UTILIZATION PATTERN AND CONTROLLING SYSTEM OF ANTIBIOTICS IN TERTIARY CARE HOSPITAL IN NEPAL

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A Dissertation Submitted in Partial Fulfillment of the Requirements
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รูปแบบการใช้ยาและการควบคุมยาปฏิชีวนะของโรงพยาบาลระดับตติยะภูมิในประเทศเนปาล

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วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
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Thesis Title	UTILIZATION PATTERN AND CONTROLLING SYSTEM OF ANTIBIOTICS IN TERTIARY CARE HOSPITAL IN NEPAL
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คาเดีย อลัม: รูปแบบการใช้ยาและการควบคุมยาปฏิชีวนะของโรงพยาบาลระดับตติยะภูมิในประเทศเนปาล. (UTILIZATION PATTERN AND CONTROLLING SYSTEM OF ANTIBIOTICS IN TERTIARY CARE HOSPITAL IN NEPAL) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ.ภญ.ดร.นิยดา เกียรติยิ่งอังศุลี อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: รศ.ดร.ปราณะยา มิสารา, 161 หน้า.

มีรายงานจำนวนมากที่เสนอว่านโยบายการพัฒนาและระบบควบคุมยาปฏิชีวนะในประเทศนำไปสู่การลดการใช้ยาปฏิชีวนะที่ไม่เหมาะสมและปัญหาเชื้อดื้อยา การวิจัยครั้งนี้มีวัตถุประสงค์เพื่อศึกษารูปแบบการใช้ยาและทำความเข้าใจระบบควบคุมการใช้ยาปฏิชีวนะในโรงพยาบาลระดับตติยะภูมิในประเทศเนปาล โดยใช้แบบจำลองคุณภาพการรักษาพยาบาลโดนาบีเดียน การเก็บข้อมูลใช้รูปแบบผสมผสานระหว่างการวิจัยเชิงปริมาณและเชิงคุณภาพ ผลการศึกษารูปแบบการใช้ยาปฏิชีวนะพบว่าประมาณ 44% และ 29% ของผู้ป่วยที่เข้ารับการรักษาที่โรงพยาบาลได้รับยาปฏิชีวนะในโรงพยาบาลเขตภาคตะวันตก (WRH) และโรงพยาบาลแพทย์มะนิปาล (MTH) ตามลำดับโดยมีค่าเฉลี่ยของจำนวนยาปฏิชีวนะคือ 2.25 ± 1.14 และ 1.84 ± 0.915 ตามลำดับ โดยรวมแล้วการใช้ยาปฏิชีวนะใน WRH (68.45 DDD/100 วันเตียง) สูงเป็น 3 เท่าของ MTH (22.21 DDD/100 วันเตียง) ค่าใช้จ่ายเฉลี่ยของยาปฏิชีวนะเป็น 1,007.78 รูปีเนปาล (USD 14) ใน WRH และ 892.88 รูปีเนปาล (USD 12.8) ใน MTH ผลการศึกษาเชื้อดื้อยาพบว่าเชื้อ *E. coli* ดื้อต่อยาต่อยากรด Nalidixic, erythromycin, Co - trimoxazole และ Cephalexin ใน WRH อัตราความไม่สมเหตุผลการใช้ยาปฏิชีวนะรักษาโรค enteric fever ใน WRH และ MTH เป็นร้อยละ 40 และ 32 ตามลำดับ นอกจากนี้ระบบควบคุมยา (โครงสร้าง, บุคลากร, นโยบายหรือแนวทางปฏิบัติและการเฝ้าระวัง) ในโรงพยาบาลโรงเรียนแพทย์ที่เป็นเอกชนดีกว่าโรงพยาบาลของรัฐเล็กน้อย เนื่องจากมีการทำงานเชิงนโยบายและระดับปฏิบัติการบางส่วน ร่วมกับการมีแผนกเภสัชกรรมภายในโรงพยาบาล ผลการศึกษาพบว่ามีช่องว่างของการสื่อสารระหว่างส่วนกลางคือศูนย์เฝ้าระวังเชื้อดื้อยากับกลุ่มบุคลากรสุขภาพในโรงพยาบาล พบการขาดความตื่นตัวของบุคลากรในโรงพยาบาลต่อนโยบายแห่งชาติด้านยา ผู้วิจัยเสนอให้มีการปฏิบัติตามนโยบายแห่งชาติด้านยาและนโยบายยาปฏิชีวนะที่ได้รับการแนะนำจากผู้เชี่ยวชาญ ต้องมีการรวบรวมข้อมูลการสำรวจระดับชาติและเผยแพร่สู่บุคลากรให้มาก

ภาควิชาเภสัชศาสตร์สังคมและบริหาร	ลายมือชื่อนิสิต.....
สาขาวิชาเภสัชศาสตร์สังคมและบริหาร	ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก.....
ปีการศึกษา 2554	ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์ร่วม .....

5077114033: MAJOR SOCIAL AND ADMINISTRATIVE PHARMACY
KEYWORDS: ANTIBIOTICS UTILIZATION / CONTROLLING SYSTEM / ANTIBIOTIC POLICY / RATIONAL USE OF MEDICINE / NEPAL

KADIR ALAM: UTILIZATION PATTERN AND CONTROLLING SYSTEM OF ANTIBIOTICS IN TERTIARY CARE HOSPITAL IN NEPAL. ADVISOR: ASST. PROF. NIYADA KIATYING-ANGSULEE, Ph.D., CO-ADVISOR: ASSOC. PROF. PRANAYA MISHRA, Ph.D., 161 pp.

Antibiotic policy in many developed countries reported to be successful in reducing the irrational use of antibiotics and antibiotic resistance. The study was aimed to study utilization of antibiotics and to understand the controlling system of antibiotics at tertiary care hospitals in Nepal using Donabedian model of quality of medical care. Combinations of quantitative and qualitative methods were used in this study. Utilization pattern of antibiotics revealed that about 44% and 29% of admitted patients received antibiotics in Western Regional Hospital (WRH) and Manipal Teaching Hospital (MTH) with the mean number of antibiotics 2.25 ±1.14 and 1.84±0.915 respectively. Overall, antibiotic use in WRH (68.45 DDD/100 bed-days) was 3 fold higher than MTH (22.21 DDD/100 bed-days). The mean cost of antibiotics was NRs. 1007.78 ($14) in WRH and NRs. 892.88 ($12.8) in MTH. *E. coli* showed 100% resistance to Nalidixic acid, Erythromycin, Co-trimoxazole and Cephalexin in WRH. About 40% and 32% of treatment of enteric fever were inappropriate in WRH and MTH respectively. Structure components (Organizational, Personnel, Policy or guideline and Surveillance) were slightly better in the private hospitals than public hospitals because of existence of semi-functional and scattered policy and guideline. Process components were also relatively better in Private hospitals because of good prescribing process and existence of their own hospital pharmacy. The study found the huge communication gap between healthcare professionals on National Surveillance Program and lack of awareness on national drug policy. Hence, we strongly recommend the implementation of antibiotic policy recommended by the expert as well as national drug policy. We also recommend the proper compilation and dissemination of national surveillance data.

Department : Social and Administrative Pharmacy Student's Signature .....

Field of Study : Social and Administrative Pharmacy Advisor's Signature .....

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LIST OF ABBREVIATIONS

ABR	Antibacterial Resistance
AC	Antimicrobial Committee
AMR	Antimicrobial Resistance
ATC	Anatomical Therapeutic Classification
CME	Continue Medical Education
DDA	Department of Drug Administration
DDD	Defined Daily Dose
DTC	Drug and Therapeutics Committee
ESAC	European Surveillance of Antibiotic Consumption
IDS	Infectious Disease Specialist
MTH	Manipal Teaching Hospital
MSIS	Norwegian Surveillance System for Communicable Diseases
NDP	National Drug Policy
NORM	Norwegian Surveillance System for Antimicrobial Drug Resistance
NPHL	Nepal Public Health Laboratory
OTC	Over-the-counter
WHO	World Health Organization
WRH	Western Regional Hospital

CHAPTER I

INTRODUCTION

1.1 Rationale:

Rational drug use mean that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community. Inappropriate use of medicines can lead to wastage of resources, therapeutic failure, adverse drug reaction, poor outcomes etc (WHO, 2002). When it comes to irrational use of antibiotics, it adds another risk of antibacterial resistance. World Health Organization (WHO) defines the appropriate use of antibiotics as "the cost-effective use of antibiotics, which maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of antibiotic resistance (WHO, 2002).

Antibacterial resistance is the result of excessive use of antibacterial in last six decade which triggers a combination of genetic and biomedical mechanisms within the bacteria which secured the survivality in the antibiotic environment. Literature review suggests the vary degree of resistance rates among hospitals, among specialties within hospitals and between patients within specialities in both developed and Asian countries (Vieira et al., 2008; Sandiumenge et al., 2006; Priest et al., 2001; Akram et al. 2007; Song et al. 2004).

Antibiotic utilization studies from developed world suggest the increasing use of antibiotics (Vaccheri et. al., 2008; Muller-Pebody, et al., 2004). Studies from Asian countries suggest 30-80% of prescription contain antibiotics (Chatterjee et al., 2007; Rehan et al., 2001). Further, studies from both developed and developing countries suggest the increased use of newer and broad spectrum antibiotic (Filius et al., 2005; Marra et al., 2006; Gupta et al., 2004; Boriboonhirunsarn, et al., 2007).

In developed countries, half of the antibiotics consumed in community are considered to be based on incorrect indications and most common indications are viral infections (Melander et al., 1998 and Wise et al., 1998). Further, study analyzing

prescribing practices in teaching hospitals worldwide suggests that 41-90% of all antimicrobials prescribed were considered inappropriate (Hogerzeil, 1995). A study from Thailand suggests that the incidence of inappropriate antibiotic use was 25% (Apisarnthanarak et al., 2006).

Various tactics have been suggested to combat antibiotic resistance. Some of them include increasing awareness; improve surveillance of antibiotic resistance, improving antibiotic use, regulating antibiotic use in animal and farm, framing policies and guidelines etc. A meta-analysis of 36 studies on interventions and strategies to improve the use of antimicrobials in developing countries (WHO, 2001) found education and managerial intervention can improve the use of antimicrobial but they did not found sufficient study from the private doctors, hospital inpatients, drug sellers, and patient and community use to generalize their finding.

A quantification study conducted by Pharmaceutical Horizon of Nepal (PHON) (Kafle, 2007) reveals that total consumption of allopathic drugs in fisical year 2005/2006 was Rs.9 billion 61 million (approx US$ 127 million; US$ 1= Rs. 71.35) and about 30% of total consumption of drugs was covered by antibiotics. Moreover, the study has listed the top 15 individual drugs based on their selling in the countries and the list is headed by amoxicillin (9.7% of total drug) with the highest individual consumption across the countries. Other antibiotics in the top 15 selling were ciprofloxacin (4.1%), Ofloxacin (2.7%), Cefixime (2.4%), Ampicillin + Cloxacillin (2.3%), co-trimoxazole (2.3%) and metronidazole (2.2%).

Drug utilization studies show that around 20-60% of out patients (Joshi et al., 1991; Shankar et al., 2005) and 50-92% of in-patients (Kafle et al., 1992; Rehana et al., 1998; Shankar et al., 2003; Paudel et al., 2008) receive antibiotic during their therapy. However, the detailed study on antibiotic utilization and about their rational use is lacking.

In Nepal, the antibiotic resistance is not different with the other developing countries and there are increasing resistance of first line drugs like co-trimoxazole,

amoxicillin, norfloxacin against common organisms like *E.coli, Klebsiella, Pesudomonas aureginosa, Staphylococcus aureus* etc. Moreover, there is emergence of multi-drug resistance (Jha et al., 2005; Guha et al., 2005; Mathura et al., 2005; Khanal et al. 2007).

Antibiotic policy in many developed countries reported to be successful in reducing the irrational use of antibiotics and antibiotic resistance (Bassetti et al., 2000; Ludlam et al., 1999; O'Connor et al., 2004). Recent amendment of National Medicine Policy (NMP 2007) of Nepal mentioned about the prudent use of antibiotics which states the supervision and monitoring on use of antibiotics, classification of antibiotics into different groups for prescribing purposes, constitution of a national antibiotic control committee and constitution of a national antibiotics therapeutics advisory committee but it is not implemented. Therefore, it is aimed to study utilization of antibiotics as well as to understand the system that control antibiotics uses in tertiary care hospitals.

1.2 Objectives

1.2.1 General objectives: To analyse the situation of antibiotic policy related to antibiotics controlling system in tertiary care hospital in Nepal

1.2.2 Specific objectives: Specific objectives in this study was

1. To evaluate the antibiotic utilization pattern in tertiary care hospitals
2. To study the controlling system related to antibiotic use in tertiary care hospitals
3. To propose antibiotic policy for tertiary care hospital implementation

1.3 Expected outcomes:

1. The study result on utilization pattern and situation analysis will be helpful in implementing intervention and policy on antibiotic in the future
2. Moreover, the study analyzed the controlling system of antibiotics in tertiary care hospitals and recommend policy option for hospitals. This will be helpful in implementing National Drug policy (NDP) especially policies on antibiotic component in NDP.

1.4 Conceptual Framework:

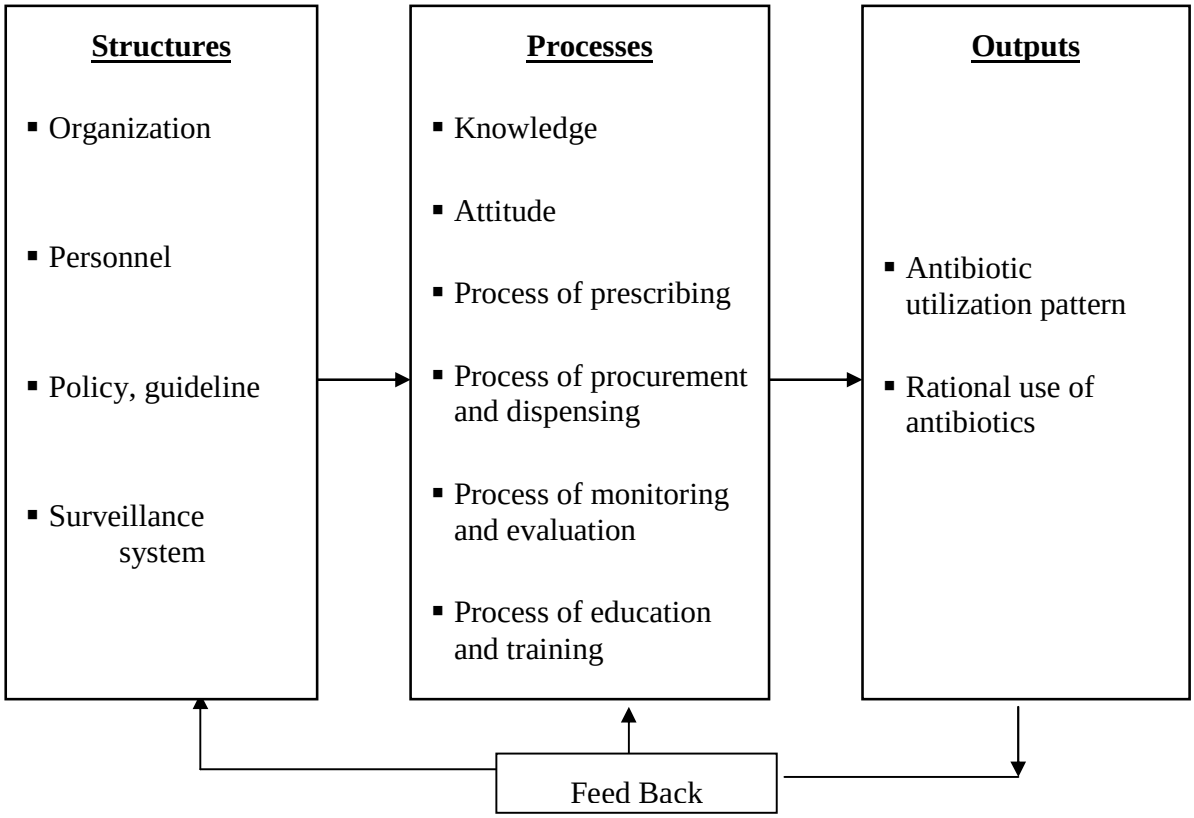


Figure 1.1 Conceptual Framework for the study based on Donabedian model for quality of medical care (Structure-Process-Outcome)

Quality of care can be viewed differently from the patient's and practitioner's satisfaction prospective. However, to measure quality of medical care, Donabedian proposed "Structure", "Process" and "Outcome" as approaches to the acquisition of information about the presence or absence of the attributes that constitute or define quality, rather than "Structure", "Process" and "Outcome" as attribute of quality.

Structure in quality of medical care posses the relative stable characteristics of providers of care. The concept of structure includes the human, physical and organizational settings in which they work. The structure provides the indirect measure of quality of care. The presence of features of structure believed to have a salutary effect on quality of care and is taken to be indirect effects of quality where as its absence believed

to have a deleterious effect which are taken as evidence of poor quality. Hence Donabedian describe “Good structure, that is a sufficiency resources and proper system design is probably the most important means of protecting and promoting the quality of care.”

Donabedian implies a set of activities that go on within and between practitioners as a “Process of care”. A judgment concerning the quality of that process may be made by direct observation or by review of recorded information, which allows a more or less accurate reconstruction of what goes on. Good medical care implies the application of all the necessary services of modern scientific medicine to the need of all people.

Donabedian use “Outcome” to mean a change in patient’s current and future health status that can attribute to antecedent healthcare. The study of outcome is another indirect approach that used to access quality of care.

There are three major approaches to quality assessment “Structure”, “Process” and “Outcome”. The three-fold approaches have the fundamental functional relationship between the three elements which can be shown schematically as follow

Structure → Process → Outcome

This means that structural characteristics of setting in which care takes place have a propensity to influence process of care so that its quality is diminished or enhanced. Similarly changes in the process of care on its quality will influence the effect of care on health status.

In this study the three components of structures, processes and outcomes are described as below.

1.4.1 Structure:

Structures in this study refer to the organizational structures related to the antibiotic use. This includes the organizational structures, personnel, policy, guidelines, surveillance system and monitoring evaluation.

Organization: Organization in this study stands for the existence Antibiotic Resistance / Infectious Control Committee, Drug and Therapeutics Committee and any other related committee working toward the proper use of antibiotics.

- Antibiotic Control Committee / Infectious Control Committee / Drug and Therapeutic Committee

Personnel: Personnel in this study refers to expertise's like Infectious Disease Specialist, Clinical Pharmacist, Nursing specialists etc and their role in antibiotic use

Guideline: Guideline in this study means the availability of guideline on antibiotics which guide the medical practitioner for the better use of antibiotics

- Guideline on antibiotic use
- Guideline on antibiotic resistance
- Guideline on specific disease

Policy: Policy in study refers to the hospital antibiotic policy imposed by the institution for improvement of antibiotic use.

- Restriction
- Prior authorization
- Formulary
- Guideline implementation

Surveillance system: Surveillance system in this study state the existence of system responsible for monitoring of antibiotic consumption at local, regional or national level

1.4.2 Processes:

The processes in this study refer to knowledge, attitude of the health care provider, process of prescribing, procurement, dispensing & medication and education and training involved in the process of drug utilization.

Knowledge: Knowledge in this study refers to the knowledge of healthcare professional (like medical doctor, pharmacists, nurse) related to

- Awareness on Policies
- Knowledge on antibiotic use
- Control mechanism
- Intervention

Attitude: Attitude in this study refers to the attitude of healthcare professional (like medical doctor, pharmacists, nurse) related to

- Attitude towards antibiotic policy
    - Restriction
    - Prior authorization
    - Formulary process
- Attitude towards rational antibiotic use
- Attitude towards education

Prescribing process: Prescribing process in this study refers to

- Checking microbial report
- Consultation with IDS
- Type of prescription (Written/Verbal/Telephonic)

Process of Monitoring and Evaluation: Monitoring and evaluation in this study refers to

- Monitoring of antibiotic use
- Monitoring of antibiotic resistance
- Monitoring of promotion

Procurement and Dispensing process: Procurement and dispensing process in this study refers to

- Special purchase procedure
- Purchase on request
- Dispensing with prescription

Education and Training: Education and training in this study refers to the any training and education on

- Use
- Resistance
- Infection control

Process of Monitoring and Evaluation: Show mainly antibiotic use evaluation and evaluation and monitoring of resistance in the hospital.

1.4.3 Outcomes: Antibiotic utilization pattern was the ultimate outcomes or outputs in this study.

Antibiotic Utilization Pattern: Antibiotic utilization pattern in this study represents the multiple tasks. They are

- Number of antibiotic per hundred patients
- Disease wise antibiotic use
- Department wise antibiotic use
- Appropriateness of antibiotics

CHAPTER II

LITERATURE REVIEW

2.1. Introduction to healthcare and drug use situation in Nepal:

Nepal is a developing country between two huge countries India (from east, west and south) and China (from north). The total surface area of the country is 147,181 sq.km. The total population as per 2007 report is 25.8 million with the population growth rate 2.25 per year. The gross national income per capita is NRs. 1530. Nearly one-third population lives below national poverty line. The country can be divided into three ecological belts from north to south, the Mountains in north, the Hills in the middle and the Terai planes, in he the south. Nearly 85% of the people live in villages, in remote and difficult to access terrain (Central Bureau of Statistics, 2007).

2.1.1 Healthcare status in Nepal: Healthcare statuses in Nepal are described in Table 2.1.

Table 2.1 Healthcare status in Nepal

S. N.	Indicator	data
1	Population below minimum level of dietary energy consumption (%)	47
2	Infant mortality rate (per 1000 live births)	48
3	Expectation of life at birth (ELB) (years)	61
4	Three major causes of deaths 0-14 years (% of total death) – Male/(Female)	
	Pneumonia	13 / (12)
	Diarrhea	12 / (12)
	Measles	3
	(Complication of Pregnancy and Delivery)	(9)
5	Doctors of modern system (per 10,000 population)	2
6	Nurses (per 10,000 population)	2
7	Dentists (per 10,000 population)	0.1
8	Pharmacists (per 10,000 population)	0.1
9	Private expenditure on health [Out of total health expenditure (%)]	72
10	Insurance coverage	
	Social security expenditure on health out of general Govt. expenditure on health (%)	<0.5

Source: 11 health questions about the 11 SEAR countries (Nepal-pp 192-19)

2.1.2 Top ten diseases accounting for morbidity: The most common diseases which account for morbidity is given below in table 1. Most of them are infectious disease.

