin 500 mg tablets	Tablets	31008	0.3071	9522.56	8.59	60.63
Erythromycin 500 mg tablets	Tablets	13020	0.73	9504.60	8.57	69.20
Chloramphenicol 1g injection	Vials	2580	2.2462	5795.196	5.23	74.43
Ampicillin injection 500mg vial	Vials	2997	1.58	4735.26	4.27	78.70
AmoxyClav 375 mg tablets	Tablets	2055	1.977	4062.74	3.66	82.36
Amoxycillin 250mg/5ml suspension, 100ml	bottles	315	7.85	2472.75	2.23	84.59
Cotrimoxazole 240 mg/5ml suspension, 100ml	bottles	423	4.61	1950.03	1.76	86.35
Amoxycillin 125 mg/5ml suspension, 100ml	bottles	261	6.25	1631.25	1.47	87.82
Cloxacillin 500mg caps	Capsules	4470	0.3375	1508.63	1.36	89.18
Cephalexin 500 mg caps	Capsules	2088	0.63	1315.44	1.19	90.37
Ceftriaxone 1g injection	Vials	186	6.727	1251.22	1.13	91.50
Chloramphenicol 250 mg capsule	Capsules	7968	0.15415	1228.27	1.11	92.60
Ampicillin 500mg caps	Capsules	3012	0.36	1084.32	0.98	93.58
Norfloxacin 400 mg tablets	Tablets	5136	0.173	888.53	0.80	94.38
Gentamycin 80 mg/2ml injection	Ampoules	2706	0.3238	876.20	0.79	95.17
Doxycycline 100 mg caps	Capsules	5322	0.16375	871.48	0.79	95.96
Amoxycillin 250 mg capsule	Capsules	5640	0.1512	852.77	0.77	96.73
Cotrimoxazole 480 mg tablets	Tablets	7920	0.10687	846.41	0.76	97.49
Spectinomycin 2 g injection	Vials	21	38	798.00	0.72	98.21
Procain penicillin fortified 4 mil units inj.	Vials	225	2.294	516.15	0.47	98.68
Cloxacillin 500mg injection, vial	Vials	462	1.058	488.796	0.44	99.12
Chloramphenicol 125 mg/5ml suspension, 100ml	bottles	39	7	273.00	0.25	99.36
Clarithromycin 500mg tabs	Tablets	42	3.35	140.70	0.13	99.49
Erythromycin 250 mg tabs	Tablets	342	0.365	124.83	0.11	99.60
Ceftriaxone 500 mg injection	Vials	30	3.61	108.30	0.10	99.70
Ampicillin 125mg/5ml suspension, 100ml bottle	bottles	15	6.25	93.75	0.08	99.79
Benzathine pencillin 2.4 mil units inj	Vials	45	1.63	73.35	0.07	99.85
Cloxacillin 125 mg/5ml suspension, 100ml	bottles	9	7.25	65.25	0.06	99.91
Ampicillin 250mg caps	Capsules	231	0.151	34.88	0.03	99.94
Ampicillin 250mg/5ml suspension, 100ml bottle	bottles	3	7.85	23.55	0.02	99.96
Benzathin penicillin 1.2 Million units inj	Vials	9	1.661	14.95	0.01	99.98
Cloxacillin 250 mg caps	Capsules	60	0.2104	12.62	0.01	99.99
Tetracycline 250 mg caps	Capsules	90	0.12	10.80	0.01	100.00
				110887.84	100	

4.4.2 Cost per antibiotic day

Cost per antibiotic day for both hospitals was calculated by dividing the total antibiotic expenditure in the hospital outpatient and inpatients in the year by the total number of antibiotic days prescribed in the year (Mylotte *et al.*, 2005:1119). Based on this the cost per antibiotic day for the West Wollega hospitals was 6.29 ETB ($0.66). For each hospital the cost per antibiotic day was 7.29 ETB ($0.77) and 4.85 ETB ($0.51) at Gimbie and Nedjo Hospitals respectively.

4.4.3 Cost of antibiotic per patient care day

The cost of antibiotic per patient care day was calculated by dividing the total expenditure on antibiotics used in inpatients in the year by the total patient bed days in a year (Mylotte *et al.*, 2005: 1119). As shown in Appendices VI and VII the total cost of inpatient antibiotic expenditure at Gimbie and Nedjo Hospitals was 74166.50 ETB ($7807.00) and 52280.26 ETB ($5503.19) respectively. The number of patient care days in a year i.e. occupied patient bed days in a year, was 22028 and 10950 at Gimbie and Nedjo Hospitals respectively.

The cost of antibiotic per patient care day in the study year was 3.37 ETB ($0.35) and 4.77 ETB ($0.50) at Gimbie and Nedjo Hospitals respectively. For the two West Wollega zone hospitals the cost of antibiotic per patient care day in the study year was 3.84 ETB ($0.40).

The aggregate antibiotic use indicators are summarized in Table 4.10 for both hospitals.

Table 4.10 Summary of aggregate antibiotic use indicators at Gimbie and Nedjo Hospitals, 2007

	Gimbie hospital		Nedjo hospital		West Wollega	
	Outpatient	inpatient	outpatient	inpatient	outpatient	Inpatient
Hospital Antibiotic utilization ratio, outpatient (antibiotic days/person/year)	0.19		0.042		0.16	
Incidence of antibiotic Use (prescrip/1000inhabitants/year)	18.9		15.7		17.25	
No. of DDD/1000 inhabitants/year	200.8		116.8		158.61	
% of Drug budget spent on antibiotics, OP & IP	34.0		33.0		33.70	
Cost per Antibiotic day (ETB/USD), OP & IP	7.29/0.77		4.85/0.51		6.29/0.66	
Cost of Antibiotic per patient care day (ETB/USD), OP & IP	3.37/0.35		4.77/0.50		3.84/0.40	
Incidence of Antibiotic use /100beds/day		28		15		23.56
No. of DDD/100 beds/day		66.1		77.1		70.00

4.5 Correlation between antibiotic prescribed and infectious diseases diagnosed

Approximately 22 different types of infectious diseases that may require antibiotic treatment were diagnosed at Gimbie Adventist Hospital in the selected four months of the study period. The number of infectious episodes diagnosed was 1368 as detailed in Table 4.11.

Table 4.11 Type and number of infectious diseases diagnosed at Gimbie Adventist hospital, 2007

ICD Code	Disease Type	Jan.	April	July	Oct.	Total
11.4	Lymphogranuloma Venerum	2	0	0	0	2
11.7	Other unspecified veneral diseases	12	3	3	5	23
012	Typhoid fever	75	83	19	49	226
016.4	Food poisoning	0	0	0	2	2
018	Streptococcal sore throat	8	17	0	7	32
023	Meningococcal infections	0	0	01	01	2
026	Tetanus	1	0	1	0	2
035	Unspecified typhus	0	0	1	0	1
043.9	All other infections	37	97	22	37	193
077	Otitis media and mastoditis	4	0	2	0	6
087	Acute upper respiratory infections	18	16	13	33	80
089	Lobar pneumonia	10	19	16	18	63
090	Bronchopneumonia	64	105	36	70	275
092	Acute bronchitis	13	22	0	7	42
093	Bronchitis, chronic and unspecified pneumonia	30	13	6	5	54
108	Acute nephritis/	24	30	0	0	54
109	Chronic, other and unspecified pneumonia	0	24	44	19	87
110	Infection of kidney	5	0	4	0	9
119	Abortion with sepsis	5	0	0	0	5
120.5	Other complications of pregnancy and childbirth	35	7	20	13	75
121	Infection of skin and subcutaneous tissue	18	22	28	60	128
126.1	Ulcer of leg	6	1	0	0	7
	Total	**367**	**459**	**216**	**326**	**1368**

To determine the correlation between the infectious diseases diagnosed and the antibiotics used, the treatment guidelines developed by the DACA of Ethiopia were used (DACA, 2004). DACA has developed treatment guidelines for different level of health institutions. According to these guidelines 14033 antibiotic days would have been sufficient to treat the infectious diseases diagnosed in this hospital (Appendix III). However, the number of

antibiotic days prescribed during the specified period was 32990 which was far more than the antibiotic days needed as shown in Table 4.12.

Table 4.12 Infectious diseases diagnosed and antibiotic days prescribed at Gimbie Adventist Hospital, 2007

	No of infectious diseases	Antibiotic days required	Antibiotic days prescribed
January	367	3922	7003
April	459	4384	8154
July	216	2363	7798
October	326	3364	10035
Total	1368	14033	32990

The number of antibiotic courses started, as indicated in section 4.1 above, for outpatients alone at this hospital was 3299 whilst the number of infectious diseases diagnosed in the same department was 1210. This shows that the average number of antibiotic courses started per infectious disease diagnosed was 2.7. However, patterns of antibiotics prescribed and antibiotic days required was similar as shown in Figure 4.9.

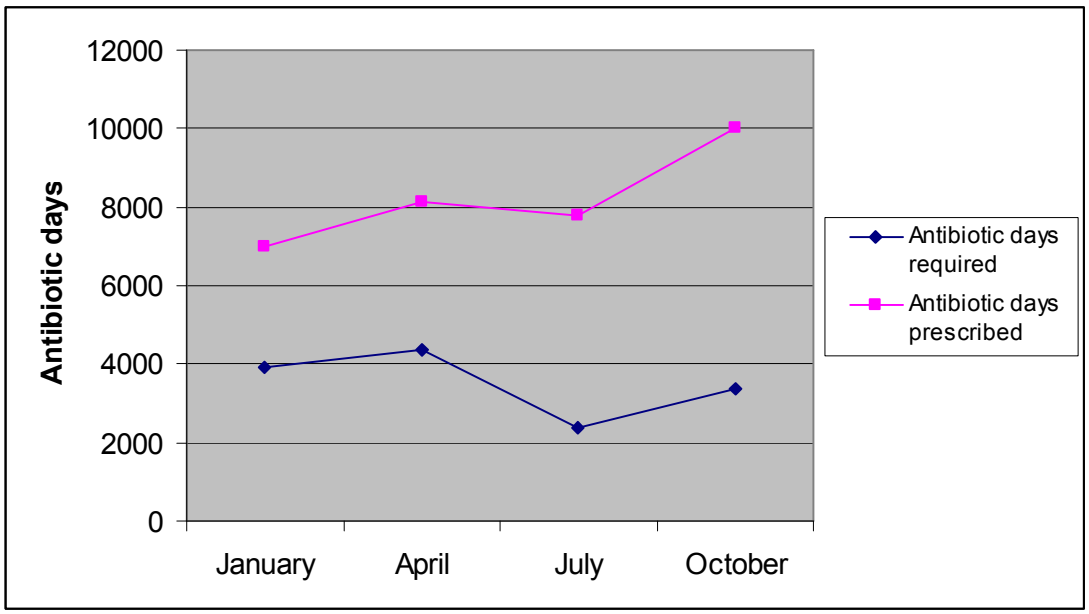

Figure 4.9 Comparison of antibiotic days required versus prescribed at Gimbie Adventist hospital, 2007

There were only eleven different types and 418 cases of infectious disease diagnosed at Nedjo Hospital in the four months, as shown in Table 4.13.

Table 4.13 Type and number of infectious diseases diagnosed at Nedjo Hospital in 2007

ICD code	Disease type	Jan.	April	July	Oct.	Total
011.7	Other unspecified veneral diseases	3	4	3	3	13
012	Typhoid fever	0	6	2	6	14
016.5	Other unspecified dysentry	1	0	0	0	1
021	Diphtheria	2	0	0	0	2
071.2	Meningitis due to pneumococcus	0	1	0	0	1
087	Acute upper respiratory infections	14	22	31	32	99
090	Bronchopneumonia	9	14	0	0	23
091	Primary atypical and other unspecified pneumonia	57	37	38	43	175
115	Sepsis of pregnancy childbirth and puerperiuma	0	3	0	0	3
121	Infection of skin and subcutaneous tissue	5	30	16	26	77
124	Osteomyelitis and periotitis	2	4	4	0	10
	Total	**93**	**121**	**94**	**110**	**418**

For the 418 infectious diseases diagnosed, according to the treatment guidelines this would have suggested a necessity of 4151 antibiotic days, however the actual number of antibiotic days prescribed was 20966 (Appendix-V), which is approximately five times more than the required. Table 4.14 shows the antibiotic days required and prescribed in the four months of the study period.