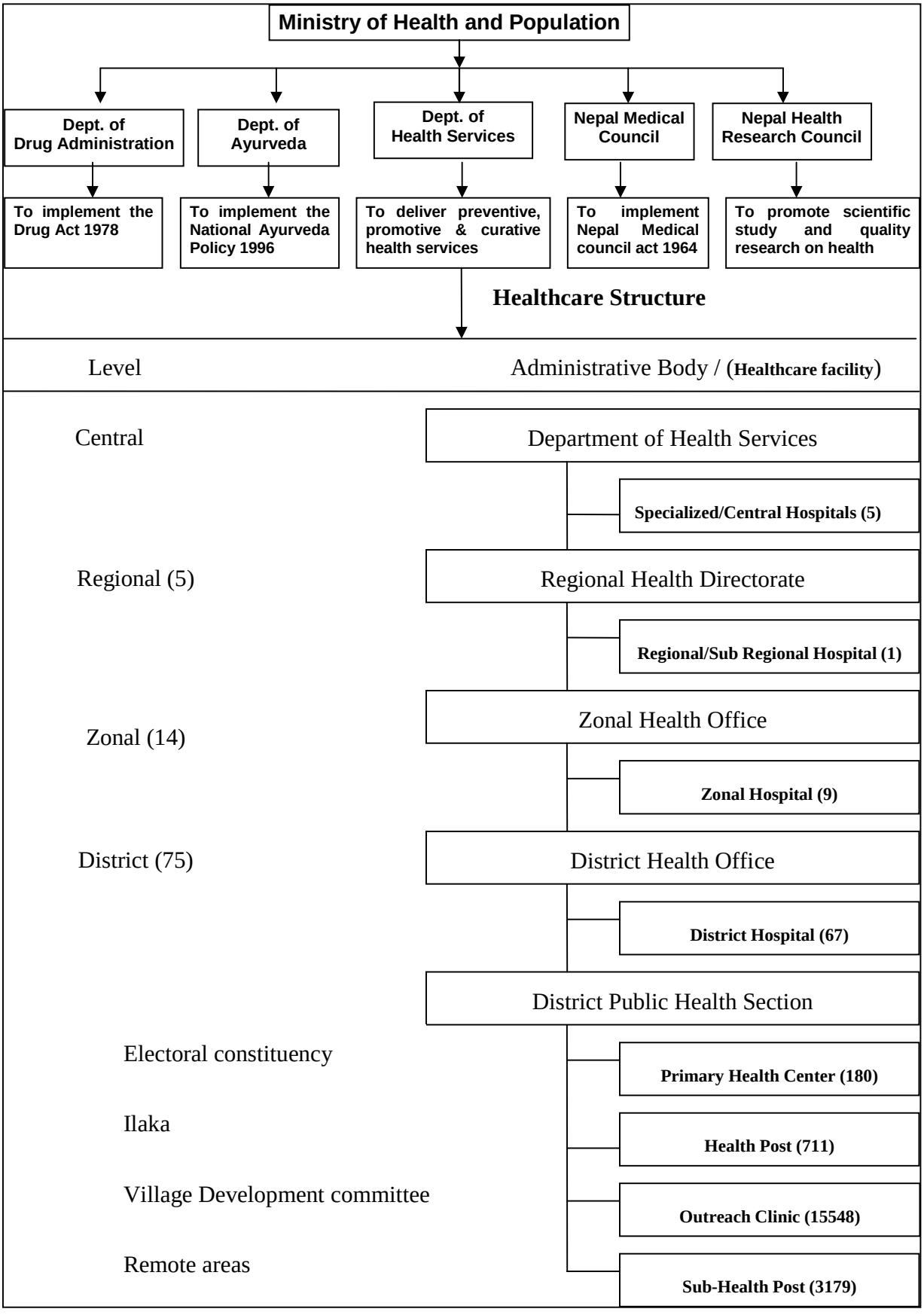
Table 2.2 Top 10 diseases accounting for morbidity in Nepal

Diseases	National Total
Skin Diseases	5.51
Diarhoeal Diseases	3.35
Acute Respiratory Infection	3.13
Intestinal worms	2.82
Pyrexia of unknown origin	2.02
Gastritis	1.95
Ear Infection	1.4
Chronic Bronchitis	1.06
Abdominal Pain	0.96
Sore Eye and Complaints	0.93

Source: Ministry of Health and population (available on www.moh.gov.np accessed on 30th August 2009)

2.1.3 Healthcare system in Nepal: The flow chart of Health System in Nepal is given below in Fig 2.1.

Figure 2.1 Flow chart of health system in Nepal



2.1.4 Medicines policies in Nepal: The various acts and policy on medicine in Nepal is summarize in the figure below

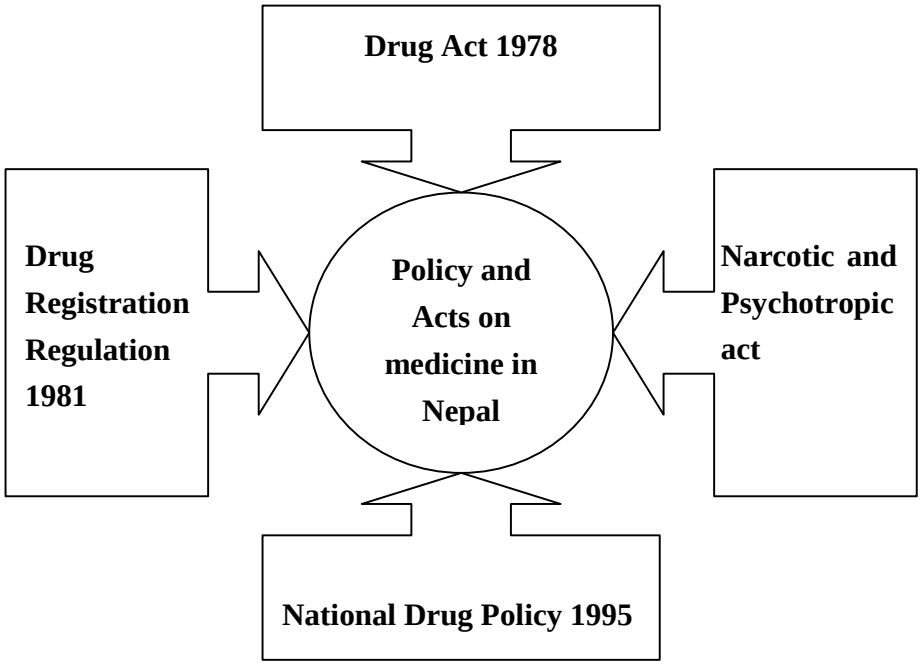


Figure 2.2 Various acts and policy on medicine in Nepal

2.1.5 Act and Regulation on antibiotics in Nepal: Antibiotic is a class of drug which is used to treat the bacterial infection. Due to lack of health education and poor sanitation, the infectious diseases are the most prevailing disease in Nepal. Hence the antibiotic is an important class of drug and has immense role in fighting with infectious diseases. Despite this, there is not any special act or regulation particularly to antibiotic in Nepal. It is regulated similar manner as other drugs by existing Drug Act.

Drug Act was enforced in 1978 to provide the regulation of drugs to prohibit the misuse or abuse of drugs and allied pharmaceutical materials as well as the false or misleading information relating to efficacy and use of drugs and to regulate and control the production, marketing, distribution, export-import, storage and utilization of those drugs which are not safe for the use of the people, efficacious and of standard quality.

As per Drug Act 1978, Drugs have been classified in to three categories to prevent the misuse or abuse of drugs.

Group **'Ka'**: Narcotics, psychotropic and potent therapeutic agents

Group **'Kha'**: Antibiotics, hormones and general therapeutic agents

Group **'Ga':** Other safer drugs (Over-the-counter)

Drugs in group Ka and Kha are prescriptive drugs which can be prescribed only by registered medical practitioner who are registered in Nepal Medical Council where as Group 'Ga' are over-the-counter drugs.

2.1.6 Antibiotic registration in Nepal:

As per Drug Registration Regulation 1981 (amended in 2001), each individual generic as well as different brand of generic should be registered prior to its sale and distribution. In Nepal, there is not any special registration policy for antibiotic. But as like other drugs, it should be registered in the Department of Drug Administration (DDA) before its sell and distribution in Nepal. A new molecule of antibiotic is registered in the DDA based on the recommendation of Drug Advisory Committed who check its inclusion in recognized pharmacopoeia, extensive studies on safety and efficacy of drugs, prices etc. The process of registration of antibiotics is shown in flowchart below.

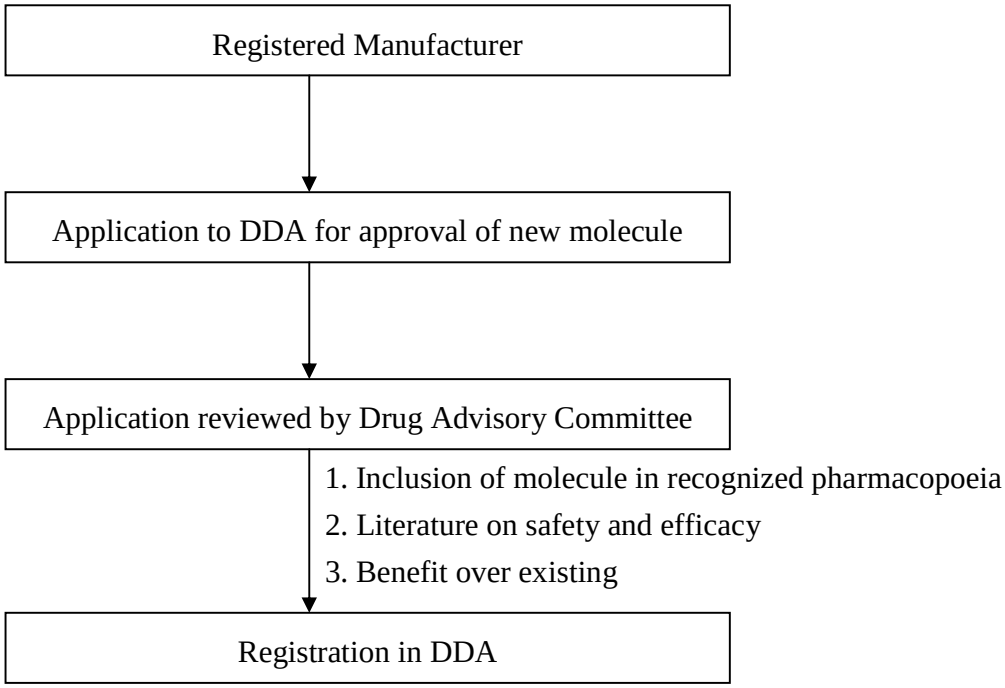


Figure 2.3 Flowchart: registration of new molecule

2.1.7 Policies on Antibiotics: In Nepal, there is no separate polices on antibiotic as such. However, to start with policies, at first National Health policy was announced in 1991 with the objective to safeguard, the health standard of the most of rural population by extending basic primary healthcare services up to village level and making modern medical facilities accessible to rural population.

National Drug Policy (NDP) was promulgated for implementation in 1995 with the aim of the National health policy, to fulfill the commitment of government to provide health for all and to improve and manage by establishing coordination between governmental and non-governmental and private organizations involved in the activities related to drug production, import, export, storage, supply, sales, distribution, quality assessment, regulatory control, rational use and information flow.

The main policy of NDP is to maintain, safeguard and promote the health of people by making the country self- reliant in drug production; ensuring the availability of safe, effective, standard, and quality drugs at affordable price in quantities sufficient to cover the need of every corner of the country; and to manage effectively all the drugs-related activities including production, import, export, storage, sale, supply and distribution.

In the year 2001, policy on prudent use of antibiotics was added in National Drug Policy 1995 which states

a) Prevailing antibiotics used in food products, animal feeds and agriculture substances will be managed properly
b) Supervision and monitoring on use of antibiotics will be carried out. Misuse will be controlled and proper recording system will be developed
c) Antibiotic will be classified into different groups for prescribing purposes by medical Doctors, veterinary doctors and other health personnel
d) Government of Nepal will constitutes a national antibiotic control committee comprising of experts from human and animal health, agriculture and representation from professional organizations/councils and organizations involved in consumers right and other sectors for prudent use of antibiotic

e) Government of Nepal will constitutes a national antibiotics therapeutics advisory committee (NATAC) comprising of experts from relevant sectors to advice a prudent use of antibiotics

2.1.8 Medicine use issues in Nepal: There are several drug use problem exists in Nepal. Some of them include polypharmacy, irrational pharmaceutical promotion, price variation and affordability, access to essential medicine, adverse drug reaction, irrational use of antibiotics etc. (Fig 2.4)

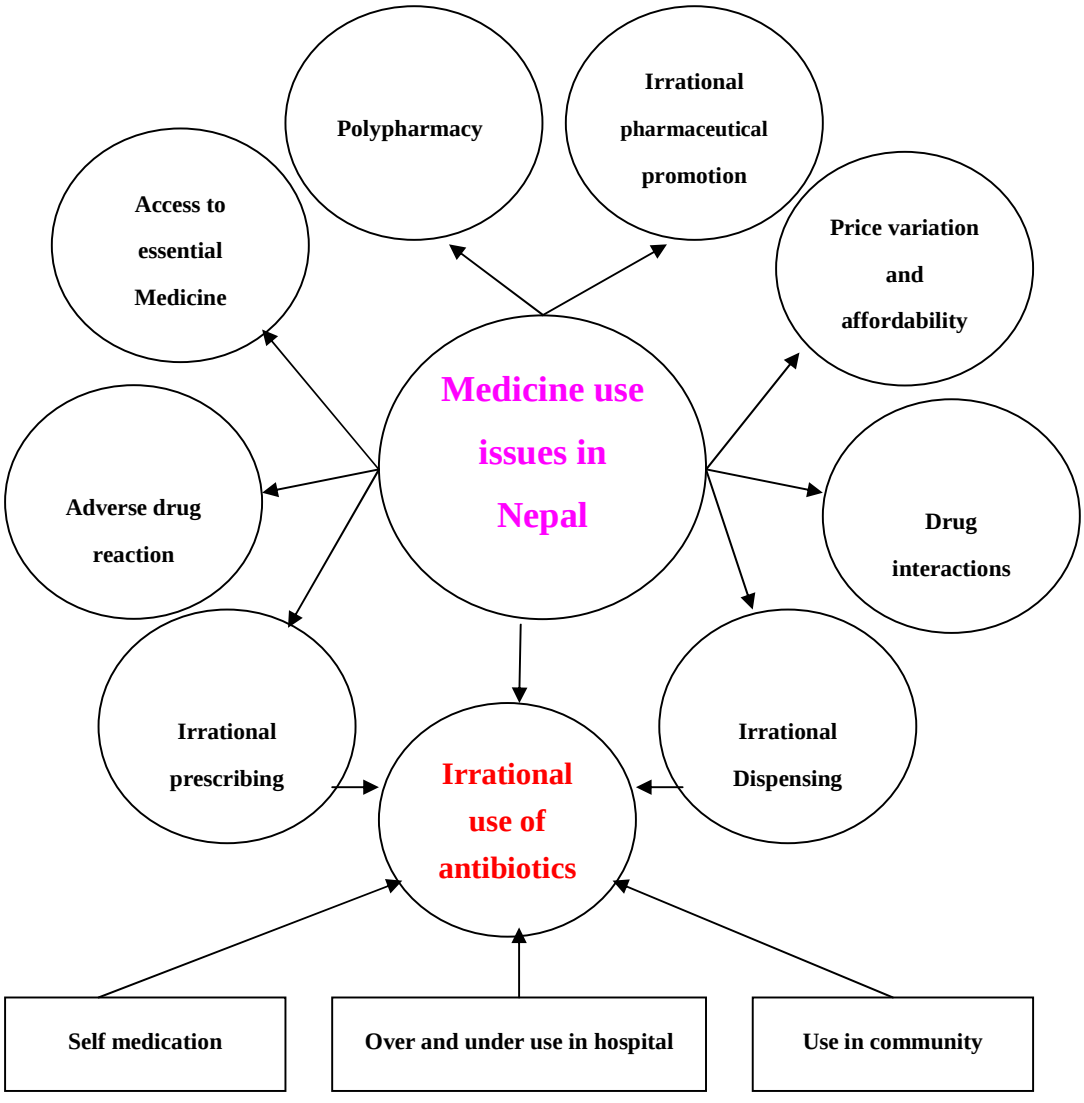


Figure 2.4 Medicine use problem in Nepal

Among the above problem irrational use of antibiotic is one which occurs in hospital and in community from prescriber and as self medication. In this study we after irrational use of antibiotics in hospital practices.

2.2 Antibiotic use in human:

Irrational use of drug is a major concern for both developed and developing countries (Joshi, 1996)**.** The major concern about the misuse of antibiotic is due to antimicrobial resistance which is a matter of worldwide concern (Shankar et al., 2003)**.** The third world countries spend 30-40% of their total health budget on drugs (Melrose et al., 1983) and antibiotic as a groups account for 15-30% of the total health budget (Rehana, 1998). This section of literature survey will describe the study on extent of antibiotic use, pattern of antibiotic use, common cause for which antibiotic is used and rationality of antibiotic use in developed world, Asian countries and in Nepal.

2.2.1 Antibiotic use in human in the developed world: Irrational use of antibiotic is common global problem. This section of literature review describes the extent of antibiotic use, pattern of antibiotic use, common cause for which antibiotic is used and rationality of antibiotic use in developed world.

Study on trends in antibiotic prescribing for adults in the United States (Roumie et al., 2005) suggests decrease in antibiotic prescriptions from 17.9% (1995-1996) to 15.3% (2001-2002). Further, study noted that entire reduction was because of a decrease in antibiotic prescriptions associated with visits for ARIs where antibiotics are rarely indicated from 59.9 to 49.1%. However, there was increase in antibiotic prescription for broad-spectrum antibiotic from 41.0% to 76.8%. This study is retrospective study which analyses the secondary data. Although the study suggests the decrease in antibiotic prescription which was really due to modest decrease in patient visit to doctors for acute respiratory tract reactions. In addition, the study has failed to include the pediatric population, patient with Chronic Obstructive Pulmonary Disease (COPD) and Acquired Immuno Deficiency Syndrome (AIDS) where antibiotics are most commonly prescribed. Other limitation in this study was the determination of appropriateness of an antimicrobial prescription in condition where diagnosis was not mention.

Study on antibiotic treatment of children with sore throat (Linder et al., 2005) found that physician prescribed antibiotics in 53% (95% CI, 49%-56%) of estimated 7.3 million annual visits for sore throat and non recommended antibiotics to 27% (95% CI, 24%-31%) of children who received an antibiotic. Antibiotic prescribing decreased from 66% of visits in 1995 to 54% in 2003 (P=0.01 for trend). This decrease was attributable to a decrease in the prescribing of recommended antibiotics (49% to 38%; p= 0.002).

Study on changing use of antibiotics in community-based outpatient practice (Steinman et al., 2003) found decrease in antibiotics use in acute respiratory tract infection between 1991-1992 and 1998-1999. But there was significant increase in the use of broad-spectrum antibiotics from 24% to 48% in adults (P<0.001) and from 23% to 40% in children (P<0.001). In addition, study found that 22% of adult and 14% of pediatric prescriptions by 1998-1999 for broad-spectrum antibiotics were for common cold, unspecified upper respiratory tract infections, and acute bronchitis, conditions that are primarily viral.

Study on trend in antimicrobial prescribing rates for children and adolescents (McCaig et al., 2002) found the decrease in overall antimicrobial prescriptions per 1000 children and adolescents younger than 15 years from 838 (95% confidence interval [CI], 711-966) in 1989-1990 to 503 (95% confidence interval [CI], 419-588) in 1999-2000 (P for slope<0.001). Further more the visit-based rate decreased from 330 antimicrobial prescriptions per 1000 office visits (95% CI, 305-355) to 234 (95% CI, 210-257; P for slope<0.001). In addition, for the 5 respiratory tract infections, the population-based prescribing rate decreased from 674 (95% CI, 568-781) to 379 (95% CI, 311-447; P for slope<0.001) and visit-based prescribing rate decreased from 715 (95% CI, 682-748) to 613 (95% CI, 570-657; P for slope<0.001).

Study on antibiotic use among children in British Columbia, Canada (Marra et al., 2006) found the decrease in prescription rate in children <15 years of old. The study suggests that the decrease account for one third from 720 to 488 per 1000 children during period of 1996 to 2003. The largest decrease (33%) was seen children between the ages of

0-4 years (*P* value <0.05). Further, study found the decrease in use of penicillin and cephalosporin by 40% and 30% respectively. However, the use of macrolide was increased significantly (24%) during the period from 102 to 126 per 1000 children (*P* value <0.0001). More interestingly, there was decrease in the use of erythromycin in macrolide 72% (from 83 to 23 per 1000 children) but the increase in 3 fold use of clarithromycin (from 18-67 per 1000 children) and 81 fold in the use of azithromycin (from 0.4-35 per 1000 children).

A study on antibacterial prescribing in primary care in UK (Petersen et al., 2007) found most common condition where antibiotics prescribed were skin infections (31%), URTI (44%), Otitis media (63%), Sore throat (64%), Otitis externa (75%), and others like LRTI, UTI, Sinusitis Impetigo and Conjunctivitis (80%). Further, study suggests that amoxicillin and erythromycin were most commonly prescribed for URTI, LRTI and Otitis media. Penicillin, amoxicillin and erythromycin were commonly prescribed for sore throat whereas for sinusitis amoxicillin, tetracycline and erythromycin were most commonly prescribed. Similarly, Flucloxacillin and fusidic acid were most commonly prescribed antibacterial for vague skin infections and impetigo, aminoglycoside and amoxicillin were the drugs most commonly prescribed for Otitis externa.

Three year survey on the use of antibacterial agents in five Italian hospitals (Vaccheri et. al., 2008) found that there was increase in consumption of antibacterial use. The overall increase during the study period was 18% from 64.9 in 2002 to 76.7 DDD/100 bed days in 2004. The increase in use of antibacterial was found in all four units studied. The maximum increase was found in medical unit (22%) followed by surgical unit (14%), intensive care units (8%) and pediatric units (7%). Further the study found the increase in antibiotic consumption were more in combination of Penicillin and β-lactamase inhibitors by 23.2 DDD/ 100 bed days followed by Fluoroquinolones (14.6 DDD/ 100 bed days) and third generation Cephalosporin (10.1 DDD/ 100 bed days).

A cross-sectional and longitudinal study on outpatient antibiotic use in the four administrations of the UK (Davey et al., 2008) found that France was the top in antibiotic consumer list among the 28 administration of UK where Northern Ireland, Scotland 16th,

Wales 18th and England 24th position. Antibiotic use was measured as defined daily doses per 1000 inhabitants per day (DID). Total antibiotic use was 20.4 DID in Northern Ireland which is 37% higher than that in England (14.9 DID).

Another study conducted in Denmark between 1997 to 2001 (Muller-Pebody, et al., 2004) noted the increase and change pattern of hospital antimicrobial use in public hospitals each year in Denmark increased by 13% (from 2.3 million in 1997 to 2.6 million in 2001). Antimicrobial consumption of antibacterial of systemic use significantly increased by 18% from 38.0 to 44.8 DDD per 100 bed-days in 2001 ($P<0.005$). The yearly rate of increase was 1.6 DDD per 100 bed-days (95% CI 1.0 to 2.3). Most of this increase (55%) was attributed to an increase in consumption of commonly used classes of antimicrobials, mainly penicillins with extended spectrum, β lactamase-sensitive penicillin and β lactamase-resistant penicillins.

Study on an additional measure for quantifying antibiotic use in hospitals (Filius et al., 2005) found the increase in total systemic antibiotic use from 47.2 to 54.7 DDD per 100 patient days whereas it remained constant when calculated in terms of DDD per 100 admissions. However, the mean number of total DDD per hospital decreased (not significantly) between 1997 and 2001. Further study found that the use of penicillin in combination with β-lactamase inhibitors, co-amoxiclav and pipracillin-tazobactam, increased significantly when expressed in DDD per 100 patient days. Similarly, the use of lincosamides and fluoroquinolones expressed in both DDD per 100 patient days and DDD per 100 admissions increased significantly. This increased use was due to significant increases in the use of clindamycin ($P<0.0001$) and ciprofloxacin ($P<0.001$) respectively.

A study on outpatient antibiotic prescriptions from 1992 to 2001 in the Netherlands (Kuyvenhoven et al., 2003) found the decrease in prescribing of narrow-spectrum penicillins (-29%), amoxicillin (-23%), tetracycline (-24%), doxycycline (-19%) and trimethoprim and derivatives (-45%) was accompanied by an increase in prescribing of co-amoxiclav (+85%), macrolide (110%) and quinolones (+86%).