Table 4.14 Infectious diseases diagnosed and antibiotic days prescribed at Nedjo Hospital, 2007

	No of infectious diseases	Antibiotic days required	Antibiotic days prescribed
January	93	886	5035
April	121	1286	6001
July	94	939	4188
October	110	1040	5742
Total	418	4151	20966

The number of infectious episodes diagnosed and the number of antibiotic courses started in the outpatient department of Nedjo Hospital was 373 and 2846 respectively. This made the average number of antibiotic courses started per infectious disease diagnosed 7.63. Figure 4.10 is the diagrammatic representation of antibiotic days required versus prescribed.

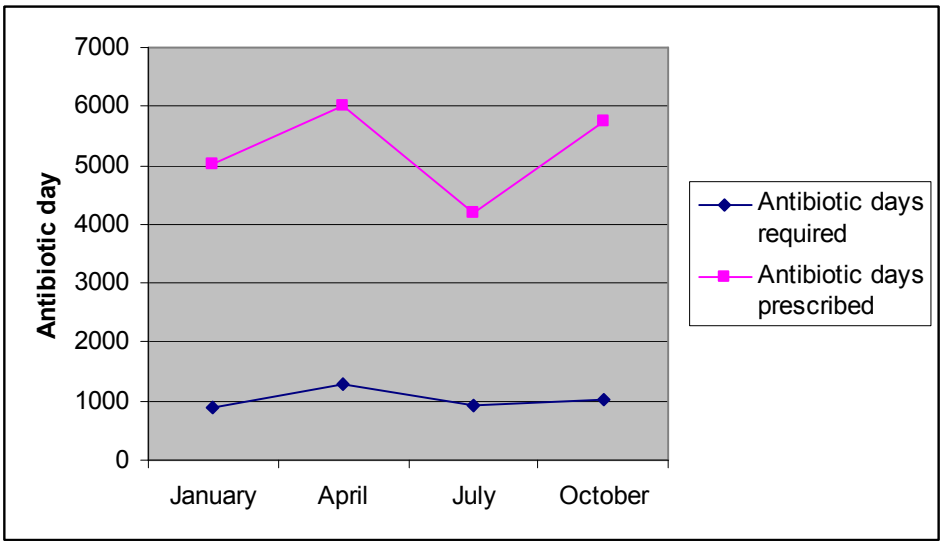

Figure 4.10 Comparison of antibiotic days required versus prescribed at Nedjo Hospital, 2007

CHAPTER 5
DISCUSSION

Antimicrobial resistance has reached worrying levels for many common pathogens. It costs money, livelihoods and lives and threatens to undermine the effectiveness of health delivery programmes. For example, penicillin resistance in *S. pneumoniae* ranges from 5.8% to 54% in different countries. The *WHO Global Strategy for Containment of Antimicrobial Resistance* attributes the growth of resistance to combination of overuse, misuse, and under-use of antimicrobials. "It has been estimated that 50% of antibiotic use is by humans (of which 80% is outside of hospitals), and 20-50% of this is unnecessary''. (Norris, 2004: 2)

One of the commonly used drug use indicators in assessing rational prescribing practice is the percentage of prescriptions that contain one or more antibiotics. The review of prescriptions in this study showed that prescriptions containing one or more systemic antibiotics constituted 47% of all prescriptions in the two hospitals in the West Wollega, a figure that is significantly higher than the values observed in other public hospitals in Yemen (22.7%) and at Jimma University Hospital in South West Ethiopia (25.6%) (Wubeante, 2005: 154).

However, this figure was lower compared to results of other studies conducted in other parts of Ethiopia: Harari region hospitals in east Ethiopia 57.0% (Menassie, 2004:35); Mizan hospital 64%, Hosana hospital 60% and Dilla hospital 57% in Southern Ethiopia (Wubeante, 2005: 154); in North West Ethiopia health centers 60% (Desta *et al*., 1997: 24); and a national average for hospitals of 55.43% (FMOH and WHO, 2003:25).

When this result was compared to other developing countries it was lower than Ikeja general hospital in Nigeria 54.8% (Odusanya, 2004: 22) and two teaching hospitals in Sudan 65% (Abdelmoneim and Hossam, 2006), national figure for Uganda 61.9% (MOH, 2002:8) and Nigeria 59% (FMOH and WHO, 2002: 31). This result is similar to that of

Serbia 45% (Slobodan *et al.,* 1999) and the same as Lao PDR 47% (Keohavong *et al.,* 2006:344).

This result was higher than the WHO ideal value of less than 25 % and also of similar study results of 40% in the Kalahari district and 12% in Durban, South Africa (Gray, 1999:2; WHO, 2004: 8); 25.6% at Jimma University Hospital in the South West Ethiopia and 22.7% in Yemen (Wubeante, 2005:154); and 42% in Tanzania (Ministry of Health of Tanzania and WHO, 2002: 2). This result suggests that antibiotics were over prescribed in the two hospitals in the West Wollega.

Moreover the correlation of antibiotic use and infectious diseases diagnosed in the West Wollega was a good indication that there is over use or misuse of antibiotics (Section 4.5). The number of infectious diseases diagnosed did not correspond to the number of antibiotic days prescribed in these hospitals. There could be some problem in the reliability of the data that was collected from the statistics departments of the hospitals as all of the infectious diseases diagnosed in the hospitals might not be accurately recorded and reported. This however, can not be the cause of such a significant difference in antibiotics prescribed. Therefore, it can be concluded that there was significant excessive use of antibiotics for conditions that do not require them or over use of antibiotics for infectious diseases that require them.

As the results of the study suggests the significant difference in the number of antibiotics required and antibiotic days prescribed could also be attributed to failure to follow the national treatment guidelines as developed by the DACA. According to this study for infectious diseases diagnosed at outpatient departments alone an average number of antibiotic courses started was 2.7 at Gimbie Adventist Hospital and 7.6 for Nedjo Hospital. When overall antibiotic days prescribed and required was compared in both hospitals, there were 2.4 and 5 times more antibiotic days prescribed than were required for Gimbie and Nedjo Hospitals respectively. This also suggests that the overuse of antibiotic is worse in the government hospital (Nedjo Hospital) than in the mission hospital (Gimbie Adventist Hospital).

The reasons for such variation in antibiotics prescribed and infectious diseases diagnosed might require a separate study as it is beyond the scope of this study. However, some of the possible reasons that might attribute to such variation could be related to the treatment guideline, the training and experience of prescribers, laboratory facility, absence of Drug and Therapeutic Committee to manage medicine use and lack of hospital specific formulary at these hospitals.