A multicenter study in Italy on antibiotic usage in intensive care units (Malacarne et al., 2004) found most patients with sepsis (99%) received antibiotics and in almost all (93%) the treatment was started empirically with broad-spectrum antibiotics. Antibiotic prophylaxis in surgical patients involved widespread use of drug combinations (31% of cases) and lasted 3 days on average. In non-surgical patients antibiotic prophylaxis lasted 4.6 days and 42% a third-generation cephalosporin was used.

Another study from Italy on antibiotic in 219257 prescriptions of children (Resi et al., 2003) found 52.9% of children received at least one antibiotic; this percentage decreased with age, ranging from 70.4%in children 1-2 years old to 35.8% in children >11 years old. Cephalosporins were mostly prescribed in the youngest children, while macrolides were most frequently used in children over 6 years old.

Study on antibiotic prescribing patterns in village health clinics across 10 provinces of Western China (Dong et al., 2008) found that On average 48.43% prescriptions were prescribed with antibiotics (range: 41.12-57.47) in the study areas. There were 49 kinds of antibiotics prescribed in total, and 17 of them accounted for 90% of all usage. The number of antibiotics per 100 prescriptions was 54.62 (range: 43.78-69.56)

Study conducted in French community on antibiotic use from 1992-2000 (Sommet et al., 2004) found the frequency of antibiotic use increased from 4.7 per 100 person-months in 1992 to 7.3 in 1995 and remained stable from 1998 to 2000. Children under 7 years of age were three times more strongly exposed to antibiotics than older subjects. Respiratory tract infections of probable viral aetiology and sore throat accounted for >50% of antibacterial prescriptions.

Summary:

- Although few studies from America suggested the decrease in antibiotic prescription, most of the studies from the Europe found the increase in antibiotic use.

- Studies from communities and hospital both suggested the increase in use of antibiotics
- Studies from both America and Europe suggested the increase in use of broad spectrum and combination of antibiotics and corresponding decrease in use of first line antibiotics.
- Studies suggested that respiratory tract infection is the most common condition for which antibiotics were used. Extent of use varies from studies to studies.

2.2.2 Antibiotic use in humans in Asia: Common features in Asian countries are poverty, poor sanitation which increases the prevalence of infectious disease. Thus the use of antibiotic is also to combat the prevailing disease. This section of literature review describes the extent of antibiotic use, pattern of antibiotic use, common cause for which antibiotic is used and rationality of antibiotic use in Asian continent. We found 24 study form India (9), Pakistan (4), Bangladesh (2), Saudi Arabia (1), Sri Lanka (1), Thailand (3), Chiana (3) and Qatar (1). Most of them were drug utilization study conducted at different facilities. The summaries of the reviews are given below and details of reviews are given in Appendix A.

Summary:

- Studies from South Asian countries suggest the varied degree of use of antibiotics in different countries like in India between 30-80% prescriptions contain antibiotics. Similarly, 20-62% in Pakistan and more than 50% of prescription contain antibiotics
- Most of the studies suggest varied degree of inappropriate use of antibiotics. Study from India suggests the incidence of inappropriate use of antibiotic is 34-49%. Similarly, 33-43% in Bangladesh and 25% in Thailand
- Studies also suggest the increased use of cephalosporin especially third generation like ceftriaxone

2.2.3 Antibiotic use in humans in Nepal: Nepal is a developing country. Like other Asian countries, infectious diseases are most prevailing diseases. This section of literature review describes the extent of antibiotic use, pattern of antibiotic use, common cause for which antibiotic is used and rationality of antibiotic use in Nepal. In this section we found 25 studies conducted between 1991 to 2008 (Table 2.3). The short summaries extracted from those studies are given below and details are kept in Appendix A.

Table 2.3 Summaries of studies on antibiotic use in human in Nepal

Study setting	Department	Type of study	Out/inpatient	No. of study
Tertiary care	Medicine	Antibiotic utilization	Inpatients	2
	Pediatrics	Antibiotic utilization	Inpatients	2
	Surgery	Antibiotic utilization	Inpatients	3
	Surgery	Antibiotic utilization	outpatients	2
	ICU	Antibiotic utilization	Inpatients	2
	Dental / ENT	Antibiotic utilization	outpatients	2
	Overall	Drug utilization	Outpatients	5
	Overall	Specific drugs utilization	Inpatients	2
	Overall	Antibioic utilization in specific disease condition	Inpatient/ outpatients	2
Primary care	Overall	Drug utilization	Outpatients	3

Summary:

- Studies suggest that more than fifty percent of prescription (50-84%) contain at least one antibiotic. Further study also suggests that 2 and more than 3 antibiotics were also prescribed in 25-37% and 15-35% respectively
- Extent of antibiotic use varied in different studies and it constitute 12 – 72% of total drugs
- Studies also suggest the increased use of newer antibiotics like third generation like ceftriaxone, fluoroquinolone
- Although studies suggests the extensive use of antibiotic, the studies on appropriateness or rationality of antibiotic use is lacking

2.2.4 Studies on appropriateness of antibiotic use: The study on evaluation of rational antibiotic use conducted to estimate the appropriateness of antimicrobial drug use in Celal Bayar University Hospital in Manisa (Tunger et al. 2000) according to the Kunin and Jones criteria found that of the patients, 16.6% (*n*=156) were receiving antibiotics, and in 63.5, 23.0 and 13.5% of these, a single, two and three agents were used, respectively. The purpose of antibiotic use was for prophylaxis in 23.9%, as an empiric decision in 71.4% and for therapeutic culture-based reasons in 4.7%. The rate of rational antibiotic use was 45.7% and it was statistically higher in those patients from whom specimens had been taken for culture than in patients receiving prophylactic or empiric antibiotics. On medical wards, rational antibiotic usage was 55.1%, while it was 26.3% in surgical wards ($P<0.0001$). The low rate of appropriate antibiotic use in our university hospital reflects the urgent need of rationalization.

The study on evaluation of antibiotic use in intensive care units of a tertiary care hospital in Turkey evaluated the appropriateness of antibiotic use relative to diagnosis and bacteriological findings in the intensive care units (ICUs) of a 1100-bed referral and tertiary care hospital with an antibiotic restriction policy in Turkey (Erbay et al 2005) found of the 368 patients admitted to the ICUs, 223 (60.6%) received 440 antibiotics. The most frequently prescribed antibiotics were first-generation cephalosporins (16.1%), third-generation cephalosporins (15.2%), aminoglycosides (12.1%), carbapenems (10.7%) and ampicillin-sulbactam (8.7%). Antibiotic use was inappropriate in 47.3% of antibiotics. ID specialists recommended the use of 47% of all antibiotics. An antibiotic order without an ID consultation was more likely to be inappropriate [odds ratio (OR) =13.2, P<0.001, confidence intervals (CI) = 4.4–39.5]. Antibiotics ordered empirically were found to be less appropriate than those ordered with evidence of culture and susceptibility results (OR=3.8, P=0.038, and CI=1.1–13.1). Inappropriate antibiotic use was significantly higher in patients who had surgical interventions (OR=3.6, P= 0.025, CI=1.2–10.8). Irrational antibiotic use was high for unrestricted antibiotics. In particular, antibiotic use was inappropriate in surgical ICUs. Additional interventions such as postgraduate training programmes and elaboration of local guidelines could be beneficial.

The study was designed to evaluate rational antibiotic use relative to diagnosis and bacteriological findings. All hospitalized patients who received antibiotics were evaluated by a cross-sectional study. Of the 713 patients hospitalized, 281 (39.4%) patients received 377 antibiotics. Among 30 different antibiotics the most frequently requested were first generation cephalosporins (19.9%), ampicillin-sulbactam (19.1%) and aminoglycosides (11.7%). Antibiotic use was appropriate in 64.2% of antibiotic requests. In analysis of appropriate use, a request after an infectious diseases consultation was a frequent reason (OR=14, PB 0.001, CI=0.02-0.24). Antibiotics requested in conjunction with susceptibility results were found to be more appropriate than those ordered empirically (OR= 4.5, P_ 0.017, CI=0.06-0.76). Inappropriate antibiotic use was significantly higher among unrestricted antibiotics than restricted ones (P<0.001). Irrational antibiotic use was high for unrestricted antibiotics. Additional interventions such as postgraduate training programmes and elaboration of local guidelines could be beneficial.

Appropriateness of Antimicrobial Therapy Measured by Repeated Prevalence Surveys to determine if prevalence surveys are useful tools to determine the appropriateness of antimicrobial therapy (AMT) and determinants of inappropriate AMT (Willemsen et al. 2007) accessed the appropriateness of AMT according to a standardized algorithm based on the local AMT prescription guidelines. On average, 684 patients were included in each survey (total, 4,105). The use of AMT as determined in the prevalence survey corresponded to the annual data from the pharmacy department. Nine hundred thirty-eight (22.9%) of the patients received AMT, and in 351 (37.4%) of these patients AMT was inappropriate. Only 25 (0.6%) patients did not receive AMT, although it was indicated. After multivariate analysis, the use of quinolones was the only statistically significant variable associated with inappropriate use. Prevalence surveys proved to be useful tools to judge the appropriateness of AMT and to identify determinants of inappropriate use. This study shows that in a setting with a low use of AMT, there are few patients who inadvertently do not receive AMT. On the other hand, a substantial number of the patients are treated inappropriate.

An antibiotic utilization review was performed for the purpose of determining the

frequency and types of infectious diseases presenting to a large, teaching hospital emergency department, and the appropriateness of the use of antibiotics in this setting (Linda et al. 2005) found that 27% of the visits a diagnosis of an infectious disease was made or an antibiotic was prescribed. The most common presenting diagnoses (comprising more than 75% of cases) were infections of the respiratory tract, skin, urogenital system, and gastrointestinal tract. Penicillins and sulfonamides were frequently prescribed in nearly two-thirds of cases. Antibiotic prescribing was determined to be appropriate in 78% of cases. Inappropriate use most often involved the use of prophylactic antibiotics in clean lacerations and the use of prophylactic antibiotic combination products following trauma to the eye.

2.3 Method to study antibiotics use: Rational use of antibiotics can be studied by obtaining following information (WHO, 2003)

Information on systems and structures: The surrounding information on antibiotic use likes how drugs are ordered delivered and administered in a hospital or health care facility

Information on the processes of antibiotic use: Common information likes which antibiotics are used, how they are used, does their uses comply with the relevant criteria, guidelines or restrictions

Information on outcomes of antibiotics use: Information like efficacy, adverse drug reactions and the use of resources such as drugs, laboratory tests, hospital beds or procedures

The common method used to study the rational uses of antibiotic in healthcare setting is prescribing pattern of antibiotic and its use. Prescribing pattern of antibiotic can be determined by following methods.

2.3.1 General drug utilization study: In this type of study, the whole data extracted from the prescription form is analyzed for various parameters like average number of drugs per prescription, percentage of drugs prescribed by generic, percentage

of encounters resulting in prescription of an injection and percentage of encounters resulting in prescription of antibiotics etc. This method can only provide the share of antibiotics among total drug used. This type of studies cannot describe the exact use.
For example: Rational drug prescribing and dispensing in outpatients in a tertiary care hospital (Alam et al., 2006) found that total of 720 drugs were studied in 247 prescriptions 12.1% were antibiotics.

2.3.2 Drug classification system: This method classifies the drugs used for the different purposes. A drug classification system represents a common language for describing the drug assortment in a country or region and is a prerequisite for national and international comparisons of drug utilization data, which have to be collected and aggregated in a uniform way. Access to standardized and validated information on drug use is essential to allow audits of patterns of drug utilization, to identify problems in drug use. The most common method used to classify the drug is ATC classification which is developed by Norwegian researchers. The system is used mostly in combination with Defined Daily Dose (DDD). For example: fluoroquinolone utilization among inpatients in a teaching hospital in Western Nepal (Shankar *et al.*, 2007) found 3.92 DDD/100 bed-days of ciprofloxacillin oral as ATC code of J01M A02.

2.3.3 Defined Daily Doses: The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD is often a compromise based on a review of the available information about doses used in various countries. The DDD may even be a dose that is seldom prescribed, because it is an average of two or more commonly used dose sizes. Antibiotic utilization figures should ideally be presented as numbers of DDDs per 1000 inhabitants per day or, when drug use by inpatients is considered, as DDDs per 100 bed-days.

DDDs per 1000 inhabitants per days: Sales or prescription data presented in DDDs per 1000 inhabitants per day may provide a rough estimate of the proportion of the study population treated daily with a particular drug or group of drugs. As an example, amoxicillin 10 DDDs per 1000 inhabitants per day indicates that 1% of the population on

average might receives amoxicillin daily. For example, a cross-sectional and longitudinal study on outpatient antibiotic use in the four administrations of the UK (Davey et al., 2008) found that total antibiotic use was 20.4 DID in Northern Ireland which is 37% higher than that in England (14.9 DID).

DDDs per 100 bed-days: The DDDs per 100 bed-days may be applied when drug use by inpatients is considered. The definition of a bed-day may differ between hospitals or countries, and bed-days should be adjusted for occupancy rate. The same definition should be used when performing comparative studies. For example, 70 DDDs per 100 bed days of antibiotics provide an estimate of the therapeutic intensity and suggests that 70% of the inpatients might receive a DDD of antibiotics every day. This unit is quite useful for benchmarking in hospitals. For example, Three year survey on the use of antibacterial agents in five Italian hospitals (Vaccheri et al., 2008) found that the overall increase in consumption of antibacterial use during the study period was 18% from 64.9 in 2002 to 76.7 DDD/100 bed days in 2004.

***DDDs per inhabitant per year*:** The DDDs per inhabitant per year may give an estimate of the average number of days for which each inhabitant is treated annually. For example, Imipenem 5 DDDs per inhabitant per year indicates that the utilization is equivalent to the treatment of every inhabitant with a five-day course of imipenem during a certain year. Alternatively, if the standard treatment period is known, the total number of DDDs can be calculated as the number of treatment courses, and the number of treatment courses can then be related to the total population.

2.3.4 Evaluation of antibiotic use process: This method evaluates the pattern of appropriateness of antibiotic use. In this type of study define criteria for inappropriateness of antibiotic use and using these criteria researcher evaluates the rationality of use. For example, Kunin define (Kunin et al., 1973) as inappropriate use of antibiotic as probably appropriate use, unjustified, excessive length of treatment, unjustified use of any antimicrobial not indicated**,** more effective drug recommended**,** unjustified, short length of treatment, less expensive drug recommended, various combinations of points listed

above and evaluated the use of antibiotics.

2.4 Strategy to improve antibiotic use: The various strategies to improve the antibiotic use suggested by the WHO (WHO, 2001) are summarized in figure below.

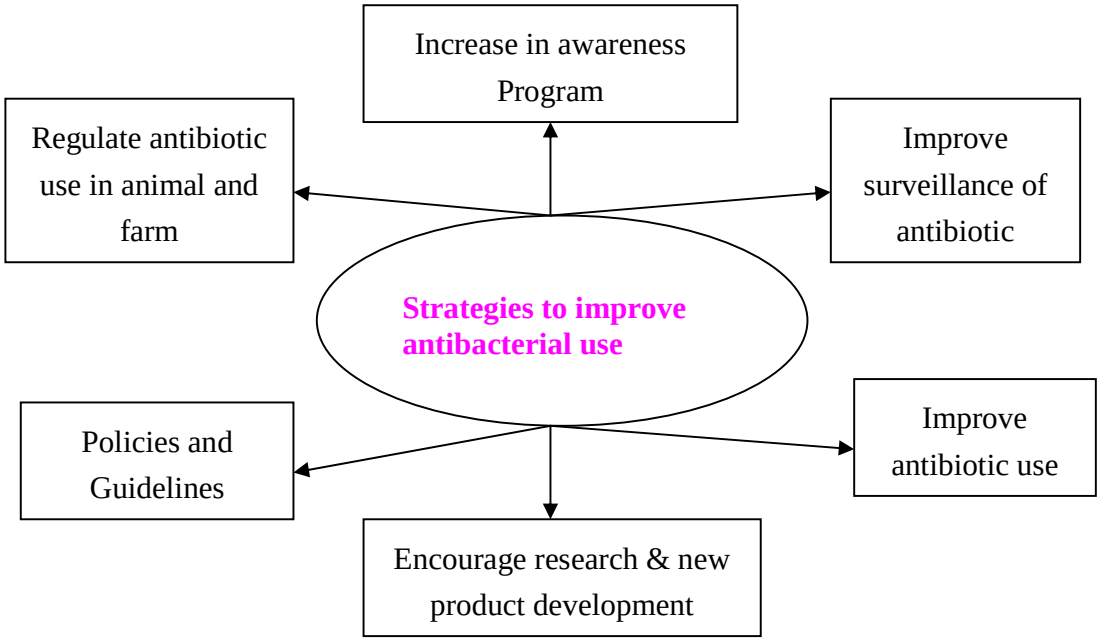


Figure 2.5 Strategies to improve antibacterial use suggested by WHO

2.4.1 Increase awareness: Education has immense role in increase awareness. WHO expert committed (WHO, 2001) has recommend awareness at different level public education; communication between academic institutions, government agency evaluation of university curricula will be beneficial in increasing awareness at the national level. At the same time, education to prescriber and dispenser, and education to general public has been advocated at institutional and healthcare level to increase awareness.

A study from Peru (Paredes et al., 1997) suggests that educational intervention directed to consumer using media, face-to-face meetings and training on use of medicine was successful in decreasing the inappropriate use of antidiarrheal and antimicrobials for simple diarrhea

2.4.2 Improve surveillance of antibiotic resistance: Surveillance is a tool that

can facilitate the prevention of infection and the amelioration of its immediate ant long-term effects by providing the necessary information for action. Surveillance of antibacterial resistance should involve the collection and collation of both clinical and microbiological data. Various recommended strategies to improve surveillance of antibacterial resistance includes coordination with local surveillance networks, recruiting leaders for surveillance network, establishing and supporting reference laboratory, sharing results with international organization, monitoring resistance in food, animal and human are recommended at the National level. Development of local surveillance networks, laboratory maintenance are recommended at healthcare level. Whereas, post marketing surveillance and support surveillance network are suggested at the pharmaceutical company level.

The 18-year surveillance of antibiotic susceptibility patterns among Shigella isolated in Belgium (Vrints et al., 2009) Suggests that cotrimoxazole should no longer be considered appropriate as empirical therapy for treatment of shigellosis in Belgium when antibiotics are indicated and hence improve the antibiotic use.

Study from Norway (Simonsen, 2009) suggests that there are three systems for surveillance of antimicrobial resistance in Norway: The Norwegian Surveillance System for Communicable Diseases (MSIS), the Norwegian Surveillance System for Antimicrobial Drug Resistance (NORM), and the European Antimicrobial Resistance Surveillance System (EARSS). Surveillance results and individual studies show that the prevalence of resistance is lower in Norway than in other countries.

A study on surveillance for antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* over a 7-year period on treatment guidelines in Alberta, Canada (Plitt et al., 2009) found importance of surveillance in monitoring trends in AMR in gonorrhea in timely changing of treatment recommendations in response to changing epidemiology.

European surveillance of antibiotic consumption (ESAC) on hospital consumption of antibiotics in 15 European countries (Vander Stichele et al., 2006) found cumbersome but feasible to collect ecological data on hospital antibiotic consumption in a set of 15

European countries on a retrospective basis, illustrating substantial cross-national variations in the extent and distribution of exposure to antibiotics in hospital care.

2.4.3 Improve antibiotic use in human: Appropriate use of antibiotics is not only cost-effective but also maximizes clinical therapeutic effect while minimize both drug-related toxicities and the development of antibacterial resistance. There are various strategies have been suggested to improve antibiotic use in human. Those strategies at different level have been suggested. Strategies at national level includes, framing of antibiotic policies, creation and update of national and regional guideline, Enforcement of prudent use of antibiotics, regulation of manufacturing, registration and advertisement of antibiotics, creating economic incentives for the appropriate use of antibiotics, limit general access to new drugs etc. Similarly at the health care institution level strategies includes establishment of Infection Control Committee, establishment of Drugs and Therapeutics Committee, development of guidelines for appropriate antibiotic use, monitoring of use of antibiotic through pharmacy report and resistance pattern, education of to employee and laboratory maintenance. However, improving hygiene and prescribing antibiotic prudently at the health care worker level.

Study on effect of formulary policy decisions on antimicrobial drug utilization in British Columbia (Marra et al., 2005) found listing of antimicrobials on provincial or countrywide formularies is followed temporally with increased utilization. However, before governmental agencies can institute reference-based pricing or co-payment programmes, the effect of such a programme on the emergence of antimicrobial resistance and on patient outcomes needs further study.

A study on effectiveness of education and an antibiotic-control program in a tertiary care hospital in Thailand (Apisarnthanarak et al., 2006) found that education and antibiotic control program were effective and cost-saving strategy to optimize antibiotic use in tertiary care center in Thailand.

2.4.4 Regulate antibiotic use in animal and farm: Since, the use of antibiotics has extended to animal and farm and its volume is about 50% of total antibiotic use in some countries (Moulin, et al. 2008). Hence, regulation of antibiotic in animals and farm are equally important. Strategies recommended at national level are increase awareness of antibiotic resistance problem, regulation of antibiotic prescription for animals, restriction of growth promoter use in animals, setting risk standard risk standards for resistance, establishing regulatory system, monitor simultaneous use of antibiotics in animals and human. Strategies at veterinarian level include promotion of prudent use of antibiotics in animals and guideline development for antibiotic use in animals. Similarly, improve farm hygiene reduce use of antibiotics as growth promoters and improve animal husbandry at the animal producer level. In addition, risk-benefit analysis of growth promoter use, environmental impact, and food processing and distribution methods has been recommended at the researcher's level.

A study on impact of an antibiotic policy on antibiotic use in a pediatric department. Individual based follow-up (Berild al., 2002) shows that antibiotics were chosen according to diagnoses and bacterial findings suggests that implementation of Guidelines and clinical Cupertino for rational antibiotic use in a Norwegian pediatric department in 1994 decreased the use of antibiotics and expenditures by 50%. Moreover, there was an 80% decrease in the use of cloxacillin, a 74% decrease of aminoglycosides and a 59% decrease of cephalosporins. The use of penicillin V and G increased by 14% and ampicillins by 8%.

2.4.5 Encourage new product development: Since, resistance to existing drug is increasing and becoming resistant. So, development of new antibiotic is very important. The strategies recommended for development of new antibiotics are providing incentives to industries, protection of intellectual property rights, and facilitation of networking at national level where as, increase in research and development in several areas at pharmaceutical industries level

2.4.6 Increase resources to curb antibiotic resistance in the developing world: Antibiotic resistant bacteria are found in industrialized and developing countries alike and

with the international travel can pass easily from country to country. Hence, the strategies recommended are ensuring availability of antibiotic, sharing resources with other countries and decreasing risk of infectious disease at national level. Similarly, sharing results of surveillance internationally, secure technical and financial support for developing countries, invest in a worldwide vaccine strategy to reduce antibiotic use, ensure the availability of vaccines and quality drugs, facilitate communication among the countries of world, safeguard privacy and human rights, promote appropriate international laws at international organizations level.

2.4.7 Increase funding for surveillance, research and development: Increasing resistant to the antibiotic has increased expenditure. Hence, to increase the surveillance, research and development funding is equally important. Thus nation should increase funding for surveillance network, research and education.