It seems that the treatment guideline that is developed by DACA of Ethiopia for district hospitals lacks comprehensiveness; as not all infectious diseases that require antibiotic treatment are mentioned in it. In such case the prescribers are forced to use their own judgment which in turn can lead to overprescription of antibiotics. In addition the guideline is not available to all of the prescribers.

The prescribers were health care personnel with different levels of training. These antibiotics were prescribed by Specialists, general practitioners, BSc Nurses and sometimes by diploma holder clinical nurses. In addition, some of these prescribers are new graduates with very limited experience and there is also lack of problem focused in-service training particularly on pharmacotherapy. On top of that, there were no senior medical practitioners like surgeons, as is in the case of Nedjo Hospital and, internists in both hospitals, for consultation. This means some of the prescribers might lack adequate training and experience which lead to overprescription of antibiotics.

The laboratory settings of these hospitals lack some important tests, to diagnose and treat infectious diseases, like culture and sensitivity whereby the sensitivity of the microbes to a given antibiotic could be identified. This could lead to multiple antibiotic prescriptions by the clinicians to cover for all possible pathogens that could cause a given infectious disease. Moreover, both hospitals do not have formularies that are specific to the hospital which contributes to the prescription of different antibiotics by different practitioners for the same condition in the same hospital.

There appear to have been no similar study findings that relate the infectious disease diagnosed to the antibiotic days prescribed.

This study also analyzed which antibiotic class was the most used in terms of antibiotic days (Section 4.3). Penicillins were the most frequently used antibiotic class in both inpatients and outpatients departments in the two West Wollega zone hospitals. This was encouraging as penicillins are not among the newer antibiotic class that should be reserved for severe infections and also have a narrower spectrum of action.

However, this study showed that two of the most important newer antibiotics, the quinolones and cephalosporins, were, after penicillin, amongst the most frequently used antibiotics. Quinolones were the second most frequently used antibiotics in outpatients accounting for 26.71% of antibiotic days prescribed. They were also the second most frequently prescribed antibiotic class when both inpatient and outpatient antibiotic days were analyzed constituting 24.08% of all antibiotic days prescribed in both hospitals which is similar to the study findings of rural hospital in US (Mylotte & Weislo, 2000: 417). Cephalosporins are also amongst the highest antibiotics prescribed to inpatients, next to penicillins, accounting for 14.43% of all antibiotic days prescribed.

The overuse and misuse of these antibiotics can have serious consequences for antimicrobial resistance. A study conducted in a managed care population in the US in 2002 and 2003 showed an increase in the prescribing of antibiotics of concern which include quinolones (Wong e*t al*., 2005: 3471). Similarly the use of the newer quinolones at outpatient departments of both hospitals was the second highest, ciprofloxacin and norfloxacin being the specific agents used in this class.

Cephalosporins, in particular third generation cephalosporins, are one of the classes of antibiotics that similar to the newer quinolones need careful attention to ensure their rational use in this era of increased threat due to microbial resistance. However, this study revealed that this was lacking as there was excessive use of these classes of antibiotics. Almost all of the cephalosporins used in the inpatient department of West Wollega zone

Hospitals particularly at Gimbie Adventist Hospital were third generation cephalosporins, especially ceftriaxone. According to the national drug list for district hospitals ceftriaxone which was not included on the list, is supposed to be used at higher level only (DACA, 2002:16-18). The use of ceftriaxone was low at Nedjo Hospital where cephalosporins were one of the least used antibiotics in the inpatient department, although it was available for use in the hospital.

Since there was no laboratory data or other study evidence available that confirmed development of resistance to other narrower spectrum antibiotics, which would justify the use of these newer agents, in the zone, it is of utmost importance that special attention be given to minimize such overuse or misuse of these agents.

In this study the average number of antibiotics per encounter for the West Wollega zone was 1.09 for outpatients and 1.33 for inpatients. This result was higher than the finding in Zimbabwe - 0.72 among dispensing doctors and 0.54 for non-dispensing doctors (Norris, 2004:8). As this finding was specific to antibiotics only it would not be accurate to compare with other research findings that were not limited to antibiotics.

The percentage of encounters with antibiotic injections prescribed varied significantly between outpatient and inpatient departments. At inpatient departments 83.2% of antibiotic prescribed were parentral formulations. This is a little higher than the finding of 79.4% in Sari Emam University Hospital in Iran in 2005 (Ebrahimzadeh *et al.*, 2008: 275). In the outpatient departments however, the percentage of encounters with antibiotic injections prescribed was low (4.6%). This low rate of injections prescribed is important in minimizing the risk of diseases transmission like HIV/AIDS, hepatitis and other blood-borne diseases (WHO, 2002:1).

The number of antibiotics prescribed from the EDL in this study was 74.8% in inpatient and 63.0% in outpatient departments. This result is lower than that reported in other studies like Harari Region Hospitals in East Ethiopia, 96.53% (Menassie, 2004:35) and Lao PDR, 84% (Keohavong *et al.,* 2006:344); Northern Cape province in South Africa, 92.5% (Gray,

1999:2). However, this result is higher than the study result for the city of Kragujevac in Serbia, 21-65% (Slobodan *et al.,* 1999). This result suggests that the percentage of antibiotics prescribed from the EDL was low and requires attention with a view to intervention.

With respect to the LDDH, 90.8% of outpatient and 76.1% of inpatient antibiotic prescriptions were for drugs included on the list as developed by the DACA of Ethiopia. This is higher than the percentage of drugs prescribed from the EDL of Ethiopia. However, the percentage of antibiotics prescribed from the LDDH particularly for inpatients is low compared to what was supposed to be (100%), although it is better in outpatient departments (90.8%). As this drug list is developed to regulate the rational use of drugs by the various levels of health institutions it is of utmost importance that health facilities adhere to this drug list especially to minimize misuse and overuse of antibiotics. This is also an area that needs to be addressed, by the policy makers and regulatory bodies of health institutions, in order to ensure that the institutions adhere to the nationally developed drug lists which contribute to improving the rational use of antibiotics.

The possible reason for better compliance to LDDH than EDL could be related to the number and type of antibiotics that is included in the list. The LDDH contained more antibiotics than the EDL. All antibiotics that are in the EDL are also in the LDDH but there are antibiotics that are in the LDDL but not in EDL. For example cephalosporins and quinolones, among the most prescribed antibiotic class according to this study, are not included in the EDL while they are in the LDDL. (DACA, 2002)

The percentage of prescribed antibiotics actually dispensed in this study was 90.8% and 97.0% for outpatients and inpatients respectively. This finding was encouraging although the ideal value of 100 % was not attained. This result was similar to that of the Harari region 93.7% (Menassie, 2004:53). This is higher than other studies 39-68% in Serbia (Slobodan *et al.,* 1999). This suggests that the actual availability of antibiotics in West Wollega hospitals is adequate although it needs improvement to reach the ideal value of 100%.