2.5 Antibiotic policy in around the world:

Study on impact of antibiotic policy on prescribing in a London Teaching Hospital A one-day prevalence survey as an indicator of antibiotic use (Cooke, et al. 1983) found that out off 921 in-patients, 196 (21%) received 269 antibiotic prescriptions on the survey day. Approximately 40% of in-patients received prophylaxis and 60% received treatment. Among 1521 out-patients, 292 (19%) were given a prescription on the survey day and 102 (7%) received an antibiotic prescription. Choice of antibiotic was largely in accord with antibiotic policy, but was considered inappropriate in 12.5% of 81 in-patients given prophylaxis and 2.5% of 120 in-patients given treatment Dosage of some major agents and timing of surgical prophylaxis was also considered inappropriate in many patients.

Use of antimicrobial drugs in adults before and after removal of a restriction policy (Himmelberg, et al. 1991) found that for the restricted agents, the total number of courses of therapy increased by 158% after the restriction policy was removed and total expenditures increased by 103%. Thus the removal of an antimicrobial restriction policy resulted in increased use of and higher expenditures for previously restricted agents, as well as an increase in the inappropriate use of at least one agent.

Antibiotic restriction policies in public hospitals (Kuitert, and Thomas 1991) found that Use of restriction policies within specialist units was associated with reduced total hospital antibiotic expenditure per bed per year.

Effect of a selective restriction policy on antibiotic expenditure and use: an institutional model (Suwangool et al., 1991) found that Strictly enforced antibiotic formulary restriction in combination with formulation of agreed guidelines for antibiotic use in common infection problems such as septicemia, febrile neutropenia, urinary tract infection, biliary sepsis, liver abscess, peritonitis, nosocomial pneumonia, soft tissue infection and purulent meningitis, generated a combined savings of 307,748.5 bahts or 13.5 per cent cost reduction over a 6 month period, and improved quality of use, appropriate 54.8 vs 67.5 per cent, statistically significance (*P* less than 0.002).

Enforcing a policy for restricting antimicrobial drug use (Maswoswe, and Okpara, 1995) suggests declined use of the restricted antimicrobials, and increased use of nonrestricted antimicrobials. After two months, acquisition costs for the restricted drugs had been reduced by more than $82,000; however, a similar increase in acquisition costs for nonrestricted antimicrobials occurred.

Study on hospital antibiotic control measures in the UK: Working Party of the British Society for Antimicrobial Chemotherapy (Ansari et al., 1994) found that A written policy for surgical prophylaxis was available in 51% of hospitals, 62% had a policy for therapy and 79% an antibiotic formulary. The policies for prophylaxis and therapy both gave recommendations on individual drugs in 95% of hospitals, on dosage in 81% and 60% and duration of prophylaxis/treatment in 90% and 51% respectively. Eighty-eight per cent believed policies for prophylaxis and therapy to be beneficial. A restricted list was operated in 77% of hospitals and 90% of respondents believed formularies to be beneficial.

Antibiotic policies in Dutch hospitals for the treatment of patients with serious infection (Janknegt et al., 1994) assessed the guidelines available in Dutch hospitals for the treatment of patients with serious infection of unknown aetiology, 39 antibiotic formularies used in 88 hospitals were analyzed. Beta-Lactam antibiotics (most commonly

amoxycillin and cefuroxime) were the preferred agents for empirical therapy of infections of all types; an aminoglycoside was also included in the majority of regimens, irrespective of the clinical presentation. However, there were wide variations in the choice and dosages of the drugs administered. Because of the absence of local data for the susceptibilities of blood culture isolates, the appropriateness of the recommendations could not be properly evaluated.

Trends in hospital antibiotic prescribing after introduction of an antibiotic policy (Gould and Jappy, 1996) found that during the period of the study 30 new antibiotics were considered for inclusion in the hospital formulary, but only seven were incorporated, and all for restricted use only. Despite this, expenditure on antibiotics has more than doubled since 1986, two thirds of the increase being due to the use of new drugs. There was also an increased use of older antibiotics (DDDs increased by 33%), often for no clear reasons, and an overall increase of 46% in DDDs. Antibiotics have increased from 11.9-18.7% as a proportion of the drug budget. Findings highlight the current difficulty in controlling prescribing budgets, the increasing use of antibiotics and the consequent spread of resistance.

A review of the role of antibiotic policies in the control of antibiotic resistance (Gould, 1999) suggests that the optimal antibiotic control measures remain to be described and probably vary between institutions. Nevertheless, various control measures have been shown to be useful in reducing costs of therapy and total amounts of prescribing, while maintaining quality of care. More recently, interest has turned to whether antibiotic policies can reduce the spread of resistance and even reverse current high levels. However, early studies indicated this was feasible.

Audit of antibiotic policies in the South East of England, 2004 (Mayon-White, and Wiffen, 2005) suggests that Twenty-three hospital and 25 primary care policies were examined. The average age of policies was 12 months, but 13 were more than 2 years old. The commonest format was an A4-sized document available in an electronic version. Primary care policies were more uniform than hospital policies. More primary care than hospitals' policies gave evidence to support their guidance. Ten policies used plain

English for dosages, and 38 (79%) policies made few or no cautionary points about the drugs recommended. Respiratory and urinary infections were covered in most policies, but guidance on gastroenteritis and antibiotic prophylaxis was less frequent. There was little advice in the policies on the management of methicillin-resistant *S aureus*.

A time-series intervention analysis on improving compliance with hospital antibiotic guidelines (Mol et al., 2005) found that at baseline, compliance with the drug choice guidelines was 67%. The first intervention showed a significant change in the level of compliance of +15.5% (95% CI: 8%; 23%). Academic detailing (AD) did not lead to statistically significant additional changes in already high levels +12.5% (95% CI:-3%; 28%) of compliance. Post-intervention compliance was stable at 86%.

Study evaluating compliance with a gentamicin prescribing policy after introduction of a monitoring form (Rogers, et al. 2005) found that following introduction of the monitoring form, the proportion of appropriate starting doses had increased from 13 out of 20 to 18 out of 20 prescriptions. The timing of initial serum levels was significantly better: 18 timed correctly, compared with 12 in initial audit. Subsequent administration and monitoring appeared more compliant with fewer doses inappropriately omitted and more levels checked appropriately. No improvement was seen in the quality of dose adjustment.

Studies on antibiotic prescribing policy and Clostridium difficile diarrhea in a hospital in UK (Ludlam et al., 1999; O'Connor et al., 2004) found that antibiotic policy was successful in reducing both the use of intravenous cephalosporin and significant decrease in *C. difficile* diarrhea infection in elderly patients.

A study on antimicrobial prescribing policy and practice in Scotland: recommendations for good antimicrobial practice in acute hospitals (Nathwani, 2006) suggests the 6 key component of the antimicrobial policies including establishment of standard structures and line of responsibility and accountability of board member, defining structure and responsibility for multidisciplinary and generic undergraduate and postgraduate training related to antimicrobial prescribing, defining the minimum dataset requirements and standard procedures for collecting information related to antimicrobial

resistance patterns, defining the minimum dataset requirements and standard procedures for consumption and quality of prescribing at and organizational level and/or ward-specific level, defining the key areas for acute hospital policy and recommendation for audit and development and define performance indicators that could be used to access or gauge performance related to antimicrobial prescribing in acute hospital. Further the study suggests 20 recommendations on national and hospital structures, responsibility, accountability, prescribing policy, monitoring and etc.

A study on impact of an antimicrobial formulary and restriction policy in the largest hospital in Italy (Bassetti et al., 2000) resulted in clear and immediate saving. The policy also improves the antibiotic use and better resistance pattern.

Study on antibiotic policy to prevent emergence of resistant bacilli (de Man et al., 2000) found that Policies regarding the empiric use of antibiotics do matter in the control of antimicrobial resistance.

A review on antibiotic policies and the role of strategic hospital leadership (Masterton, 1999) suggests that achieving effective antimicrobial control require a combined approach from all levels and disciplines within and across organization and also depend on potent hospital leadership delivered to focus of antimicrobial program.

A review on Antibiotic policies in Central/Eastern Europe (CEE) after 1990 (Krcmery and Gould, 1999) suggests that at the beginning of 1990 there were significant political and social change including decentralization of drug policies and several strategies to decrease consumption and/or resistance were implemented such as restriction of outpatient use, national and hospital formularies and Health Management Organizations-based restrictions. Probably due to the short time scale, no significant reduction in resistance has been documented although antibiotic consumption has declined.

A study assessing the antibiotic policies in Central Europe through questionnaire on the prevalence of resistance, antibiotic consumption and antibiotic policy (Cizman et al., 2004) found that Data on antibiotic resistance and consumption of antibiotics at

national levels are limited and vary considerably among countries. Over the counter sales of antibiotics are available in some countries. Antibiotic policy interventions do not exist or only apply to specific problems or interventions. Further study recommends better implementation of antibiotic interventions and education on antibiotic use should be a high priority in this region. An effective strategy requires close co-operation, consultations and partnership at national and international level in particular, via existing international organizations.

A study evaluating antibiotic use in a hospital with an antibiotic restriction policy (Erbay et al., 2003) found that inappropriate antibiotic use was significantly higher among unrestricted antibiotics than restricted ones ($P<0.001$). Irrational antibiotic use was high for unrestricted antibiotics. Study further recommend additional interventions such as postgraduate training program and elaboration of local guidelines could be beneficial.

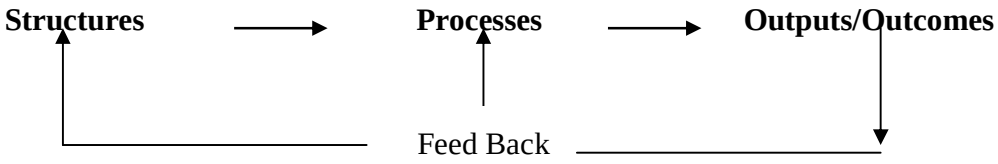
2.6 Antibiotic policies in the hospitals: In this section we review the available antibiotic policies in the hospital. We found 5 studies on antibiotic policies from Turkey (2), Canada (1), Taiwan (1) and United Kingdom (1). Among them two policies from national level, another 2 at Hospital level and one at state level. The details of antibiotic polices are given in Appendix A

2.7. Total Quality Management (Structure-process-Output/Outcome): Total Quality Management (TQM) is a management philosophy and operating approach that aims to consistently exceed the current and future expectations of all stakeholders (i.e., customers, employees, shareholders and the community). TQM is based on continuous improvement in all processes, goods and services, as a result of the creative involvement of all stakeholders.

The history of TQM can be traced back to early 1920s when statistical theory was first applied to product quality control. This concept was further developed in Japan in the 1940s and 1950s, and was led by “quality gurus” such as Deming, Juran and Feigenbaum. The focus widened from quality of products to quality of all issues within an organisation – the start of TQM. But, TQM gained prominence in western countries in the 1980s as a

response to the competitive advantage gained by Japanese companies, particularly in the automobile and electronics industries.

Avedis Donabedian, a leader of health quality assurance applied the principle of TQM in healthcare to audit quality standard of medical care into a dynamic framework of three components namely structure, process and outcome (Fig 1.) where structures relate organization characteristic of healthcare setting. Processes relate to the interaction between practitioners and patients and include clinical interventions and the use of treatments and investigation. Outcomes represent quality of healthcare. Since outcome is difficult to measure with degree of accuracy. Thus, process and structure can be used as a proxy for outcome, when relationship between outcome, process and structure are known (Donabedian, 1966).



Donabedian model for quality of medical care

Due to established relationship among structures/inputs, processes and outputs/outcomes of Donabedian Model, it is used widely in variety of research. It has been used in determining quality of medical care, organizational structure, evaluation of surveillance system, clinical outcome, satisfaction, quality of life measurement, evaluation of drug related problem etc. In the model, relation among structures/inputs processes and outputs/outcomes further strengthen by influence of feed back from the outcome to structures and process.

CHAPTER III

METHODOLOGY

3.1 Study Design:

This study had the three different objectives, to study these we used mix up of quantitative and qualitative methods. Such as quantitative method likes prescription survey were applied to study utilization pattern and quantitative method likes interview was used to study controlling system (Table 3.1).

3.2 Study sample and sample size: Sample in this study was different as per the study objective and method of study. They are described as below in the individual objective's head.

3.2.1 Sample in prescription survey in antibiotic utilization study: Sample in the survey was individual patient prescription. Drug utilization studies suggest that around 50-92% of inpatients (Kafle et al., 1992; Rehana et al., 1998; Shankar et al., 2003; Paudel et al., 2008) receive antibiotics. However, there is lack of data on appropriateness of antibiotic use. Hence assuming 50% of prescribed antibiotics were inappropriate. Then the required sample size was calculated from formula

$$n = Z^2_{\alpha/2}\ p(1-p)/M^2$$

Where, M = margin of error, P = Prevalence of the characteristic

Thus, the sample size (n) at 95% confidence interval and 5% margin of error will be

$$n = 1.96^2 \times 0.5 \times 0.5 / (0.05)^2 = 384.16 \sim 385$$

Although, the required sample size was only 385, research was carried out for the duration of 4 months starting from 1st April 2010 to 31 July 2010.

3.2.2 Sample size for assessing appropriateness: Enteric fever as most prevalent disease at that point of time was found after antibiotic utilization pattern study. Separate 100-100 patients from WRH and MTH from 1st August 2010 till 100 patients including all patients diagnosed as Enteric fever was studied for appropriateness.

Table 3.1 Study Design

Objectives	Design	Study Object	Expected Outcomes
1. To study the antibiotic utilization pattern	Prescription survey	▪Patient file	▪Mean no. antibiotics prescribed ▪DDD/100 bed-days ▪ Antibiotic use in co-morbidity ▪Department wise antibiotic use ▪Appropriateness of antibiotics
2. To study the system control related to antibiotic use	Documentation	▪Reports ▪Bulletin ▪Meeting minutes ▪Proceeding ▪Published literature	▪Antibiotic procurement ▪Antibiotic use evaluation ▪Training/Education ▪ Organization ▪ Personnel
	Observation	▪Prescribing Process ▪Dispensing Process ▪Medication process	▪Prescribing process ▪Dispensing Process ▪Medication Process
	Interview	▪Prescriber ▪Microbiologist ▪Pharmacists ▪Hospital Director	▪Structure Organization Personnel Policy/guideline Surveillance ▪Process Knowledge Attitude Process of prescribing and dispensing Education and training Monitoring and Evaluation ▪Rational Use of Antibiotics
3. To analyze antibiotic policy from tertiary care hospital	Expert-panel discussion	▪Hospital administrator ▪Microbiologists ▪Pharmacists ▪Expert from DDA ▪Expert from Ministry ▪Expert from academia	▪Policy for Hospital Management ▪Recommendation to Government ▪Strategy for implementation

3.2.3 Semi-structured interview for situation analysis: Altogether 47 professionals from five different hospitals, Ministry of Health and DDA were interviewed for the necessary information. Stakeholders were Clinician (26), Pharmacists (7), Microbiologist (6), Hospital Administrators or DTC Chairperson (6), Pharmacologist (1) and Nurse (1) (Appendix D).

3.2.4 Expert-panel: The experts from the different fields were identified and invited. There were 15 members in the expert-panel including Hospital Directors or DTC chairperson from study hospitals, experts from Ministry of Health, DDA, Academics, APUA-Nepal, Universities (Table 4.10).

3.3. Study Site: The study sites include Manipal Teaching Hospital (MTH) and Western Regional Hospital (WRH) for utilization pattern whereas additional three hospitals including Bir Hospital, KIST Hospital and Dhulikhel Hospital were included to study controlling system of antibiotic use. The characteristic features of all hospitals are given in Table 3.2.

Table 3.2 List of Hospitals included in study

Parameter	MTH	WRH	Bir Hospital	Dhulikhel Hospital	KIST Hospital
Location	Pokhara	Pokhara	Kathmandu	Kavre	Lalitpur
No. of bed	825	350	458	317	311
Occupancy	40%	70%	>90%	-	-
Specialties	▪ Medicine ▪ Surgery ▪ Pediatric ▪ Gynecology ▪ Orthopedics ▪ ICU ▪ ENT ▪ Others	▪ Medicine ▪ Surgery ▪ Pediatric ▪ Gynecology ▪ Orthopedics ▪ ICU ▪ ENT Others	▪ Medicine ▪ Surgery ▪ Pediatric ▪ Gynecology ▪ Orthopedics ▪ ICU ▪ ENT Others	▪ Medicine ▪ Surgery ▪ Pediatric ▪ Gynecology ▪ Orthopedics ▪ ICU ▪ ENT Others	▪ Medicine ▪ Surgery ▪ Pediatric ▪ Gynecology ▪ Orthopedics ▪ ICU ▪ ENT Others
Training center for	▪ MBBS ▪ M.D. ▪ Nurse	▪ Nurse ▪ (MBBS)	▪ MBBS ▪ M.D. ▪ Nurse	▪ MBBS ▪ M.D. ▪ Nurse	▪ MBBS ▪ M.D. ▪ Nurse
Affiliated University	Kathmandu University	-	NAMS	Kathmandu University	Tribhuvan University

*NAMS-National Academy of Medical Sciences

Hospitals for the utilization pattern were selected mainly based on feasibility and access to the data. Moreover, due to lack of resources limited the number of hospital to two. In Nepal most of the Tertiary Care Hospitals are centralized in the capital city, Kathmandu. Looking at centralization, three hospitals were selected near Kathmandu for studying controlling system.

3.4 Scope of the study: The study scope of the antibiotic utilization study was the admitted patient in two tertiary care hospitals and who were prescribed with at least one antibiotic during their hospital stay. Similarly, for situation analysis the scope was 5 tertiary care hospitals in Nepal.

3.5 Operational Definition:

Organization: Organization in this study stands for the existence Antibiotic Resistance / Infectious Control Committee, Drug and Therapeutics Committee and any other related committee working toward the proper use of antibiotics.

Personnel: Personnel in this study refer to expertises like Infectious Disease Specialist, Clinical Pharmacist, Nursing specialists etc.

Policy: Policy in study refers to the hospital antibiotic policy imposed by the institution for improvement of antibiotic use.

Guideline: Guideline in this study means the availability of guideline on antibiotics which guide the medical practitioner for the better use of antibiotics.

Surveillance system: Surveillance system in this study state the existence of system responsible for monitoring of antibiotic consumption at local, regional or national level.

Knowledge: Knowledge in this study refers to the knowledge of healthcare professional (like medical doctor, pharmacists, nurse) related to the use of antibiotics.

Attitude: Attitude in the study refers to the attitude of healthcare professional (like medical doctor, pharmacists, nurse) toward the use of antibacterial.

Process of checking microbial report: This refers to the procedure of checking antimicrobial reports before assigning the antibacterial therapy.

Procurement and dispensing process: This indicates the process of purchasing antibiotics for the hospital and dispensing to the patients.

Antibiotic use evaluation system: This refers to the system of evaluation of antibiotic use within the institution.

Antibiotic Utilization Pattern: Antibiotic utilization pattern in this study represents the multiple tasks. They are

- Number of antibiotic per hundred patients
- Disease wise antibiotic use
- Department wise antibiotic use
- Appropriateness of antibiotics

3.6. Ethics: Ethical approval was obtained from the Nepal Health Research Council (NHRC), a national research authority under ministry of health and also permission were obtained from individual institutional research committee of the all five hospital where research conducted. Ethical approval obtained from NHRC and individual hospital research committee is given in Appendix B.

3.7. Method of Data Collection: Data collection in this study was collected in three phases

3.7.1 Antibiotic Utilization: Inpatient on antibacterial chemotherapy was identified and descriptive data on antibiotic utilization was collected from the patient file prospectively in data collection form Appendix B. The detailed information regarding demography, diagnosis, drug therapy etc. was recorded. Concerned prescriber were consulted in case of any confusion.

3.7.2 Appropriateness of the antibiotic use: The appropriateness of treatment of enteric was analyzed using 10 point Medication Appropriateness Index (MAI) criteria (Hanlon et al., 1992) given below. In the past, MAI index was used successfully to access the appropriateness of Antibiotic Prescribing in Community-Acquired Pneumonia, Sinusitis, or Acute Exacerbations of Chronic Bronchitis (Taylor et al., 2001 and Tobia et al., 2008).

1. Is there an indication for the drug?
2. Is the medication effective for the condition?
3. Is the dosage correct?
4. Is the duration of therapy acceptable?
5. Are the directions correct?
6. Are there clinically significant drug-drug interactions?
7. Are there clinically significant drug-disease interaction?
8. Are the directions practical?
9. Is this drug the least expensive alternative compared to others of equal utility?
10. Is there unnecessary duplication with other drugs?

Each criterion was judged as appropriate, marginally appropriate or inappropriate based on the WHO guideline on enteric fever and score 0 to incorrect and 1 to correct was assigned. Finally average score of appropriate, marginally appropriate and inappropriate was calculated. Assessments of individual points are given in separate heading.

3.7.2.1 Indication for the drug: WHO guideline suggests the indication of antibiotics as appropriate when it is microbiologically proven. Hence in this study the evaluation criteria for indication were

Appropriate indication: When a patient with fever (38°C and above) that has lasted for at least three days, with a laboratory-confirmed positive culture (blood, bone marrow, bowel fluid) of *S. typhi* whereas fever 38 ^{o}C or above for at least 3 days with positive serodiagnosis or antigen detection and presence of other clinical features like Hepato-spleenomegaly, Leucopenia and non-specific sign and symptoms (Bradycardia, Anorexia, Malaise, Abdominal pain, Constipation) was termed *marginally appropriate*.

Inappropriate: The absence of either confirmed positive culture or serodiagnosis or antigen detection was of termed inappropriate.

3.7.2.2 Effectiveness for the condition: The effectiveness of antibiotic therapy can be well known by sensitivity pattern. However, in this study only very few patients microbioigical assay were referred. So, clinical outcome with the therapy was taken in the consideration.

Appropriate: When treatment of medicine therapy was proven by microbiological

assay with positive outcome then it was termed as appropriate or when medicine therapy was not microbiologically proven but produced positive outcome with initial therapy was termed *marginally appropriate*.

Inappropriate: When there was treatment failure termed inappropriate. In this study, when there was no positive outcome with the initial therapy which require addition of another antimicrobial in between the therapy then it was termed as treatment failure of the therapy.

3.7.2.3 Correct dosage: The WHO recommended therapy is given below in the Table 3.3. The dose of treatment therapy was compared with the WHO recommended dose. If it lies within the recommended dose it termed *appropriate*. An error margin within 20% was termed as *marginally appropriate* and error of more than 20% was called as *inappropriate.*

Table 3.3 WHO recommended therapy for treatment of Enteric fever

Name of Medicine	Daily dose	Days of treatments
Amoxicillin	75-100 mg/kg	14 days
Chloramphenicol	50-100 mg/kg	14-21 days
Co-trimoxazole	8-40 mg/kg	14 days
Floroquionolone (Ciprofloxacin or Ofloxacin)	15 mg/kg	5-7 days (up to 14 days in case of complication)
Cefixime	15-20 mg/kg	7-14 days
Azithromycin	8-10 mg/kg	7 days
Cefotaxime	80 mg/kg	10-14 days
Ceftriaxone	60-75 mg/kg	10-14 days

3.7.2.4 Duration of therapy: As like dose the duration of therapy was also compared with WHO recommended therapy given in the Table 3.3. If it matched with it then termed *appropriate*. An error margin of less than 20% was termed *marginally appropriate* and error more than 20% of that was called as *inappropriate*.

3.7.2.5 Correct direction: In this direction refers to the medication to the patients where we assessed the route of administration, relationship to food and liquid, the schedule, and time of the day. In this correct direction was termed as *appropriate* whereas minor change which did not have any effect on patients outcome termed as *marginally appropriate* and incorrect direction was termed as *inappropriate.*

3.7.2.6 Drug-drug interactions: Drug-drug interaction between the treatment therapies was evaluated using Micromedex 2 healthcare series. Where none existence of interaction was termed *appropriate* and the existence of minor drug interaction was termed *marginally appropriate*. The existence of interaction (moderate, major or contraindicated) was termed as *inappropriate.*

3.7.2.7 Drug disease interaction: Drug-disease interactions, which can be defined as exacerbations of preexisting diseases, conditions, or syndromes by medications. In this non-existence of drug-disease interaction was assigned as appropriate, whereas minor interaction was termed marginally appropriate and existence of major interaction was termed as inappropriateness.

3.7.2.8 Are the directions practical? In this we assessed whether the directions for use were practical for the patient to take and took into consideration the potential for patient adherence without sacrificing efficacy, as well as patient's clinical conditions. In this study if practical directions were termed *appropriate,* with minimal discomfort of the patients without effect on efficacy of drug were termed *marginally appropriate* whereas impractical directions were termed *inappropriateness*

3.7.2.9 Least expensive alternative: WHO has regarded Fluoroquionolone as optimal treatment in terms of least expensive alternatives based on culture and sensitivity. In this study we considered Fluoroquinolone as Least expensive alternative for the treatment of Enteric fever based on culture and sensitivity reports and other oral therapy with Azithromycin or cefixime as *marginally appropriate*. However, direct treatment with 3rd generation cephalosporin without culture and sensitivity report was considered as *inappropriate*.

3.7.2.10 Unnecessary duplication with other drugs: WHO guideline advocates the treatment of enteric fever with single antibiotics. Even in first line multidrug resistant enteric fever, single antibiotic therapy with third generation cephalosporin is advocated. Hence, duplication of therapy in this study means that treatment with two antibiotics simultaneously in a manner that is non-beneficial.

3.7.3 Situation Analysis: Combination of methods like documentation, structured observation and semi-structured interview were used in situation analysis. The data collection method for each method was described below.

3.7.3.1 Documentation: This method was applied for the reviewing the available documents which describe the process related to the antibacterial use in the hospitals.

3.7.3.2 Structured Observation: This method was used to observe the process of prescribing, dispensing and handling of antibiotics.

3.7.3.3 Interview: Identified stakeholders, medical doctors and other healthcare prescriber were interviewed with the pre formulated questionnaire to obtain the necessary information. Guideline to interviewers is given in Appendix B.

3.7.4. Policy Options: After completion of utilization data collection and controlling system study, experts were invited for expert discussion on the situation and the expert-panel after analyzing the situation. Experts were requested to recommend the policy for identified problem to improve the antibiotic use as well as to suggest the possible strategy to implement the policy.

3.8 Data Analysis: The data obtained from the utilization study was analyzed using Microsoft Excel 2003 and SPSS statistical package 17.0 for window.

Statistics: Descriptive statistic was used to characterize patients socio-demographic and data were described as mean, standard deviation. Independent sample t-test was used to compare mean and chi-square to find the association. 2-way ANOVA.

CHAPTER IV

RESULTS

4.1 Antibiotic Utilization: In this section, we have studies the following parameters.

1. Demography of the patients received antibiotics
2. Medicine use
3. Antibiotics use
4. Cost of antibiotics
5. Antibiotic Resistance

4.1.1 Demography of the patients: Altogether there were 6964 and 5401 patients treated in Western Region Hospital (WRH) and Manipal Teaching Hospital (MTH) respectively. Among them about 3034 (44%) and 1534 (29%) patients received antibiotics in WRH and MTH respectively. Demography of the patients who received antibiotics suggests that there were significantly different distribution of age, gender and races in two hospitals. Further, the age of patients in MTH was significantly (*P*= .000) higher than the age of Patients in WRH. Similarly, there were association between gender of patients, races of the patients and Hospitals (*P*=.001, .000). The patients' demography is given in Table 4.1.

Table 4.1 Demography of the patients

Demographic	**Groups**	**WRH** (n=3034)	**MTH** (n=1534)
Age of the patients	Mean	24.36 ± 28.017	26.83 ± 37.370
Gender of Patients (%)	Male	47.33	41.97
	Female	49.77	54.77
	Missing	2.50	3.26
Races of Patients (%)	Brahman	29.41	36.28
	Chhetri	14.28	16.18
	Mangolian	15.96	15.78
	Newar	5.11	2.62
	Others	31.52	20.76
	Missing data	3.73	8.38

4.1.2 Medicine Used for the treatment: Altogether 16895 and 8781 medicine were use in the treatment of 3034 and 1534 study patients over 4 months of period in WRH and MTH respectively. Average number of medicine use in MTH (5.75 ± 2.64) was significantly higher (*P*=.000) than average number of medicine used in WRH (5.59 ± 3.06). Anatomical therapeutic classification (ATC) of prescribed medicine suggests Antimicrobial (J) were highly prescribed medicine (40% in WRH and 32% in MTH) in both the hospitals followed by Drug acting on musculo-skeletal system (M) and Drug acting on alimentary tract (A). Further information is given in Fig 4.1.

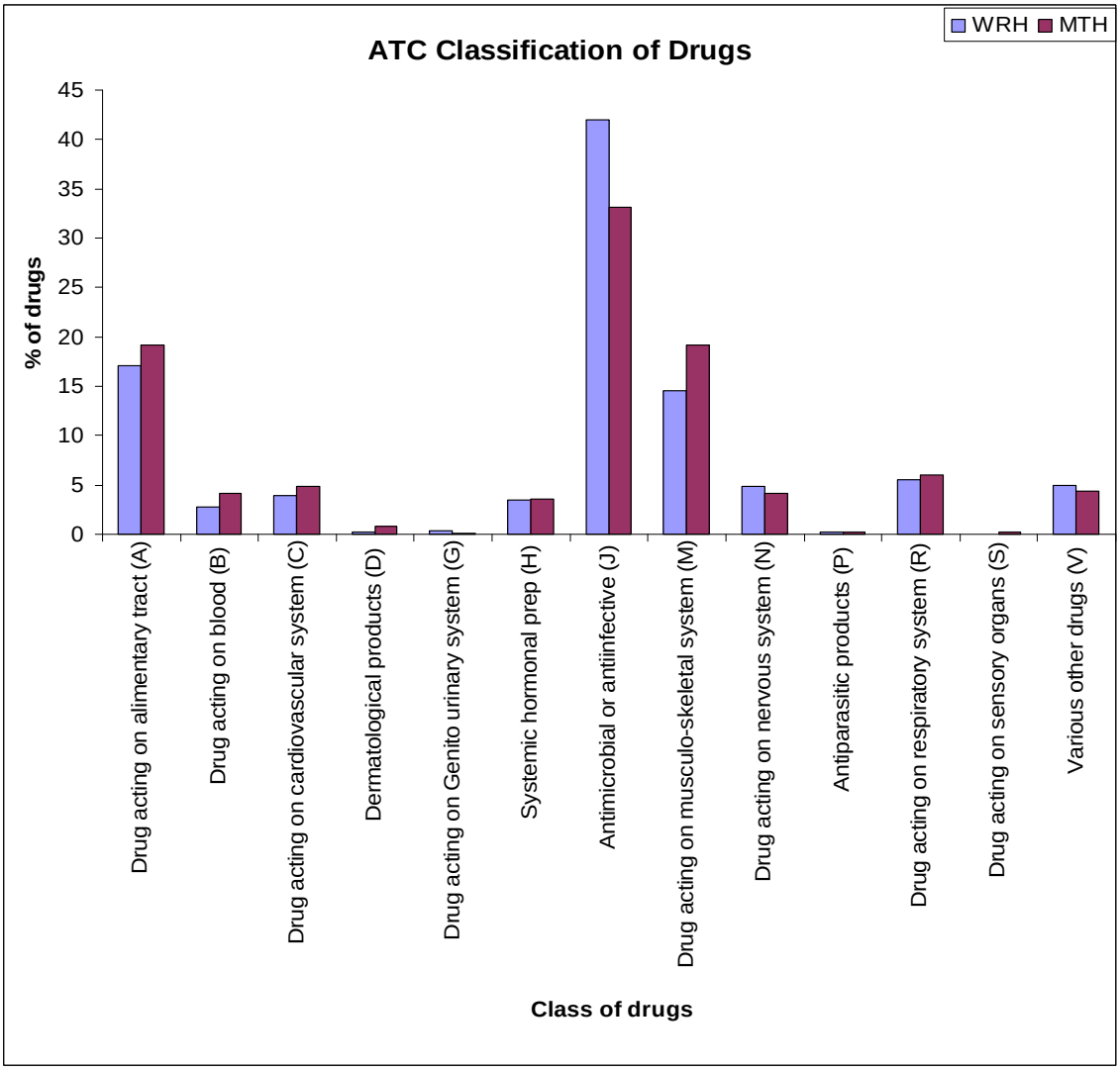


Figure 4.1 Anatomical therapeutic classification of prescribed medicine

4.1.3 Antibiotics use: Altogether there were 6825 and 2808 antibiotics were used in 3034 and 1534 patients in WRH and MTH respectively. Mean number of antibiotics use in WRH (2.25 ± 1.14) with range (Min 1 and Max 9) was significantly higher (*P*=.000) than MTH (1.84 ± .915) with range (Min 1 and Max 7). Further study found that 24% and 42% of patents received 1 antibiotic in WRH and MTH respectively. Around 45% of patients in WRH and 40% of patients in MTH were treated with 2 antibiotics during their treatments. Further few patients received up to 8-9 antibiotics during their treatment periods (Fig.4.2).

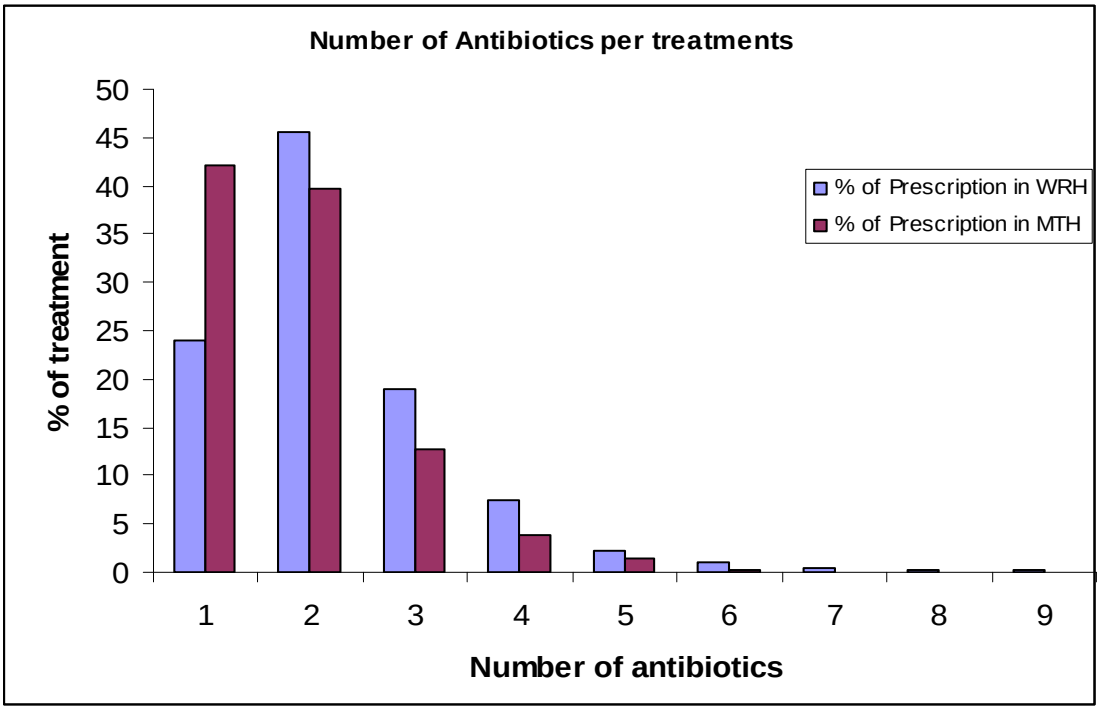


Figure 4.2 Number of antibiotics per treatment

Further it suggests that Cephalosporin, Penicillin and Quinolone were prescribed alone in 519, 91 and 60 treatments in WRH and 276, 183 and 84 treatments in MTH. Aminoglycoside and Cephalosporin were prescribed together in 651 and 173 patients in WRH and MTH respectively. Similarly, Cephalosporin and Macrolides were prescribed together 308 and 63 times in WRH and MTH respectively. Combinations of antibiotics used in the treatments are elaborated in Appendix C.

4.1.3.1 Category of antibiotic used: A total of 6825 and 2808 antibiotics were prescribed in WRH and MTH respectively over the period of 4 months. While categorizing we found that Cephalosporin group of antibiotic was highly prescribed constituting 27 and 34 percent of total antibiotic prescribed in WRH and MTH respectively followed by Penicillin (24% in WRH and 13% in MTH) refer Fig 4.3.

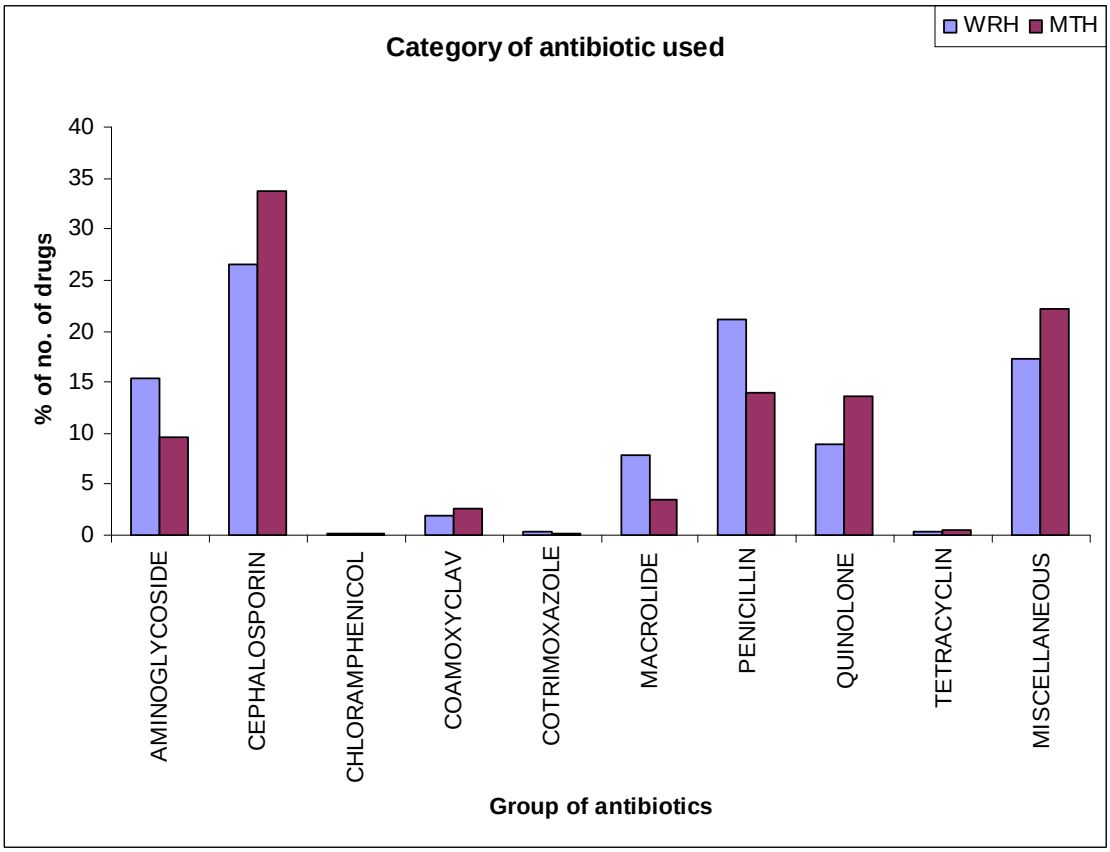


Figure 4.3 Category of antibiotics used

Further, we calculated the number of antibiotics per prescription which again suggests about 0.62 and 0.60 Cephalosporin per treatment in MTH and WRH respectively and was significantly higher in MTH (*P*=.000). Similarly, use of Aminoglycoside and Macrolide were significantly high in WRH shown in Table 4.2.

Table 4.2 Category of antibiotic per treatment

Group of Antibiotics	WRH	MTH	*P*-value
Aminoglycoside	.35 ± .49	.18 ± .39	.000
Cephalosporin	.60 ± .58	.62 ± .64	.000
Co-amoxyclav	.04 ± .22	.05 ± .23	.321
Cotrimoxazole	.01 ± .09	.00	-
Macrolide	.18 ± .39	.06 ± .25	.000
Penicillin	.48 ± .82	.25 ± .49	.000
Quinolone	.20 ± .42	.25 ± .48	.000
Tetracycline	.01 ± .08	.01 ± .09	.249
Others	.39 ± .62	.40 ± .59	.684

4.1.3.2 Antibiotics Vs Departments: We found that antibiotic were most frequently prescribed by the departments of Pediatrics (34%), followed by Medicine (25%), Surgery (16%), OBG (15%), Orthopedics (4%), NICU (3%), ICU (1), Neurosurgery (0.53%), Oncology (0.16), ENT (0.13) and Dental (0.03) in WRH whereas, department of Medicine (29%), OBG (20%), Pediatrics (15%), Surgery (15%), ENT (6%), Orthopedics (6%), NICU (3%), Dental (1%), Oncology (0.46), ICU (0.39%) Neurosurgery (0.39%), Dermatology (1%) and Emergency (052%) in MTH. The study also found that mean number of antibiotic used by departments and WRH were significantly higher than mean number of antibiotic use by departments and MTH (*P*= .000, .000). The Fig. 4.4 shows the marginal means of antibiotics in the various departments in two hospitals.

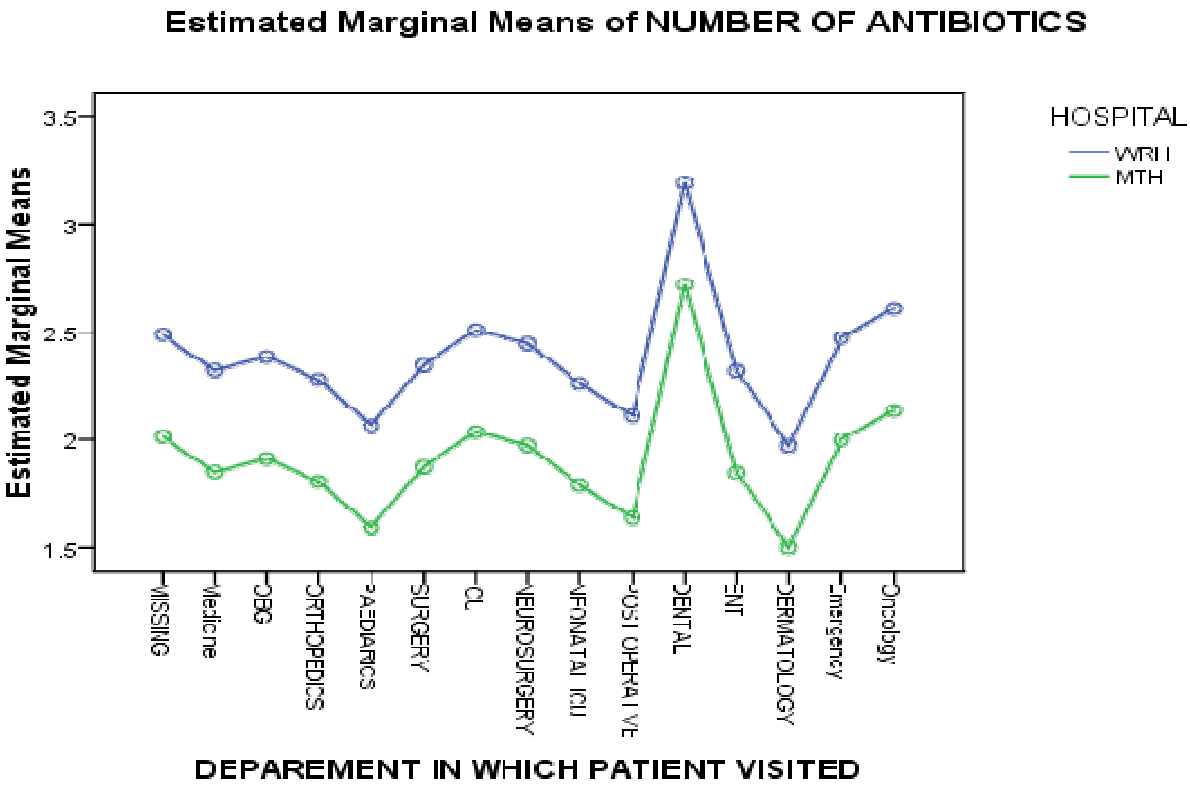


Figure 4.4 Mean of number of antibiotics used in various departments of two hospitals

4.1.3.3 Antibiotics Vs co-morbid conditions: The study found that more numbers of times antibiotics were used for prophylactic purpose (34% in WRH and 53% in MTH) in both the hospitals. Other co-morbid conditions include Respiratory Tract Infections (RTI) [21%], intra-abdominal infection (13%), soft tissue infection (11%), Sepsis (5%), Urinary Tract Infection (UTI') [4%], Gastroenteritis (4%), Bone and Joint Infection (4%), Others (2%), CNS Infection (0.89%), Surgical site infection (0.2%), Pelvic Infection (0.07%) and Ear-nose-throat Infection (0.07%) in WRH. Similarly, Respiratory Tract Infection (15%), Urinary Tract Infection (7%), Intra-abdominal infection (6%), Gastroenteritis (5%), Ear-nose-throat Infection (5%), Bone and Joint infection (4%), Sepsis (2%), others (0.85%), Soft tissue Infection (0.26%), Pelvic Infection (0.26%), CNS infection (0.13%) and Surgical Site infection (0.07%) were in MTH. Further, study suggests that antibiotic used in different co-morbid condition and

WRH were significantly higher in WRH compared to MTH (*P*=.000, 0.001). Fig. 4.5 shows the marginal mean of antibiotics in different department in two hospitals.