The DDD (the assumed average maintenance dose per day for a drug when used for its main indication in adults), for most drugs have been defined by the World Health Organization. Inpatient usage of drug is usually expressed per occupied bed days (OBD). This study demonstrated that the number of DDDs of antibiotics per 100 occupied bed days for the West Wollega zone hospitals was 70, i.e. 70 defined daily doses of antibiotics has been dispensed per 100 occupied beds per day in the West Wollega zone hospitals in the year 2007. This result was lower than the DDD/100 OBDs found in UK hospitals. 91.5 in a London teaching Trust with four hospital sites in the year 2004/05; 121.3 in South Manchester University NHS trust in the year 2003/04; 87.5 in City hospital Birmingham in 2003/04; 119.8 in 12 English district general hospitals and 93.8 in Royal Infirmary, Aberdeen in 2000 (Benjamin, 2006: 135). It is also lower than the result of 124 at Emam University Hospital in Iran (Ebrahimzadeh *et al.*, 2008: 275).

This result was comparable to that of eight metropolitan hospitals in Australia which was 70 and Tayside University NHS Trust of 73.1 in the UK (Benjamin, 2006: 135). However, it was higher than results observed in other European country hospitals: 39-57 in Sweden in the year 2000, 38.0-44.8 in Denmark, 37.3- 42.5 in the Netherlands, 55.2 in Germany, 40.2 in France and 55.0 in 140 hospitals in Europe (Benjamin, 2006: 135).

The number of defined daily doses in outpatient departments of the West Wollega hospitals was 158.61 per 1000 inhabitants per year or 0.435 DDDs/1000 inhabitant-days. This is lower than observed in European countries in 2006: about 33DDD/1000 inhabitants/day in Greece, 15 in Sweden, 11 in The Netherlands and 9 in the Russian Federation (Health Protection Surveillance center, 2007: 6).

This study has a limitation in respect of the number of defined daily doses expressed for outpatients in that the other primary health care facilities (health centers, clinics and other private clinics) in the region were not included in the study. Therefore, this aggregated antibiotic use indictor expressed in DDD/ 1000 inhabitant days in this study represents the antibiotic use at hospital level only. In addition the antibiotics consumed in the year were

not the exact amount consumed in the year but were extrapolated from the antibiotics used in the four months included in the study. This limitation is also true for other indicators, such as the antibiotic utilization ratio and the incidence of antibiotic use, at outpatients departments in this study.

The cost of antibiotics calculated in this study showed that antibiotics accounted for 33.7% of all drug budgets. This figure showed that the antibiotic expenditure as compared to other medicine expenditure was high. Of the expenditure on antibiotics a few antibiotics constituted the highest percentage. For example clarithromycin alone constituted more that a quarter of all antibiotic expenditure in Gimbie Adventist Hospital yet all the macrolides only constituted 11% of all antibiotic days prescribed. This means clarithromycin was the most expensive antibiotic prescribed at this hospital.

The cost per antibiotic day at the West Wollega hospitals was 6.29 ETB ($0.66). If this was used for a full antibiotic course of about seven days the cost for treatment with a single antibiotic is about 44.03 ETB ($4.6). This is not an affordable cost for the majority of the population living in the districts assuming that there are also other drugs prescribed with this. This shows that there is need for interventions to minimize the cost of antibiotics particularly in the selection of cheaper but effective antibiotics.

In general the study showed that indiscriminate use of antibiotics was common in the two West Wollega hospitals. This was evident in the high percentage of antibiotic encounters, the fact that antibiotic days prescribed were unreasonably high when antibiotic days required were considered and some expensive antibiotics like clarithromycin and newer antibiotics such as quinolones and third generation cephalosporins were used indiscriminately. In addition treatment guidelines were not always followed in treating infectious diseases.

CHAPTER 6
CONCLUSION AND RECOMMENDATIONS

This study of antibiotic prescriptions in these two hospitals has suggested that antibiotics were over-prescribed. Prescriptions containing one or more antibiotics constituted 47% of all prescriptions. This result is comparable with other studies in other parts of Ethiopia and other developing countries. It also showed that the average number of antibiotics per encounter was greater than one, for both inpatients and outpatients which is an indication of overuse of antibiotics.

This study has revealed that quinolones and third generation cephalosporins were highly used at these hospitals. These classes of antibiotics have a wide spectrum of antibacterial activity and their use should be restricted to minimize the risk of bacterial resistance. Some of the drugs used, for example ceftriaxone were not on the list of drugs for district hospitals yet it was one of the most commonly used antibiotics for hospitalized patients. This suggests that standard treatment guidelines and drug formularies were not closely followed in treating infectious diseases. This was also confirmed by the finding that the percentage of antibiotics prescribed from the EDL and LDDH was low.

It is also known from this study that the number of antibiotic days prescribed does not correspond to the number of infectious diseases diagnosed since up to 5 antibiotic courses were prescribed per infectious disease diagnosed. Although there was a possibility of under reporting of infectious diseases in the hospitals, the results of this study suggest overuse use of antibiotics.

This study indicated that the percentage of prescribed antibiotics that were actually dispensed was encouragingly high – a result that needs to be maintained. The number of DDDs per 1000 inhabitants per year was 158.5 and the number of DDDs per 100 bed days was 70. This result was comparable to similar studies conducted in other countries including developed countries.

It was also known from this study that antibiotics constituted 33.7% of all drug budgets, the cost per antibiotic day was 6.29 ETB ($0.66) and the antibiotic cost per patient care day was 3.84 ETB ($0.40). More studies and other factors need to be investigated to determine if this finding was within an acceptable range.

As this study was the base line assessment of antibiotic use in the West Wollega zone, it is recommended that further studies need to be conducted to identify the underlying causes and nature of this indiscriminate antibiotic use. It needs to be determined if antibiotics are prescribed for infections for which they are indicated, or if multiple antibiotics or broader spectrum antibiotics are used for infections that could be treated by a single narrow spectrum antibiotic.