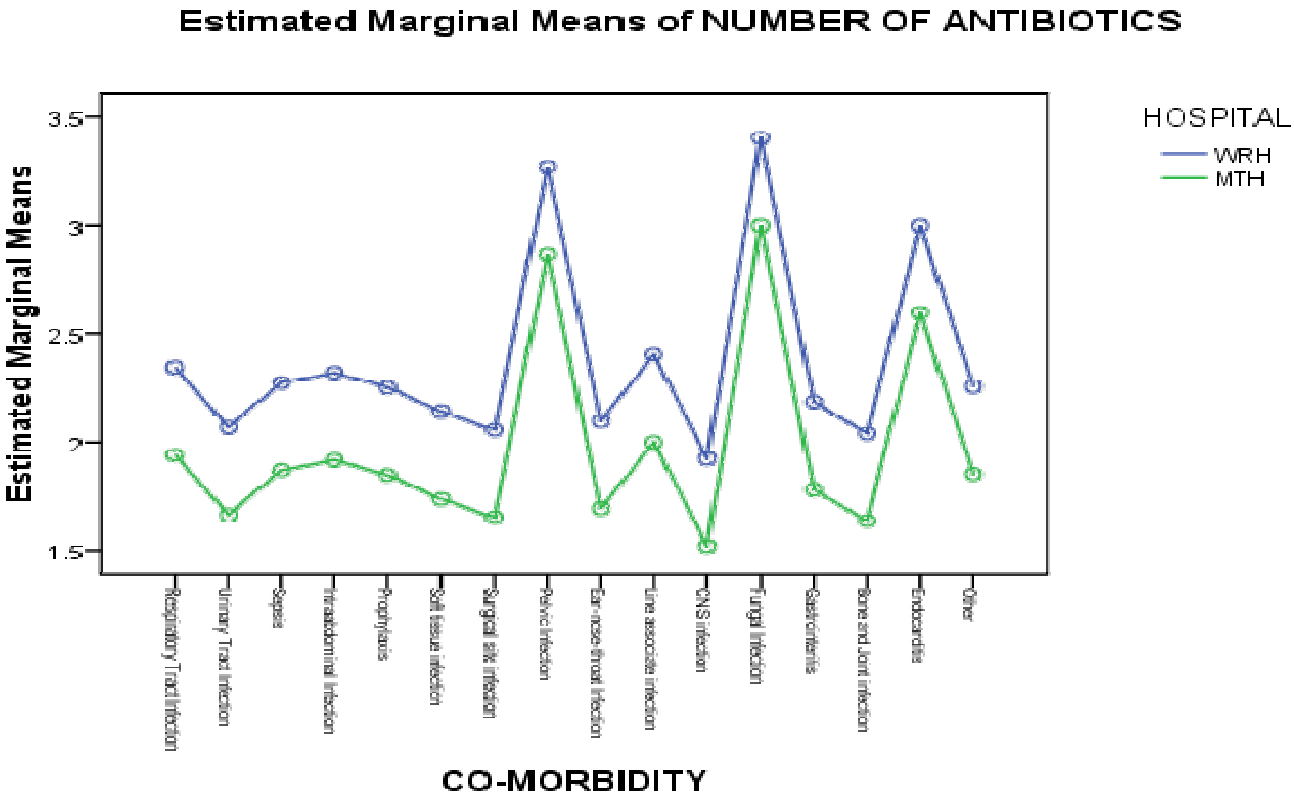


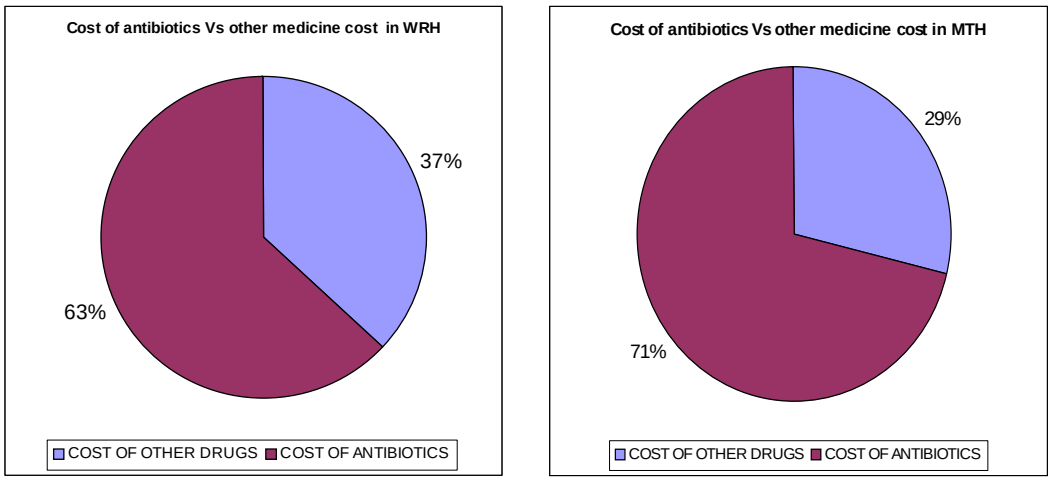
Figure 4.5 Mean of number of antibiotics used in various co-morbid conditions of two hospitals

Further, while studying the group of antibiotic in per treatment of co-morbid condition found that Cephalosporin group of antibiotics were highly prescribed in most of infectious conditions which include Sepsis (0.81 in WRH and 0.53 in MTH), UTI (0.8 and 0.52), Respiratory tract infection (0.50 and 0.53), Intraabdominal Infection (0.57 and 0.93), CNS infection (0.89 and 0.34), Gastroenteritis (0.81 and 1.05), Prophylaxis (0.53 and 0.58) and so on in WRH and MTH respectively. Similarly, Aminoglycoside were highly prescribed in Sepsis (0.87 in WRH and 0.83 in MTH). Like wise penicillin (0.67 and 0.33) and Macrolide (0.38 and 0.19) were highly prescribed in RTI in WRH and MTH respectively (Appendix C).

4.1.3.4 Defined Daily Dose of Antibiotics: Study found that DDD/100 bed-days of Cloxacillin (6.9), Cefuroxime (P) [0.28], Cefotaxime (5.49) and Cefriaxone (11.57) in WRH were 8.6, 8.5, 4.6 and 2.2 fold higher than DDD/100 bed-days of MTH. Similarly DDD/100 bed-days of Co-Amoxyclav (P) [1.84], Azithromycin (10.21), Gentamicin (3.42), Amikacin (2.56), Ofloxacin (1.28), Ciprofloxacin (4.58) and Metronidazole (P) [11.50] in WRH were 4.1, 8, 3.9, 3.1, 42.7, 3.2 and 4 fold higher than DDD/100 bed-days in MTH respectively. Overall, antibiotic use in WRH (68.45 DDD/100 bed-days) was 3 fold higher than MTH (22.21 DDD/100 bed-days). The details of DDD Details are given in Appendix C.

4.1.4 Cost of drug therapy: A total cost of NRs 4889166.84 ($67769.08) and 1937959.18 ($26862.19) of medicine were used for the treatment of 3034 and 1534 patients who received antibiotic in WRH and MTH respectively over 4 months of times. About 63 and 70 percent of total cost of all medications were antibiotics in WRH and MTH respectively. The cost antibiotic in WRH and MTH among total costs are given in Fig 4.6 (A and B) respectively.

Similarly, study found that there was significantly higher mean cost of medicine [1611.55 ($22.54) ± 2454.81] in WRH with the range of 40309.02 (Min-7.4, Max-40316.42) compared to mean cost medicine [1266.33 ($17.67) ± 1741.72] with the range of 21991.3 (Min-5.27, Max-21996.57) in MTH. However, the mean cost of antibiotics was not statistically different in WRH [1007.52 ($14.09) ± 1509.83] and MTH [892.88 ($12.49) ± 1405.56].



(A) **(B)**

Figure 4.6 Antibiotic cost comparison in WRH (A) and MTH (B)

4.1.4.1 Comparing cost among various co-morbid conditions: Moreover, mean cost comparison in various co-morbid conditions found that cost antibiotic in treatment of CNS infection in MTH was higher (92.17%) among all other co-morbid condition. Costs of antibiotics were between 70-90% of total cost in most of the co-morbid conditions. Further more information is given in Appendix C. Likewise, mean cost of antibiotics was significantly different among the co-morbid conditions (*P*-value = .000) but not significantly different between two hospitals (*P*-value = .194)

4.1.4.2 Cost of prescription and cost of antibiotics as per department: Study found that cost of treatment of Oncology and ICU were higher among all other departments. Costs of antibiotics in most of the departments were between 50-90% of total cost (appendix C). Further, the cost of antibiotics in different departments and hospitals was highly significant in WRH than MTH (*P*-value = .000, .001)

4.1.5 Antibiotic resistance: In this study, we found 2467 samples were tested for culture MTH which include Blood (n=209), Urine (n=1238), Pus (n=386), Body fluid (n=360) and Sputum (n=274). In comparison, only 157 samples were tested for culture in WRH which include Blood (n=101), Urine (n=30), Pus (n=16), Body fluid (n=7) and Sputum (n=3). Among the specimen tested for culture only 24% in MTH and 28% in WRH showed growth (appendix C).

The comparison of resistance pattern of E.coli, S. aureus, Pseudomonas, Enterococus in two hospitals are given in Fig.4.7, 4.8, 4.9 and 4.10 respectively and where as the resistance pattern of other organism Appendix C. study found that Cephalexin, Nalidixic acid, Erythromycin, Cotrimoxazole and Tetracycline were 100% resistant to E. Coli in WRH whereas Amoxyclav, Carbenicillin were 100% resistance in MTH. Further, Piparacillin, Ampicillin, Cephalexin, Penicillin, Cefotaxime were 90, 88, 81, 89, and 76 percent resistance in MTH. Many antibiotics were not tested against E.coli in WRH.

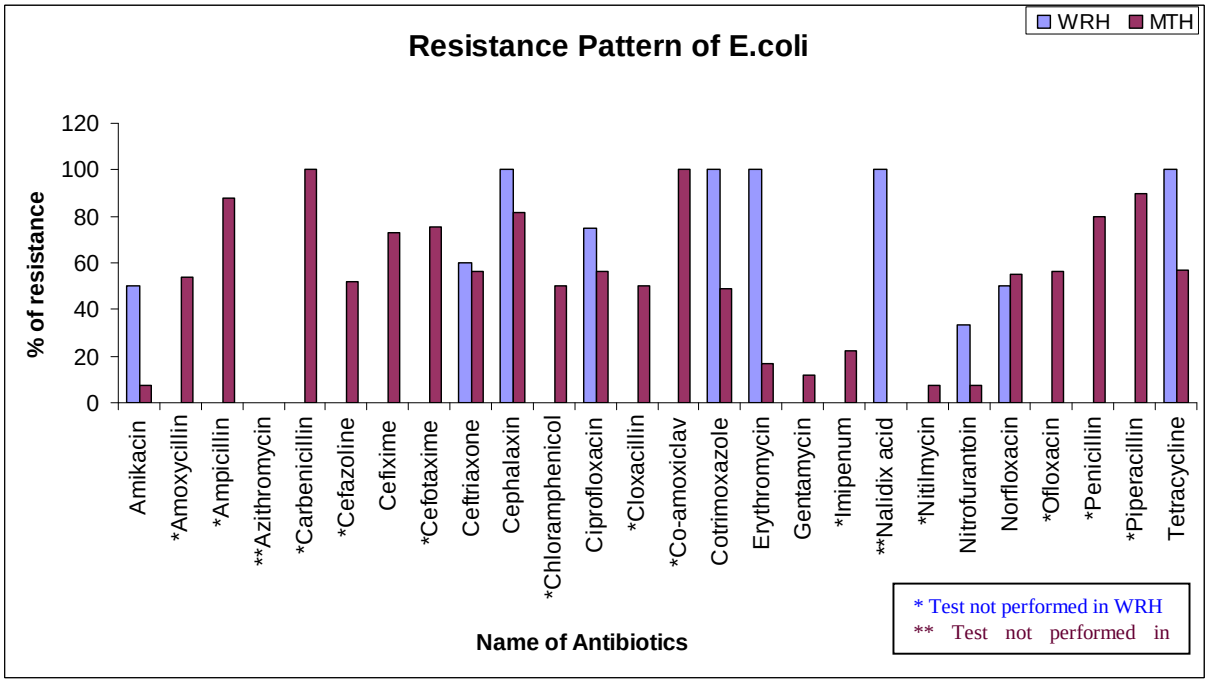


Figure 4.7 Resistance pattern of E. coli

Resistance pattern of S. aureus suggest that Cephalexin, Norfloxacin in MTH were 100% resistant. Where as Piperacillin, Cotrimoxazole, Cloxacillin and Penicillin were 88, 86, 75 and 74 percent resistant to S. aureus in MTH respectively. Similarly, Cloxacillin, Gentamicin, Ampicillin, Ceftriaxone were 100, 60, 50 and 50 percent resistance in WRH.

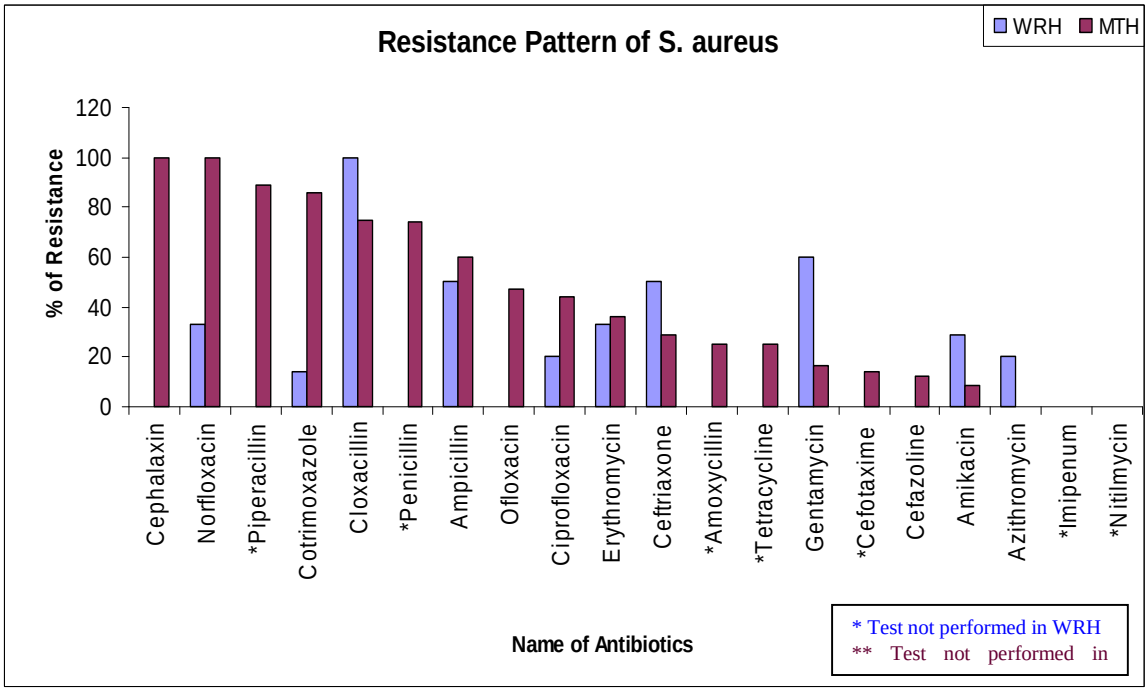


Figure 4.8 Resistance patterns of S. aureus

Further, Cephalexin in MTH was found 100% resistance to *pseudomonas* sp. Similarly, Ceftriaxone, Erythromycin and Carbenicillin were found to be 33, 33 and 30 percent resistance in MTH where as Nalidixic acid, Gentamycin and Erythromycin were 50, 33 and 33 percent resistance to *S. aureus* respectively. Antibiotic like Cephalexin, Carbenicillin, Penicillin, Cefotaxime, Tobramycin etc. were not tested in WRH.

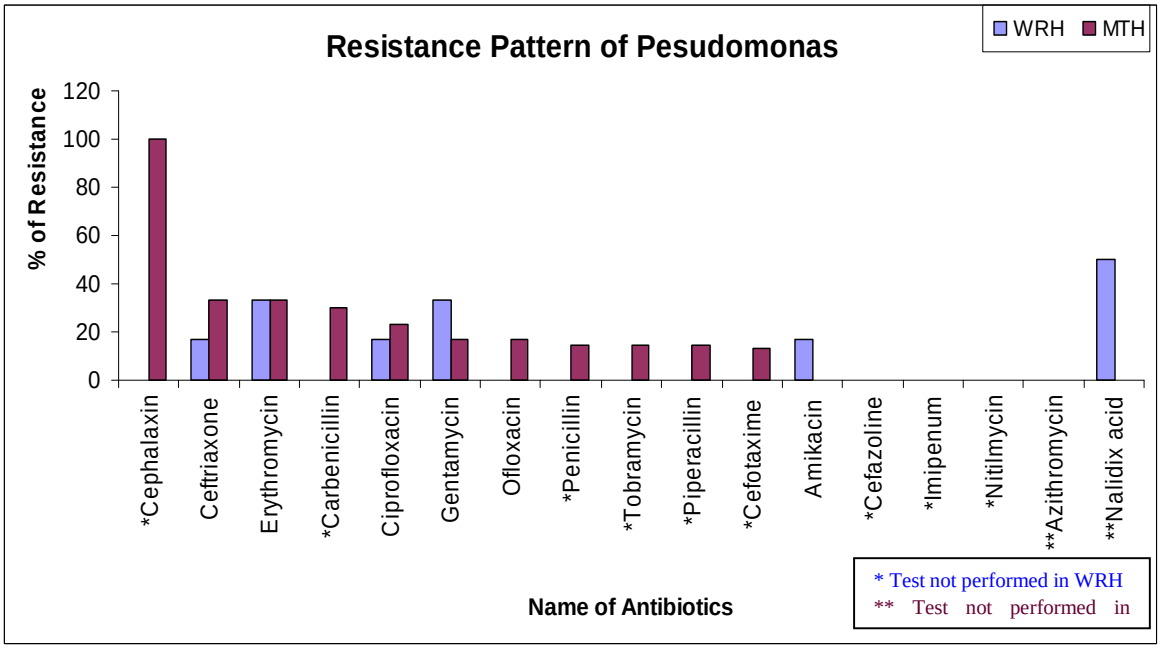


Figure 4.9 Resistance pattern of pseudomonas

Enterococcus was found 66.7, 57, 50 and 50 percent resistance to Ampicillin, Ciprofloxacillin, Co-trimoxazole and Piparacillin where as, Amoxicillin, Ceftriaxone, Cephalexin, Erythomycin, Imipenum and Nitrofurantoin each was 33.33% resistance.

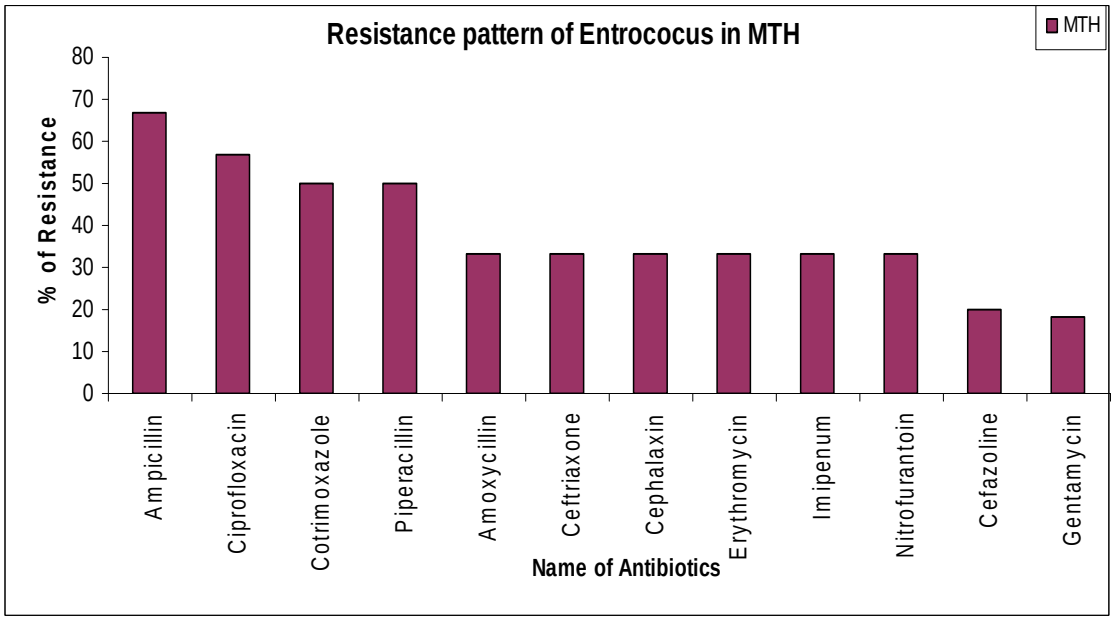
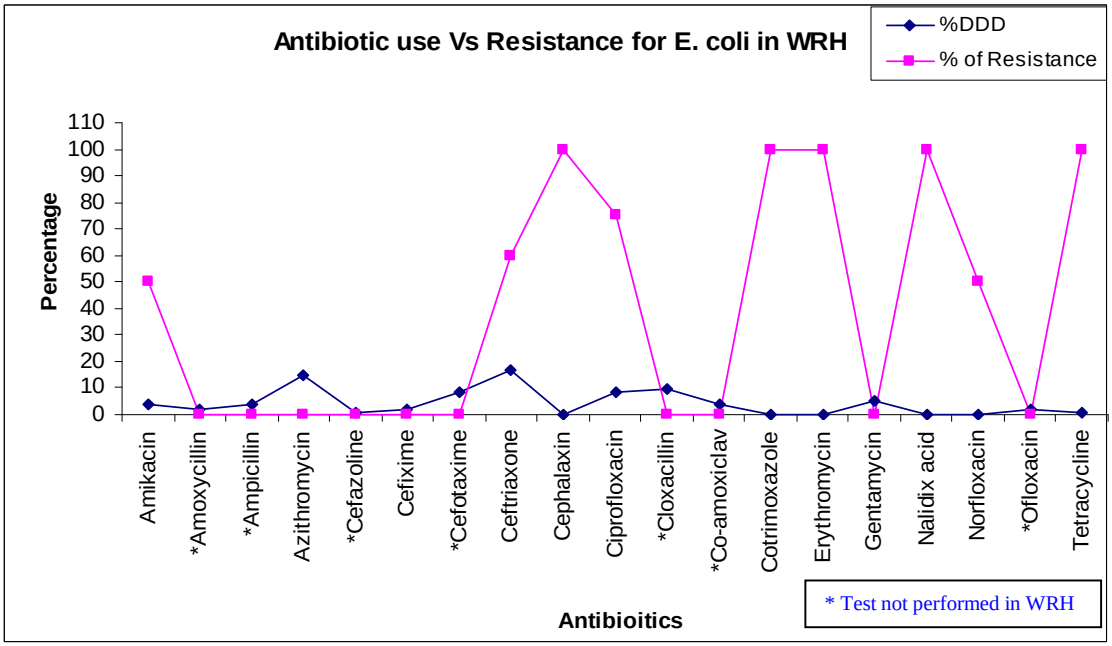
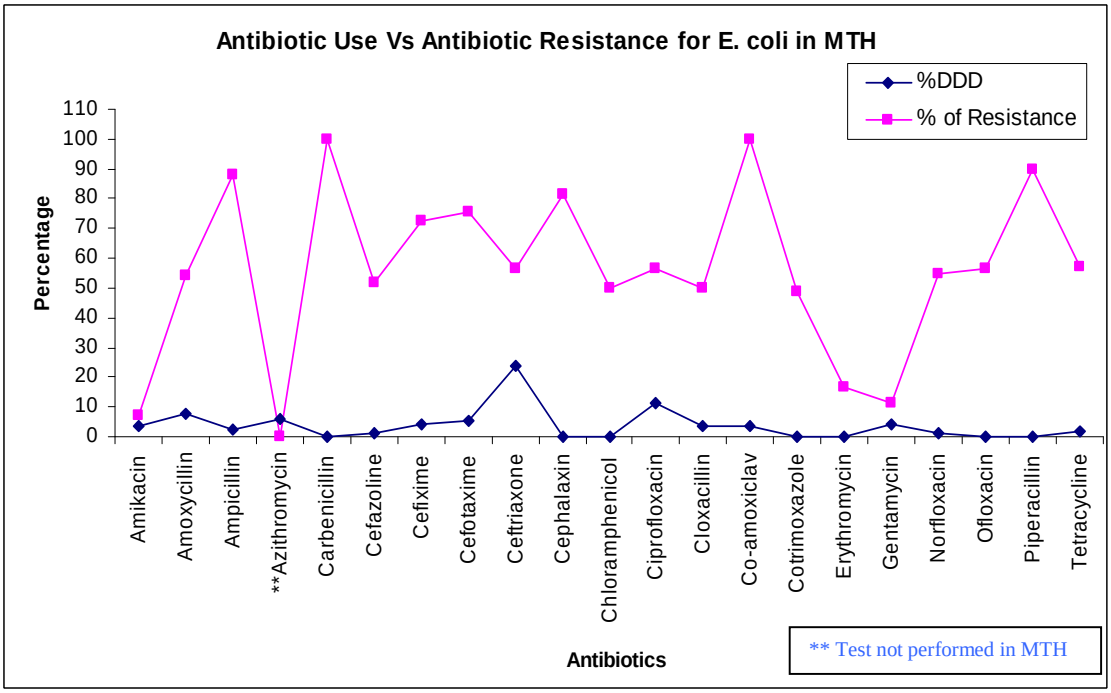


Figure 4.10 Resistance pattern of Enterococcus

4.1.5.1 Comparing use and resistance: While comparing we found that many drugs which were not used during the study periods like Co-trimoxazole, Erythromycin, and Nalidixic Acid were completely resistance to *E. coli* (Fig 4.11).



(A)



(B)

Figure 4.11 Comparing antibiotic use and resistance

4.2. Assessing Appropriateness: Appropriateness of treatment of enteric fever was assessed in separate 100 patients from each hospital. In section we studied the following parameters

- Demography of patients suffering from enteric fever
- Medicine used in the treatments
- Antibiotic use
- Appropriateness of treatments
- Cost of therapy

4.2.1 Demography of Patients suffering from Enteric Fever: The mean age of the patients was 22.81 ± 20.52 and 29.13 ± 17.84 in WRH and MTH respectively. More number of patients was from Brahman race. Mean duration of stay was higher in MTH (5.64 ± 2.34) compared to WRH (3.74 ± 1.58) (Table 4.3).

Table 4.3 Demography of Patients suffering from Enteric Fever

Demography	Parameter	WRH	MTH
Age	Mean	22.81 ± 20.52	29.13 ± 17.84
Gender	Female	45	46
	Male	55	54
Races	Brahman	54	47
	Chhetri	10	22
	Mangolian	13	6
	Newar	0	8
	Others	15	17
	Missing	8	0
Duration of stay	Mean	3.74 ± 1.58	5.64 ± 2.34
Departments	Medicine	63	84
	Pediatrics	36	15
	ICU	1	1

4.2.2 Medicine used in the treatments: Altogether, 565 and 796 drugs were used for the treatment of 100 patients from WRH and MTH respectively. Mean number of medicines used in the treatments of WRH (5.80 ± 2.37) was not statistically different (*P* = .154) from MTH (7.91± 2.85). Anatomical therapeutic classification (ATC) of prescribed medicine (Fig. 4.12) suggests antimicrobial class of drugs were highly prescribed in both hospitals.

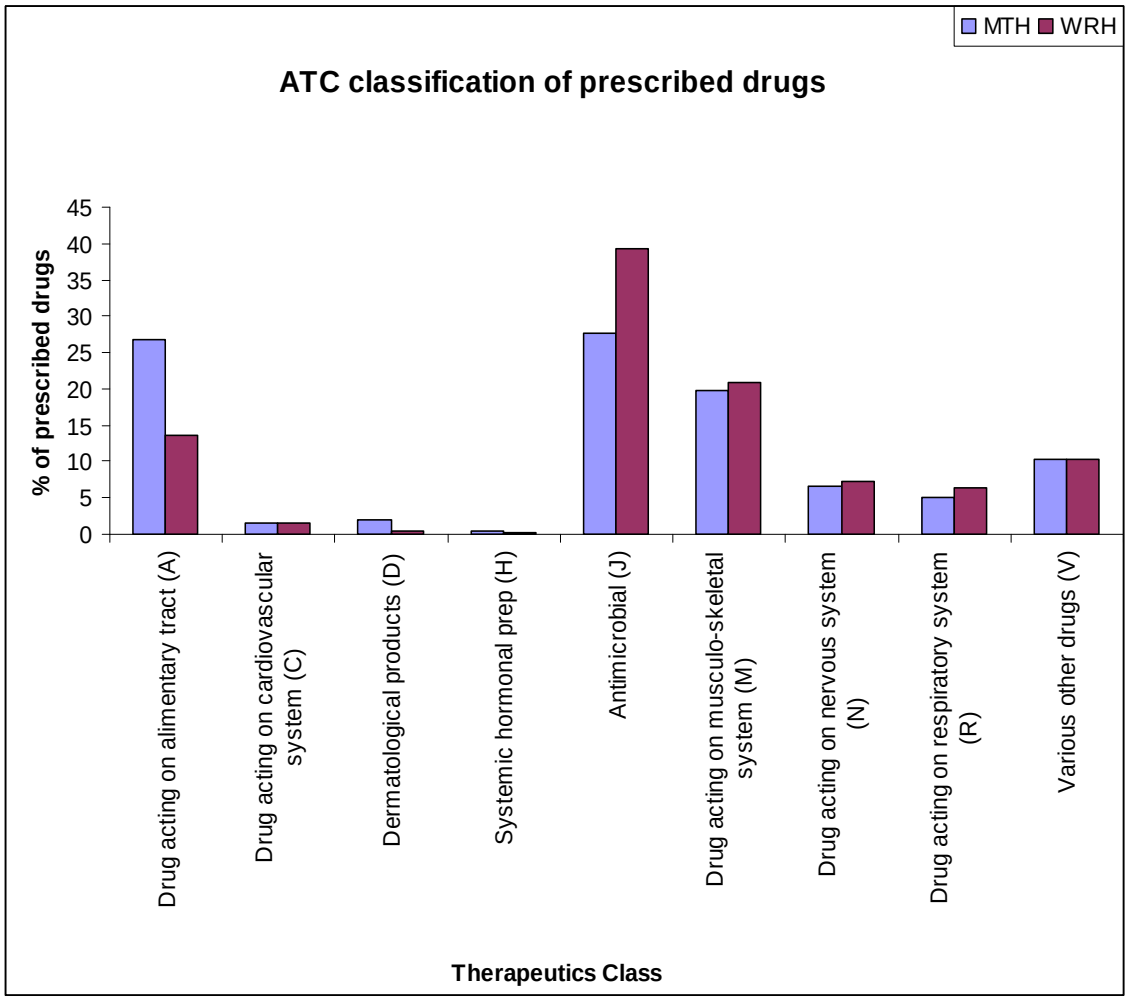


Figure 4.12 Anatomical therapeutic classification (ATC) of drug prescribed in Enteric Fever

4.2.3 Antibiotic used in the treatment of enteric fever: A total of 218 and 213 antibiotics were prescribed in WRH and MTH respectively for the treatment of 100

patients from each hospital. Mean use of antibiotics in WRH (2.18 ± .87) was not significantly different (*P* = .015) from MTH (2.13 ± 1.11). Further, study found that more than 20% of case was treated with 3 antibiotics in the both hospitals. Similarly 7% in WRH and 8% case in MTH were treated with 4 antibiotics (Fig. 4.13).

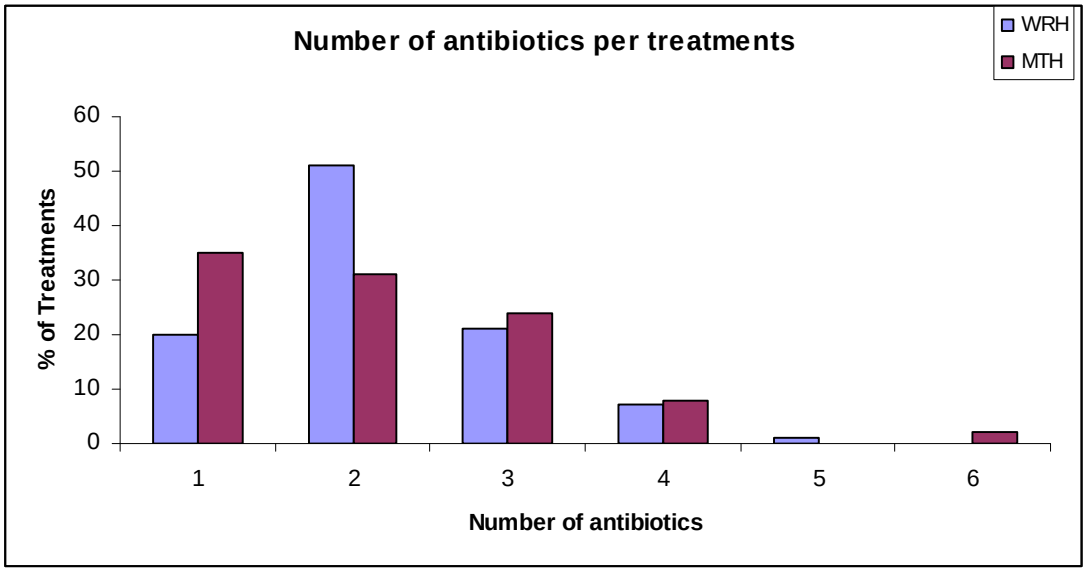


Figure 4.13 Number of antibiotic used in the treatment

Further we found that Cephalosporin was used alone for the treatment of enteric fever 16 times in WRH and 33 times in MTH. Similarly, Cephalosporin in combination with Macrolide was used in 49 times in WRH and 11 times in MTH. Likewise, Cephalosporin in combination with Aminoglycoside was used 30 times in WRH and 23 times in MTH (Appendix C).

4.2.3 Antibiotics Category: Study showed that Cephalosporin group of antibiotic were used widely to treat enteric fever in both hospitals. Around 1.12 Cephalosporin in MTH and 0.93 Cephalosporin in WRH were used per treatment. The use of Cephalosporin in two hospital is not significantly different. Where as, use of Macrolides in WRH was significantly higher than MTH (Table 4.4).

Table 4.4 Category of antibiotics used per treatment

Group of Antibiotics	WRH	MTH	P-value
Aminoglycoside	.33 ± .47	.24 ± .45	0.018
Cephalosporin	.93 ± .38	1.12 ± .50	0.052
Chloramphenicol	.02 ± .14	.00	-
Co-amoxyclav	.02 ± .14	.00	-
Macrolide	.54 ± .50	.12 ± .33	.000
Penicillin	.05 ± .22	.04 ± .20	0.497
Quinolone	.07 ± .26	.27 ± .57	.000
Tetracycline	.01 ± .10	.13 ± .34	.000
Miscellaneous	.21 ± .41	.18 ± .44	0.418

4.2.4 Appropriateness of treatments: The appropriateness analysis of the treatment of enteric fever patients was done using Medication Appropriateness Index (MAI) 10 points indicators (Table 4.5) and each indicator was evaluated by researcher using WHO guidelines (WHO 2003) as illustrated in methodology. While assessing we found that majority of indications were inappropriate based on WHO guidelines. Some common drug-drug interaction is given in Appendix C.

Table 4.5 Appropriateness analysis for Enteric Fever Treatment (n=100 / hospital)

	Appropriate		Marginally appropriate		Inappropriate	
Criterion	**MTH**	**WRH**	**MTH**	**WRH**	**MTH**	**WRH**
Indication	12	4	8	7	80	89
Effectiveness	12	1	44	47	44	52
Correct dosage	95	98	1	1	4	1
Correct direction	95	97	2	0	3	3
Drug-drug interactions	89	89	0	1	11	10
Drug-disease interaction	100	100	0	0	0	0
Practical directions	65	45	18	22	17	33
Least expensive alternative	7	7	3	1	90	92
Duplication with other drug	46	18	1	0	53	82
Duration of therapy	75	50	10	17	15	33
Average Score	**59.6**	**50.9**	**8.7**	**9.6**	**31.7**	**39.5**

4.2.4.1 Resistant pattern of Salmonella: Out of hundred patients very few were tested for culture sensitivity among the tested sample only 12 sample in MTH and 4 samples in WRH found growths. The resistant pattern showed that Nalidixic Acid and Co-timoxazole were more than 80% resistance in both hospitals whereas Ciprofloxacin were more than 50% resistant in both the hospitals. (Fig.4.14)

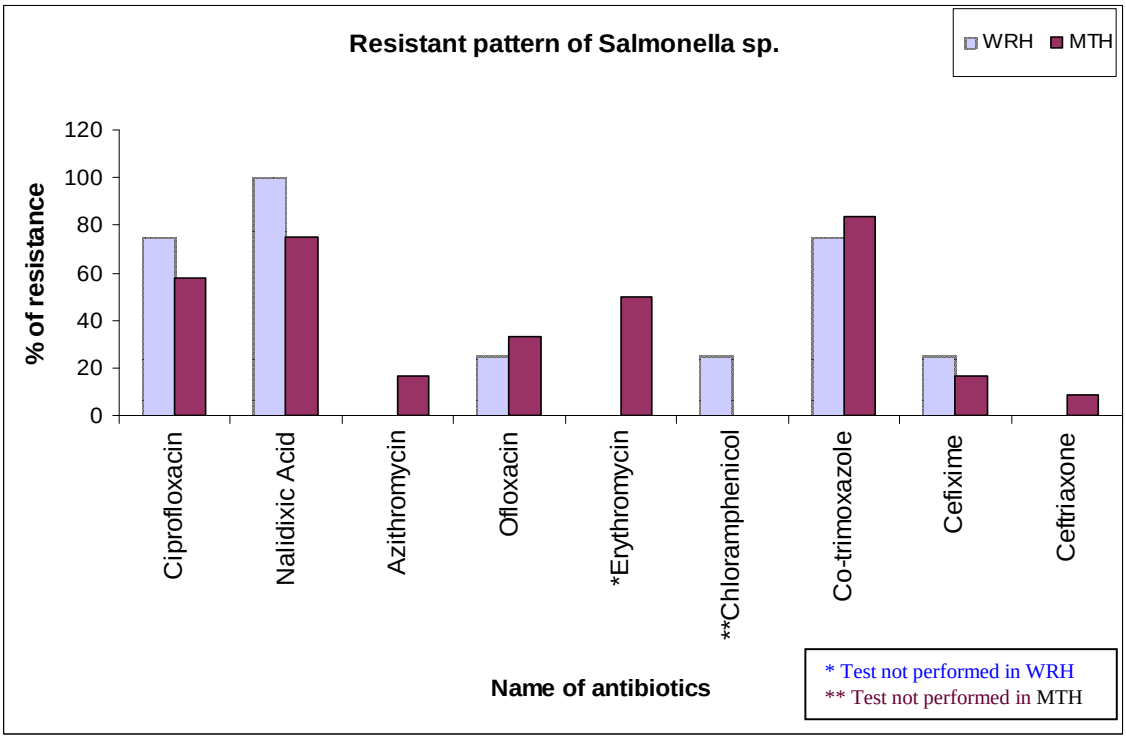


Figure 4.14 Resistance patterns of Salmonella species.

4.2.5 Cost of treatment of enteric fever: The mean cost of medication in enteric fever treatment in MTH and WRH was not significantly different. Similarly the mean cost of antibiotics in enteric fever treatment in both the hospitals was not statistically significant. The detail of cost is given in Table 4.7.

Table 4.6 Mean cost of per treatment of enteric fever in two hospitals

Parameter	WRH	MTH	*P*-value
Mean cost of prescribed Medication	1428.98 ± 1178.35	2279.07 ± 1533.49	.029
Mean cost of Antibiotics	1228.49 ± 840.28	1523.86 ± 1054.19	.422
% of Antibiotic Cost	86	67	-

4.3. Controlling System of Antibiotic in Tertiary Care Hospital: Controlling system of antibiotics were study using Donabedian model of quality of medical care which has the three component structure, process and outcome. To study the situation of controlling system of antibiotics I study the structure and process involved in the antibiotic use (Fig 1.1). Altogether 47 people were interviewed. The categorization of interviews are given in appendix C.

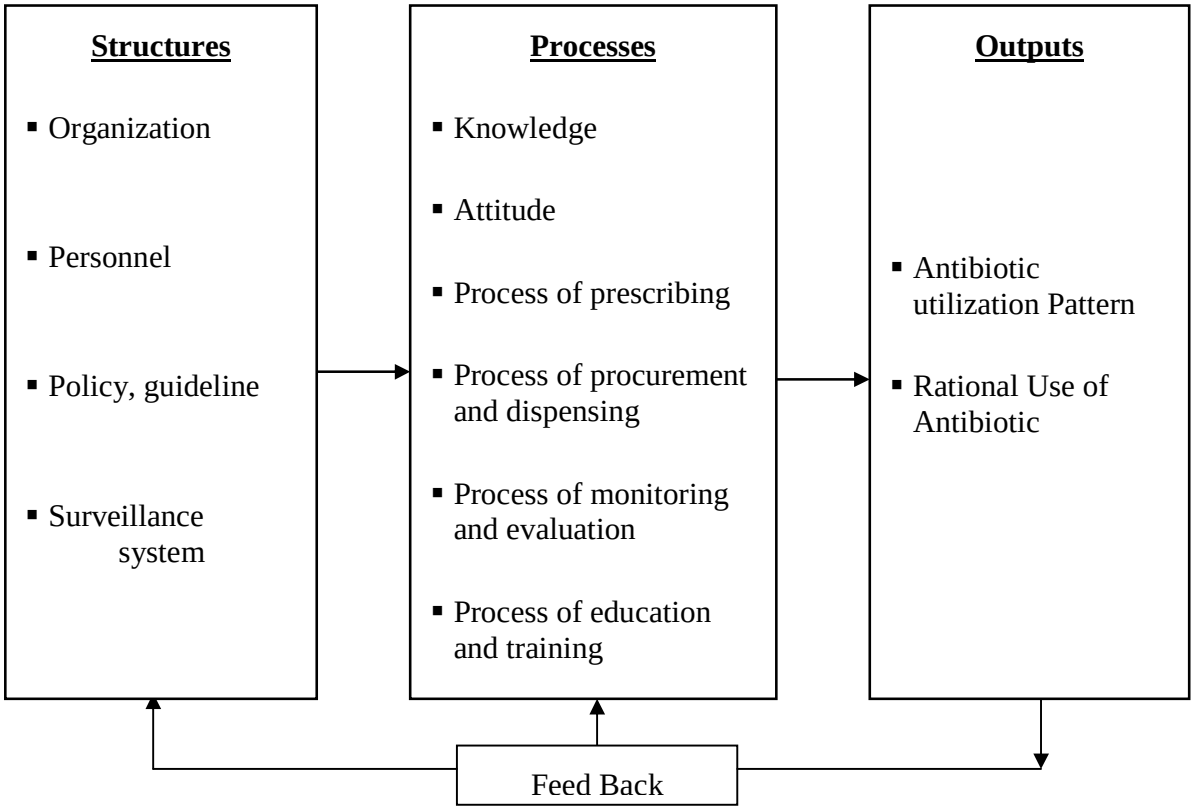


Figure 1.1 Conceptual framework of the study based on Donabedian

4.3.1 Structure Component: The elements of structure components in the controlling system of antibiotics in tertiary care hospitals include organization, personnel, policy, and guideline and surveillance system. The analysis of elements of structure components are presented below

4.3.1.1 Organizational structure

Interviews and documentation analysis provides two different picture of organization working on controlling system of antibiotics in public and private hospitals.

Public hospitals do not have any such organization working on controlling system of antibiotics.

"… we have not formulated any committee as such but we have culture sensitivity testing facility and our clinician prescribes antibiotic based on culture report." (Interview 15)

"... no committee and no mechanism to monitor, we use antibiotic by hit and trial method." (Interview 30)

Although, private hospitals are newly established as compared to the public hospitals, but it gives opposite picture. Private hospitals have both Drug and Therapeutics Committee (DTC) and Antimicrobial Committee (AC) or infectious control committee. The summaries of organizational structure in the hospitals are given below in Table 4.7.

Table 4.7 Organizational structure in the hospitals

Name of Hospital	DTC	Antimicrobial Committee
Manipal Teaching Hospital (MTH)	Yes	Yes
Western Regional Hospital (WRH)	No	No
Bir Hospital	No	No
Dhulikhel Hospital	Yes	Yes
KIST Hospital	Yes	Yes

The performances of the organizations in the private hospitals are summarized below in the Table 4.9.

Table 4.8 Performance of the organization in private hospitals

Parameter	MTH		Dhulikhel		KIST hospital	
	DTC	AC	DTC	AC	DTC	AC
Document that indicates its functions and membership	Yes	Yes	Yes (Not shared)	Yes (Not shared)	Yes (Not shared)	Yes (Not shared)
Budget allocation	No	No	No	No	No	No
% DTC members who attend > 50% of meetings	100%	100%	>90%	>90%	100%	100%
No. DTC meetings per year	2-3	2	1-2	1 (As per need)	6	Not fixed (As per need)
Are the meeting minutes recorded	Yes	Yes	Yes (Not shared)	Yes (Not shared)	Yes (Not shared)	Yes (Not shared)
Have STGs been developed/adapted and implemented?	No	No	Developed for few disease		In the process	
Has the committee organized any educational activities?	No	No	No	Yes	No	Yes

Looking at the performances and interviews comments indicate that the organizations in the private hospitals were not proactive.

"… there one committee headed by…..… trying to bring out some policy. I think there is some effort going on but so far in practice everyone is free to prescribe." (Interview 41)

"… we used to meet very frequently but now frequency has come down" (Interview 37)

"… we usually meet six monthly but it also depend on the necessity" (Interview 24)

Based on documentation analysis and interview the suggested the structure of DTC and Antimicrobial Committee is given below in Fig 4.15.

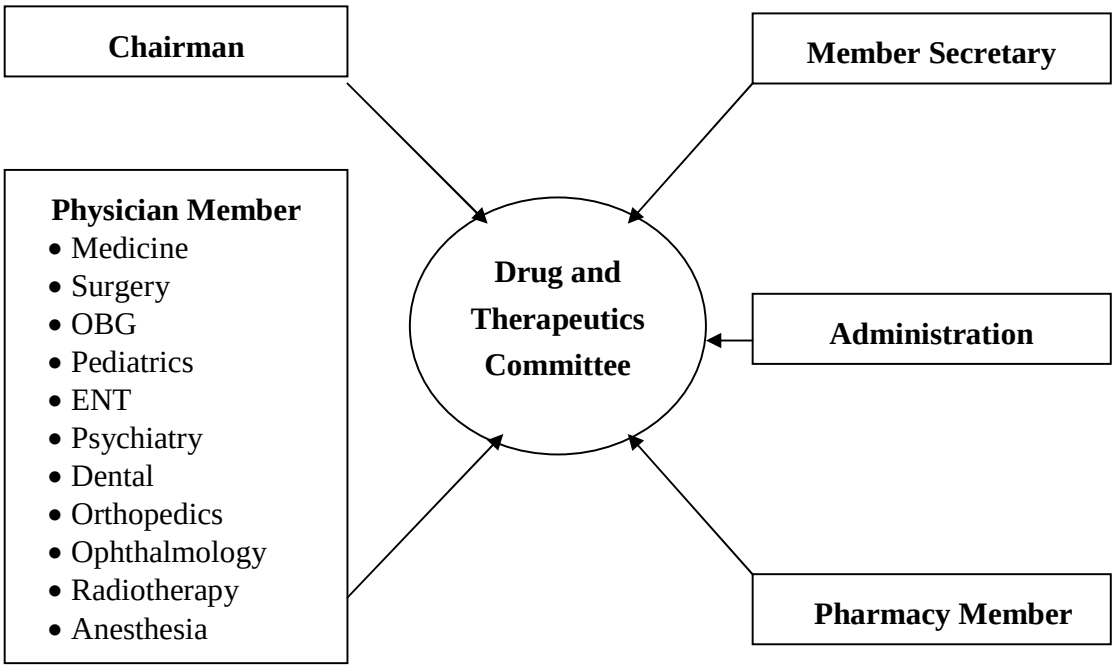


Fig 4.15 Structures of Medicine and Therapeutics Committee

Similarly the structure of antimicrobial committee includes the 5-7 members from various departments like Medicine, Pharmacy, Microbiology, Surgery, Pediatrics, Orthopedics, Obstetrics and gynecology.

The antibiotic committees are mainly focused on the formulation of antibiotic treatment guidelines for the hospital. Similarly DTC has major role in the selection of antibiotics and took some initiative like banning of the irrational combination of antimicrobial like Ampicillin+Cloxacillin, Amoxicillin+Cloxacillin etc.