From this study it is recommended that the hospitals in West Wollega address the issue of overuse of antibiotics in general. As studies have confirmed that antimicrobial control program resulted in substantial reduction in the use of selected antibiotics and expenditure (Craig, *et al.*, 2005:732), it is recommended that hospitals in the zone develop hospital specific formularies, treatment guidelines and antimicrobial policies so that standardized treatment protocols are used for the treatment of infectious diseases, to promote rational use of antibiotics.. It is strongly recommended that the health personnel, the hospital management, the zonal and regional Health Bureau, the regulatory bodies like DACA and non-governmental organizations work hand in hand to promote the rational use of antibiotics in this region so that the total cost of antimicrobial resistance can be prevented.

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Appendix I

Data Collection Form

Name of hospital _____
Month of _____2007
Date Data Collected _____
Collected by _____

No.	Rx code	Age	M/F	Antibiotic name	Formulation	Stren Gth	Daily dose	Duration	Quantity	OP or IP	D/ ND

M/F: male of female, D/ND: D if dispensed, ND if the antibiotic was not dispensed, OP/IP: OP outpatient, IP inpatient

Appendix II

Data Collection Form: Infectious Disease Diagnosed

Name of hospital _____
Month of _____2007
Date Data Collected _____
Collected by _____

ICD code	Disease type Diagnosed	Frequency	Remark

Appendix III

Recommended antibiotic days for infectious disease diagnosed at Gimbie Adventist Hospital as per DACA treatment guidelines.

ICD code	Disease type	Frequency of infection	Treatment recommended	Max AB days required per infec	Total AB days required
011.4	Lymphogranuloma venereum	2	Erythromycin 15-21 days or cotrimoxazole 7 days	21	42
011.7	Other unspecified veneral diseases	23	Usually 7-14 days Antibiotic required	14	322
012	Thyphoid fever	226	Chloraphenicol or ciprofloxacin 14 days	14	3164
016.4	Food poisoning	2	Ciprofloxacin or cotrimoxazole 5-7 days	7	14
018	Streptococal sore throat	32	Benzathine sigle dose or erythromycin for 10dys	10	320
023	Meningococcal infection	2	benzyl penicillin 7-10 dys + chloramphenicol 7 days	17	34
026	Tetanus	2	Metronidazole 7-10dys	10	20
035	Unspecified typhus	1	Tetracycline or doxycycline or chloramphenicol for 7 days	7	7
043.9	All other infections	193	Antibiotic for 7-10 dys	10	1930
077	Otitis media and mastoditis	6	Cotrimoxazole or amoxycillin for 5 dys	5	30
087	Acute upper respiratory infections	80	no antibiotic but usually 5-7 days prescribed	7	560
089	Lobar Pneumonia	63	Penicillin 7-10 dys + gentamycin 7 dys, OR Gentamycin 7days + ceftriaxone 7 dys	17	1071
090	Bronchopneumonia	275	Amoxycillin 5-7 days or erythromycin 5-7dys	7	1925
092	Acute bronchitis	42	Amoxycillin or ampicillin or erythromycin 5-7 dys	7	294
093	Bronchitis, chronic and unspecified pneumonia	54	Amox 5-7 or doxy for 7-10days	10	540
109	Chronic, other and unspecified pneumonia	87	Amox 5-7 days or doxycy 7-10dys	10	870
110	Infection of kidney	9		14	126
119	Abortion with sepsis	5	Amp + chloramph10-14 dys after IV for 48 hrs after fever subside	32	160
121	Other complications od pregnanacy and child birth	75	Amp 48 hrs after fever and then 10-14 days	17	1275
121	Infection of skin and subcutaneous tissue	128	Procain penicillin or cloxacillin or erythro or chloram for 7-10 days	10	1280
126	Ulcer of leg	7	usually 7days Antibiotic	7	49
	Total	1368			14033

Appendix IV

Recommended antibiotic days for infectious disease diagnosed at Nedjo Hospital as per DACA treatment guidelines.

ICD code	Disease type	No. of infectious episodes	Treatement recommended	Max antibiotic days required per episode	Total AB days required
011.7	Other unspecified veneral diseases	13	7-14 days antibiotics	14	182
012	Thyphoid fever	14	Chloramphenicol or ciprofloxacin 14 day	14	196
016.5	Other unspecified dysentery	1	Ciprofloxacin 5-7	7	7
071.2	Meningitis due to pneumococcus	1	Benzyl pen 7-10dys	10	10
087	Acute upper respiratory infection	99	no antibiotic but 5-7 days antibiotic common	7	693
090	Bronchopneumonia	23	Amox 5-7 days or erythro 5-7dys	7	161
091	Primary atypical and other unspecified pneumonia	175	Erythro 5-7dys or Doxy 7-10 days	10	1750
115	Sepsis of pregnancy childbirth and puerperiuma	3	Amp + chloramph 10-14 dys after IV administration for 48 hrs after fever subside	34	102
121	Infection of skin and subcutaneous tissue	77	procain pen or cloxacillin or erythro or chloramphenicol for 7-10 days	10	770
124	Osteomyelitis and periosotitis	10	Cloxacillin for 3-4 wks	28	280
	total	416			4151

Appendix V

Cost and quantity of antibiotics dispensed at outpatient pharmacy of Gimbie Adventist Hospital, 2007

Antibiotc Class/specific agent	Unit	Qty dispensed (yr)	Unit cost (ETB)	total cost (ETB)	%	Cumm %
Clarithromycin 500mg tabs	Tablets	18762	3.35	62852.70	37.77	$37.77
Amoxycillin 500 mg capsule	Capsules	76497	0.357	27314.02	16.41	54.18
Cephalexin 500 mg caps	Capsules	23163	0.63	14592.69	8.77	62.95
Amoxycillin + clavulanic acid 625 mg tablets	Tablets	3276	3.6	11793.60	7.09	70.04
Amoxycillin + Clavulanic acid 375 mg tablets	Tablets	4821	1.977	9531.12	5.73	75.76
Ciprofloxacin 500 mg tablets	Tablets	22863	0.307	7021.23	4.22	79.98
Erythromycin 500 mg tabs	Tablets	6960	0.73	5080.80	3.05	83.03
Cloxacillin 500mg caps	Capsules	11898	0.338	4015.58	2.41	85.45
Norfloxacin 400 mg tablets	Tablets	18924	0.173	3273.85	1.97	87.41
Chloramphenicol 250 mg capsule	Capsules	21180	0.154	3264.90	1.96	89.38
Ceftriaxone 1g injection	Vials	471	6.727	3168.42	1.90	91.28
Cotrimoxazole 240 mg/5ml suspension, 100ml bottle	bottles	498	4.61	2295.78	1.38	92.66
Chloramphenicol 1g injection	Vials	822	2.246	1846.38	1.11	93.77
AmoxyClavul 325mg/5ml suspension, 100ml bottle	bottles	51	31.15	1588.65	0.95	94.72
AmoxClavula 156mg/5ml suspension, 100ml bottle	bottles	57	18.18	1036.26	0.62	95.35
Amoxycillin 250 mg capsule	Capsules	6819	0.151	1031.03	0.62	95.96
Cotrimoxazole 480 mg tablets	Tablets	9429	0.107	1007.68	0.61	96.57
Ampicillin 500mg caps	Capsules	2610	0.36	939.60	0.56	97.14
Amoxycillin 125 mg/5ml suspension, 100ml bottle	bottles	150	6.25	937.50	0.56	97.70
Doxycycline 100 mg caps	Capsules	5544	0.164	907.83	0.55	98.24
Benzathine pencillin 2.4 mil units inj	Vials	456	1.63	743.28	0.45	98.69
Amoxycillin 250mg/5ml suspension, 100ml bottle	bottles	60	7.85	471.00	0.28	98.97
Benzathin penicillin 1.2 Million units inj	Vials	249	1.661	413.59	0.25	99.22
Ceftriaxone 500 mg injection	Vials	78	3.61	281.58	0.17	99.39
Chloramphenicol 125 mg/5ml suspension, 100ml bottle	bottles	30	7	210.00	0.13	99.52
Ampicillin 125mg/5ml suspension, 100ml bottle	bottles	33	6.25	206.25	0.12	99.64
Cloxacillin 250 mg caps	Capsules	660	0.21	138.86	0.08	99.72
Gentamycin 80 mg/2ml injection	Ampoules	420	0.324	136.00	0.08	99.81
Cephalexin 250 mg/5ml suspension, 100ml bottle	bottles	6	13.15	78.90	0.05	99.85
Procain penicillin fortified 4 mil units inj.	Vials	33	2.294	75.70	0.05	99.90
Cephalexin 125 mg/5ml suspension, 100ml bottle	bottles	12	5.39	64.68	0.04	99.94
Erythromycin 250mg/ml suspension, 100ml	bottles	6	8	48.00	0.03	99.97
Erythromycin 250 mg tabs	Tablets	84	0.365	30.66	0.02	99.99
Ampicillin 250mg/5ml suspension, 100ml bottle	bottles	3	7.85	23.55	0.01	100.00
Penicillin V 500 mg tabs	Tablets	60	0.15	9.00	0.01	100.00
Total				**166430.65**	**100.00**	

Appendix VI

Cost of Antibiotics dispensed to hospitalized patients at Gimbie Adventist Hospital, 2007

Antibiotc Class/specific agent	Unit	Qty dispensed	Unit cost	total cost	%	Cummul %
Ceftriaxone 1g injection	Vials	3522	6.727	23692.49	31.95	31.95
Crytalline penicillin G injection 1mil unit vial	Vials	11334	1.759	19934.24	26.88	58.83
Ampicillin injection 500mg vial	Vials	4563	1.58	7209.54	9.72	68.55
Ceftriaxone 500 mg injection	Vials	1791	3.61	6465.51	8.72	77.27
Ampicillin injection, 1g vial	Vials	1200	3.16	3792.00	5.11	82.38
Chloramphenicol 1g injection	Vials	1530	2.246	3436.69	4.63	87.01
Amoxycillin 500 mg capsule	Capsules	5538	0.357	1977.40	2.67	89.68
Ampicillin 500mg caps	Capsules	5340	0.36	1922.40	2.59	92.27
Cloxacillin 500mg caps	Capsules	3432	0.338	1158.30	1.56	93.83
Cephalexin 500 mg caps	Capsules	1452	0.63	914.76	1.23	95.07
Gentamycin 80 mg/2ml injection	Ampoules	2436	0.324	788.78	1.06	96.13
Chloramphenicol 250 mg capsule	Capsules	3336	0.154	514.24	0.69	96.82
Clarithromycin 500mg tabs	Tablets	84	3.35	281.40	0.38	97.20
AmoxyClav 375 mg tablets	Tablets	126	1.977	249.10	0.34	97.54
Cotrimoxazole 240 mg/5ml suspension, 100ml botlte	bottles	51	4.61	235.11	0.32	97.86
Amoxyclav 625 mg tablets	Tablets	63	3.6	226.80	0.31	98.16
Ciprofloxacin 500 mg tablets	Tablets	738	0.307	226.64	0.31	98.47
Amoxycillin 125 mg/5ml suspension, 100ml bottle	bottles	36	6.25	225.00	0.30	98.77
AmoxyClavul 325mg/5ml suspension, 100ml bottle	bottles	6	31.15	186.90	0.25	99.02
Norfloxacin 400 mg tablets	Tablets	912	0.173	157.78	0.21	99.23
AmoxClavula 156mg/5ml suspension, 100ml bottle	bottles	6	18.18	109.08	0.15	99.38
Cotrimoxazole 480 mg tablets	Tablets	990	0.107	105.80	0.14	99.52
Erythromycin 500 mg tablets	Tablets	120	0.73	87.60	0.12	99.64
Amoxycillin 250 mg capsule	Capsules	321	0.151	48.54	0.07	99.71
Amoxycillin 250mg/5ml suspension, 100ml bottle	bottles	6	7.85	47.10	0.06	99.77
Chloramphenicol 125 mg/5ml suspension, 100ml	bottles	6	7	42.00	0.06	99.83
Doxycycline 100 mg caps	Capsules	210	0.164	34.39	0.05	99.87
Benzathine pencillin 2.4 mil units inj	Vials	21	1.63	34.23	0.05	99.92
Cloxacillin 250 mg caps	Capsules	132	0.21	27.77	0.04	99.96
Ampicillin 125mg/5ml suspension, 100ml bottle	bottles	3	6.25	18.75	0.03	99.98
Cephalexin 125 mg/5ml suspension, 100ml bottle	bottles	3	5.39	16.17	0.02	100.00
Total				74166.50	100.00	

Appendix VII

Antibiotics dispensed to outpatients at Nedjo Hospital with their cost, 2007

Antibiotc Class/specific agent	Unit	Qty dispensed (yr)	Unit cost (ETB)	total cost (ETB)	%	Cum %
Penicillins						
Amoxycillin 500 mg capsule	Capsules	51660	0.357	18445.72	31.47	31.47
Ciprofloxacin 500 mg tablets	Tablets	31008	0.307	9522.56	16.25	47.72
Erythromycin 500 mg tablets	Tablets	12768	0.73	9320.64	15.90	63.62
AmoxyClav 375 mg tablets	Tablets	2055	1.977	4062.74	6.93	70.55
Amoxycillin 250mg/5ml suspension, 100ml bottle	Bottles	309	7.85	2425.65	4.14	74.69
Cotrimoxazole 240 mg/5ml suspension, 100ml bottle	Bottles	423	4.61	1950.03	3.33	78.02
Amoxycillin 125 mg/5ml suspension, 100ml bottle	Bottles	261	6.25	1631.25	2.78	80.80
Cloxacillin 500mg caps	Capsules	4374	0.338	1476.23	2.52	83.32
Cephalexin 500 mg caps	Capsules	2088	0.63	1315.44	2.24	85.57
Chloramphenicol 250 mg capsule	Capsules	7968	0.154	1228.27	2.10	87.66
Ampicillin 500mg caps	Capsules	3000	0.36	1080.00	1.84	89.50
Norfloxacin 400 mg tablets	Tablets	5136	0.173	888.53	1.52	91.02
Doxycycline 100 mg caps	Capsules	5322	0.164	871.48	1.49	92.51
Amoxycillin 250 mg capsule	Capsules	5640	0.151	852.77	1.46	93.96
Cotrimoxazole 480 mg tablets	Tablets	7920	0.107	846.41	1.44	95.41
Spectinomycin 2 g injection	Vials	21	38	798.00	1.36	96.77
Procain penicillin fortified 4 mil units inj.	Vials	216	2.294	495.50	0.85	97.61
Ceftriaxone 1g injection	Vials	66	6.727	443.98	0.76	98.37
Chloramphenicol 125 mg/5ml suspension, 100ml bottle	Bottles	39	7	273.00	0.47	98.84
Clarithromycin 500mg tabs	Tablets	42	3.35	140.70	0.24	99.08
Erythromycin 250 mg tabs	Tablets	342	0.365	124.83	0.21	99.29
Ampicillin 125mg/5ml suspension, 100ml bottle	Bottles	15	6.25	93.75	0.16	99.45
Benzathine pencillin 2.4 mil units inj	Vials	45	1.63	73.35	0.13	99.58
Gentamycin 80 mg/2ml injection	Ampoules	195	0.324	63.14	0.11	99.68
Cloxacillin 125 mg/5ml suspension, 100ml bottle	Bottles	6	7.25	43.50	0.07	99.76
Ceftriaxone 500 mg injection	Vials	12	3.61	43.32	0.07	99.83
Ampicillin 250mg caps	Capsules	231	0.151	34.88	0.06	99.89
Ampicillin 250mg/5ml suspension, 100ml bottle	Bottles	3	7.85	23.55	0.04	99.93
Benzathin penicillin 1.2 Million units inj	Vials	9	1.661	14.95	0.03	99.96
Cloxacillin 250 mg caps	Capsules	60	0.21	12.62	0.02	99.98
Tetracycline 250 mg caps	Capsules	90	0.12	10.80	0.02	100.00
				58607.58	100	

Appendix VIII

Antibiotics dispensed to hospitalized patients and the cost of each at Nedjo Hospital, 2007

Antibiotc Class/specific agent	Unit	Qty dispen	unit cost (ETB)	total cost (ETB)	%	Cumm. %
Ampicillin injection, 1g vial	Vials	7212	3.16	22789.92	43.59	43.59
Crytalline penicillin G injection 1mil unit vial	Vials	9183	1.759	16151.0604	30.89	74.48
Chloramphenicol 1g injection	Vials	2580	2.246	5795.196	11.08	85.57
Ampicillin injection 500mg vial	Vials	2997	1.58	4735.26	9.06	94.63
Gentamycin 80 mg/2ml injection	Ampoules	2511	0.324	813.0618	1.56	96.18
Ceftriaxone 1g injection	Vials	120	6.727	807.24	1.54	97.72
Cloxacillin 500mg injection, vial	Vials	462	1.058	488.796	0.93	98.66
Amoxycillin 500 mg capsule	Capsules	909	0.357	324.56754	0.62	99.28
Erythromycin 500 mg tablets	Tablets	252	0.73	183.96	0.35	99.63
Ceftriaxone 500 mg injection	Vials	18	3.61	64.98	0.12	99.76
Amoxycillin 250mg/5ml suspension, 100ml bottle	Bottles	6	7.85	47.1	0.09	99.85
Cloxacillin 500mg caps	Capsules	96	0.338	32.4	0.06	99.91
Cloxacillin 125 mg/5ml suspension, 100ml bottle	Bottles	3	7.25	21.75	0.04	99.95
Procain penicillin fortified 4 mil units inj.	Vials	9	2.294	20.646	0.04	99.99
Ampicillin 500mg caps	Capsules	12	0.36	4.32	0.01	100.00
Total				**52280.25774**	**100**	

Appendix IX

Letter of permission from Gimbie Adventist Hospital

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GIMBIE ADVENTIST HOSPITAL
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Ethiopia

ቀን 1/4/08
Date
Ref 2008 – 156

To: **Wakwaya Dugassa**

Re: **Research dissertation – Drug Utilization Review**

Many thanks for your application to undertake the above research at this Institution. I can confirm that Gimbie Hospital is willing to participate in this project and will give you full access to any data necessary for your research.

With best wishes,

Ruth Lawson (Dr)
Administrator

Appendix X

Letter of permission from Nedjo Hospital

Mootummaa Naannoo Oromiyaa
Biiroo Eegumsa Fayyaatii
Hospitaala Najjoo

Ref.No. ቢ 5013/7/2ዐዐ2
Date. 3/8/2ዐዐ2

To Wakwaya Dugassa Janja

RE:- Permission to conduct Research.

As you have requested to undertake drug utilization review for Research purpose, Our Hospital is Willing to cooperate you to do so. The relevant departments will be informed to cooperate you to access the date you need for your research.

Thank You!

Dr.Shumi Negassa

Medical Director

Dr Shuumii Nagaassa Waamil
F/C ዳይሬክተር ጤና ጥበቃ
Daarikteera Hospitaalichaa
Medical Director