4.3.1.2 Personnel Involved: The personnel involved in antibiotic controlling system were clinicians, microbiologists and pharmacists. The concept of Infectious Disease Specialist (IDS) working on antimicrobial use and resistance were not found in any of the study hospitals. In absences of IDS, clinicians rarely seek the advice of either microbiologists or pharmacists in case of any problem related to antimicrobial use or resistance. Usually they decide individually. However, complicated case was discussed in the department within the faculty members.

4.3.1.3 Policy and guideline: Result from documentation analysis and interview suggest none of the study hospitals have written antibiotic policy. However, certain policy was followed in certain department based on understanding i.e. verbal policy.

"…we discuss within the department and senior faculty members before starting fourth generation cephalosporin (Cefepime)." (Interview 2)

In one of the private hospital has prepared guideline follows as policy for certain disease. In another hospital, there is intradepartmental guideline.

"*…Guideline for common diseases like pneumonia, enteric fever, sepsis.*" (Interview 19)

"…In few cases of illness we have the guideline but not for all …prepared by our department from the initial time ... Like in meningitis, pneumonia, neonatal sepsis." (Interview 2)

However, in absence of guideline, majority of clinician follow standard textbooks as guideline

"…there is no policy. We go through latest text book guidelines like Harrison." (Interview 4)

"…no, we do not have any policy but it is a necessary thing… we go through the literature and books like Davidson, Harrison." (Interview 26)

Many interviews were not aware about any existing policy or guideline in the hospital. The guideline which was available in the hospital was not updated after their formulation.

4.3.1.4 Surveillance: Documentation analysis and interview suggest that there is no surveillance on antibiotic use in any of the hospital. However, there were few individual studies done in the past on drug utilization but no periodic surveillance on use.

Four out of 5 hospital enrolled in this study is involved in the national antibiotic resistant surveillance program conducted by Nepal Public Health Laboratory. The surveillance includes common 7 organism like Salmonella, Shigella, N. gonorrhea, H. influenza, S. pneumonia, ESBL- E.coli and Vibrio. The structure of National Surveillance program is given below. The highlighted hospitals in the below diagram are the hospitals where study was conducted.

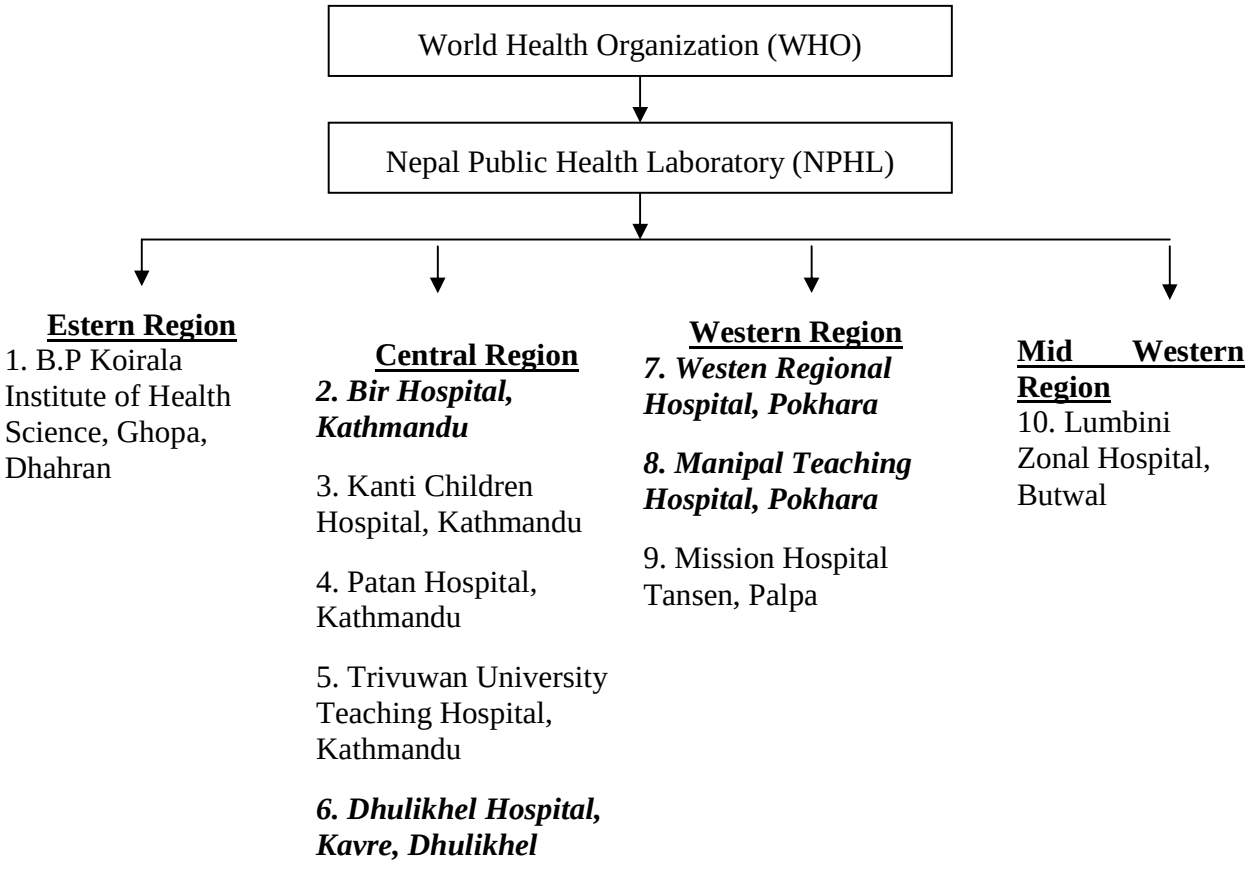


Fig 4.16 Surveillance structure in Nepal

This surveillance network disseminates their information 3 times in year by conducting workshop at 3 different places in the countries. The activities of NPHL are given below in the box.

Activities of National Public Health Laboratories

- AMR monitoring, validation and preservation of isolates
- Coordination with participating laboratories
- Monitor and evaluate the performance
- Organize training, workshops and orientation sessions
- Technical supports to the participating laboratories
- External quality control system and validation
- Feedback to participating laboratories at the end of the year
- Compiling AMR surveillance data and their dissemination

Moreover, documentation analysis suggests that one of the private hospital used to disseminate their antibiotic resistance surveillance report by publishing in their quarterly published drug bulletin. However, such activity was not found in the recent days.

4.3.2 Process Component: The element of process component included in the situation analysis of antibiotic controlling system includes knowledge, attitude, process of prescribing, process of procurement, and dispensing, process of monitoring, and evaluation, process of education and training. The detailed analysis of the process components are given below.

4.3.2.1 Knowledge: Except pharmacists, most of interviews were unaware about the National Medicine Policy and the antibiotic component of the policy. Few clinicians were also unaware about the available structure in their hospital.

"…up to now there is no national or hospital policy on antibiotic and depending on the organism and based on the clinical judgment we decide ourselves." (Interview 10)

Why National Medicine Policy not implemented?

Most of the interviews either blamed the country political situation or lack of visionary leader at higher level in the ministry and their governance. Few believe that medicine does not come in the country priority list. Other reasons from interviews include the funding problem, lack of manpower, lack of coordination, lack of commitments.

"…regularity body should do this... not blame but is universal… policy not implemented due to effective governance." (Interview 8)

"…in the Health care so that medicine is not in priority. Since medicine is not in the priority then automatically antibiotic is also not in the priority." (Interview 45)

Most of the interviews were unaware about existence of any antibiotic guideline in the country. Very few knew about the existence of national guideline on Tuberculosis, HIV/AIDS, Malaria, Kala-azar.

Although, 4 out of 5 study hospitals were involved in National Antibiotic Resistance Surveillance, none of the clinicians were aware about such surveillance indicating huge communication gap. The information of surveillance was only limited to the microbiologist and their departments.

"…not aware of this may be the infection control committee has done. But data is not disseminated." (Interview 37)

"…no any surveillance in the hospital level but some doctors may personally have done some research." (Interview 9)

The dissemination workshop conducted by the National Public Health Laboratory to disseminate the antibiotic resistance is attended by the microbiologist of the hospital and the disseminated information was limited to them. The information collected by the NPHL was not documented and published properly and hence has access to limited people.

4.3.2.2 Attitude: Most of the interviews feel the need of antibiotic policy and guideline in the hospital as well as at the national level showing positive attitude.

"…want to see the comprehensive guidelines which will touch on the common diseases and also for the uncommon disease which may require higher antibiotic." (Interview 6)

Few clinicians believe that policy at tertiary care may not be effective because of lack of awareness and education at the primary care level and further suggest the requirement of the education and policy at the primary care before tertiary care.

"… if we prepare the policy here in tertiary care it is not effective because education to the primary level is needed first…Unless there is restriction in the primary level like you can only go up to amoxicillin, it is not feasible…so first policy is required in primary level than in tertiary level." (Interview 3)

Appropriate policy for their hospital?

Most of interviews think that prior authorization and restriction of antibiotic will be appropriate to control the antibiotic misuse in their hospital. Some of interviews believe guideline implementation will be better option to control antibiotic misuse.

"…restriction and prior authorization will be better, it is required." (Interview 4)

"…restriction is necessary. It can be feasible and regular monitoring is required" (Interview 12)

"…If there will be the hospital level guideline it will be better." (Interview 29)

However, few clinicians think that policies like restriction, prior authorization may seize their right to prescribe antibiotic and may harm seriously ill patients.

"…restriction is not possible and it does not sound practical. When the patient is dying and in the last stage, for such case to take approval is not a good, If we have to use it we have to use it. … If the patient is going to die then we do not wait for authorization."

All Clinicians have positive attitude towards surveillance in the hospital and believes that surveillance system in the hospital can improve the rational use of antibiotics and decrease antibiotic resistance.

"…if surveillance data are available it will be easy to prescribe." (Interview 29)

4.3.2.3 Process of prescribing: In public hospital, clinicians rarely look for culture sensitivity result before prescribing antibiotics. Most of the time prescribe antibiotic based on clinical sign and symptom.

"…rarely see culture sensitivity report before prescribing" (Interview 15)

"…we use high antibiotic and if it works then we think that the previous antibiotic is resistance but this is not the microbiologically determined." (Interview 32)

Common reasons behind not looking for culture sensitivity was patient already consumed antibiotic before visiting them leading to no growth in culture which was noticed in my first phase of study suggesting less than 30% growth rate (Appendix C). Another reasons include patient cannot afford and few clinicians complained delay in culture reports from microbiology departments.

"…it is difficult to see in all case because patient has already taken antibiotic as antibiotics are available over-the-counter." (Interview 29)

"…If the patient is affordable I will do definitely other wise no. If the patient is educated I definitely do the culture." (Interview 3)

In contrast, the checking culture sensitivity before prescribing antibiotic is relatively higher in private hospital. However, they rarely wait for culture report, they start antibiotic empirically.

"…In infectious disease, in majority of cases we send the culture and start antibiotic and after the report we change accordingly." (Interview 3)

Among the clinician, Pediatrician think it is not possible to see culture report in the most of cases and they treat the patients empirically. Medical doctors in private hospitals mostly refer the culture reports before prescribing antibiotics whereas Medical doctors in public hospital rarely refer the culture report and send culture only when there was suspected resistance.

Unanimously all the clinicians said that they did not prescribe telephonically.

4.3.2.4 Process of procurement and dispensing: Public hospitals included in this study did not have their own hospital pharmacy as like private hospital. None of the hospital had separate antibiotic procurement policy. Antibiotics in the hospitals were procured as like any other drugs. However, antibiotic selection was done by either DTC or Antimicrobial Committee in the private hospitals. Antibiotics were dispensed base on prescription inside the hospital pharmacy.

"…no policy for antibiotic purchase so far…antibiotics are selected by DTC as likes other drugs" (Interview 5)

"…no separate purchase policy for antibiotics…. Purchase order is based on the demand after selection by antimicrobial subcommittee." (Interview 23)

Similarly, there was not separate national policy for import or export of antibiotics. However, separate antibiotic unit is requirement for antibiotic production for the pharmaceutical manufacturers.

4.3.2.5 Process of monitoring and evaluation:

There was no system of monitoring either use or resistance in any hospitals. However, two private hospitals had policy to monitor the promotion where Medical Representatives from pharmaceutical companies were not allowed to meet the clinicians individually.

"…Medical Representatives (MR) are not allowed to meet the doctors individually but they can present in the group of doctors in every Tuesday." (Interview 40)

Similarly, there is not any national policy on promotion of antibiotics. However, Department of Drug Administration (DDA) had developed guideline on ethical promotional of medicine.

4.3.2.6 Process of education and training: No separate regular education and training program related to antibiotics in any of the study hospitals. However, student training as a part of course, presentation in clinical meeting sometime, some guest lecture were the type of education run by the hospitals.

"…do have educational program in terms of student education and training and presentation in the clinical meeting." (Interview 25)

None of the hospitals had the regular educational training program either to clinician or other healthcare professionals. Moreover, none of the hospitals had any public campaigning or education program.

4.3.3 Rational use of Antibiotics: Most of the clinicians believe that antibiotic use was problem in their hospitals.

Among the clinician, Most of Medical doctors realized the over use of antibiotics in their hospitals. In contrast, Pediatrician and Orthopedician believed that antibiotic use was not big problem.

Moreover, most of Hospital Administrator and DTC/ Antimicrobial Committee chairperson viewed overuse of antibiotic in their hospitals. One administrator was highly concerned about increased use of higher generation antibiotics. When asked, what was the measure has taken to correct the problem. The common answer obtained from them include working on this problem, committee was formed, working on guidelines etc.

"…may be to some extent over use…we expect for the rational use… once the guideline will be finalized and implemented then situation will be much better." (Interview 42)

"…here most of the prescriptions contain the higher generation antibiotic…the doctors want to treat the patient very fast, this result in developing resistance for the higher generation and problem may arise." (Interview 34)

Further, Interviews suggest that there was irrational use of antibiotic in form its overuse as everybody is getting antibiotic even in non-infectious condition which was clear sign of irrational use of antibiotics. Similarly, Irrational in terms of incomplete duration and insignificant dose.

"…overuse… all gets Azithromycin as it is easy also because the therapy is of 3 day and patient has already taken one so it is also easier for us to treat." (Interview 4)

The above statement was found true in the utilization study where Azithromycin defined daily dose per hundred beds (DDD/100 beds) was found more than 4 times and 63 times higher from the WHO assumed DDD in MTH and WRH respectively (Table 4.8).

"…Yes, bit more antibiotic use is in practice … overuse, In significant number and we switch to another" (Interview 8)

"…over use, misuse, and inappropriate use … Incomplete duration due to inadequate information to patient." (Interview 20)

"…of course in all drug use there is problem in whole country so why not in this hospital… I think it is over use not only in hospital everywhere, even in cough and cold also antibiotic is prescribed." (Interview 29)

However, few clinicians think there is not overuse of antibiotic because patient requires it. Moreover, few clinicians believe that overuse is acceptable rather than patient dying because of under use of antibiotics.

"…do not think it is a problem. We give because patient requires it." (Interview 2)

"… average neither over use nor under use, our motto is patient do not die due to under use of antibiotic, over use we accept." (Interview 32)

Most of the microbiologists believe that antimicrobial resistance was emerging to be a big problem in their hospital and further concerned about emergence of multidrug resistance. Similarly, most of the clinician agreed that there was emergence of resistance in their hospital.

"…some patient primary resistance to many of the drug, and sometime in critical patient primary resistant to all first line drug and in such case it is so difficult that which antibiotic to choose because all are resistance." (Interview 29)

"…if the patient is not improving we think that it is resistance then we move towards the high generation likes third and fourth generation then if not improved then we give Meropenem, Imipenem… if still patient condition is not satisfied…add Tazobactum." (Interview 32)

Possible cause of resistance?

Majority of interviews believe that overuse of antibiotic in the hospital as well as in community is the major cause and few believes that it may be because of rampant use in agriculture, inappropriate use and underuse of antibiotics

"…. misuse, overuse, not only in the hospital side but major from the community side, due to self medication, quack practice, OTC selling, may be primary cause of resistance." (Interview 29)

"…under use, lack of duration, drug dose, compliance, no monitoring and not organism specific drug." (Interview 38)

"…increased antibiotic in the agriculture, premature stoppage of use by the patient." (Interview 40)

Majority of interviews believe that it is time for intervention to improve rational use of antibiotics where as few believe that it is late but should be intervene immediately.

The suggested possible mode of intervention include education, enforcement of guideline and policy, public education, regulation of antibiotic as OTC medication, surveillance etc. However, some believe education or formation of guideline will not be much effective. Enforcement of policy or guideline along with education will be proper.

"…education will not be effective. Enforcement is required." (Interview 3)

"…proper antibiotic policy has to be framed and it should be strictly followed." (Interview 7)

"…forming national level Guidelines which act as an intervention part and the next is implementation part in all the hospitals." (Interview 39)

4.4 Policy Recommendation: For policy recommendation based on the above finding, an expert panel was formed. Expert-panel was 15 members committee including expert from 5 Study Hospital, Ministry of Health and Population, Department of Drug Administration, academics, pharmacists, microbiologists. List of experts are given below in the Table 4.10.

Expert-panel discussion was held at Department of Drug Administration on 22nd April, 2011. The program schedule of expert-panel discussion was given below in Table 4.9.

Table 4. 9 Program Schedule for expert discussion

Time	Program	Moderator (s)
3:00-3:15	Introduction to workshop	Kadir Alam
3:15-3:30	Rational use of antimicrobials: Nepalese perspectives	Dr. Ravi Shankar & Dr. P. Subish
3:30-3:45	National Antibiotic Treatment Guidelines	Mr. Bhupendra Bahadur Thapa
3:45-4:00	International perspectives on Antibiotic policy	Dr. Niyada and Dr. Pranaya Mishra
4:00-4:30	Research finding of the nation wide study 'Antibiotic utilization and controlling system in tertiary care hospital in Nepal'	Kadir Alam
4:30-4:40	Tea Break	
4:40-6:00	Expert discussion and brain storming session	Dr. Niyada, Dr. P. Mishra and Dr. Ravi Shankar and Dr. P. Subish
6:00-700	Recommendations for policy/ Guidelines	
7:00-800	Dinner (Hosted by the organizers)	

The meeting was divided into 3 parts.

A. Results finding dissemination
B. Expert group work
C. Policy recommendation

A. Results finding dissemination:

At the beginning of the expert discussion, there were three presentations before research finding of the nation wide study 'Utilization pattern and controlling system of antibiotics in tertiary care hospitals in Nepal'. All three presentations were introductory to research finding. Which include presentation on "Rational use of antimicrobials: Nepalese perspectives" by Dr. Ravi Shankar and Dr. Subish Palaian followed by presentation on "Developing Antibiotic Treatment Guideline: an experience by Mr. Bhupendra Bahadur Thapa and then a presentation on "International perspectives on Antibiotic policy in hospital" by Dr. Niyada K. Angsulee and Dr. Pranaya Mishra. After three introductory presentations researcher presented the research finding (Appendix D).

B. Expert group work:

After presentation, there was discussion results finding and also on introductory presentations. After discussion all the experts were divided into 3 expert groups. Mixed group of experts was kept in each group. Each group of expert had at least one Hospital Administrator, Academician from Medical School and Pharmacists from Ministry of Health. The details of groups are given below in Table 4.27. Each expert group was given following task.

1. Recommend the policy for the identified problem on rational use of antibiotic in research finding in tertiary care hospital in Nepal.
2. Strategy to implement the recommended policy

Table 4.10 Experts and expert group

Group	Members	Positions
Group "A"	Dr. Rajendra Koju M.D. Cardiology	CAO, Dhulikhel Hospital
	Mr. Pan Bahadur Chettri M.Pharm	Senior Pharmacist, DDA
	Mr. Bhupendra Bahadur Thapa M.Sc. Pharm	Chief Drug Administrator, Ministry of Health
	Miss. Sushma Shakya M.Pharm	Liaison officer (WHO-DDA)
	Mr. Babu Ram Humagain M.Pharm	Associate Professor CIST College, Kathmandu.
	Dr. P. Subish Ph.D.	Associate Professor, CMS, Bharatpur, Nepal
Group "B"	Dr. PK Chakraborty M.D. Psychiatric	Director, Manipal Teaching Hospital
	Mr. Navin Chaudhary M.Sc. Microbiology	Microbiologist, CMS, Bharatput, Nepal
	Mrs. Vhabha Rajbhandari M.Sc. Pharm	Senior Pharmacist, DDA, Ministry of Health, Govt. of Nepal.
	Mrs. Gorakh Bahadru DC B.Pharm	Member, APUA-Nepal, Senior Pharmacist, DDA
	Dr. Pranaya Mishra Ph.D.	Assistant Dean, Student Affairs; Course Director, Pharmacology, Saba University School of Medicine, Netherlands-Antilles.
Group "C"	Dr. Buddhi Bahadur Thapa M.D. Medicine	Director, Western Regional Hospital
	Dr. RM Piryani M.D. Medicine	Chairman, MTC, KIST Medical College
	Mr. GM Khan M.Pharm	Associate professor, Pokhara University Lekhnath, Pokhara, Nepal
	Mr. Tirtha Ratana Shakya M.Pharm	Senior Quality Controller, National Medicine Laboratory, Ministry of Health
	Dr. P. Ravi Shankar M.D. Pharmacology	Professor, KIST Medical College

Groups were given 20 minutes time to complete above task. After completion of time, each group presented their group recommendation. The group recommendation from each group for tertiary care hospital for implementation is given in Appendix D.

C. Policy recommendation: The common policy and the strategies to implement at the tertiary care level is described below

1. Establishment of organizational structure: All three expert groups recommended the existence of Drug and Therapeutics Committee and Antimicrobial committee to address the problem. They felt the importance of organizational structure for the implementation of any policy. Moreover, for effective functioning and formulation of organizational structure the first strategy suggested was to have the hospital own hospital pharmacy which they regarded as crucial steps towards the implementation of policy and provide the basis of implementation.

2. Antibiotic Treatment Guideline/ Hospital Formulary: Antibiotic treatment guideline in the hospital was recommended by the two of the expert group for the betterment of antibiotic use and to decrease the antibiotic resistance whereas other group recommended hospital formulary in the hospital. Further, for the effective implementation expert suggested formation of antimicrobial committee for the preparation and implementation of antibiotic committee.

3. Hospital Antibiotic Policy: One of the expert group recommended the hospital antibiotic policy on the use of antibiotics either as restriction; prior authorization or rotation of antibiotic. The strategy suggested for the implementation was enforcement of policy by the hospital management.

4. Good laboratory practice and surveillance on AMR: Good laboratory practice and setting up surveillance to reduce the antibiotics resistance was recommended by the two of the expert groups. Even establishment of local level surveillance at the hospital and exchange of data was suggested for fighting the resistance.

Strategy suggested against this was to strengthening of ongoing the National Surveillance Program and inclusion of all Tertiary Care Hospital of the country and inclusion of other organism as well. Further, suggested that regular data dissemination and feed back program to decrease the communication gap among the health care professional. Release of the data in the form publication was suggested for effective dissemination rather than only dissemination through workshop.

5. Education and training: Education and training as orientation or regular CME to the clinician was another policy recommended by the two expert groups. The strategy recommended to implement this was designing of regular CME and training by the antimicrobial committee.

6. Antibiotic Use Evaluation: Antibiotic use evaluation or prescription audit was another recommended policy by two of the groups. They felt that feed back after evaluation might draw the attention of the clinician and be helpful in reducing the use and resistance. Monitoring of use and resistance at the hospital level by conducting study by existing organization (DTC or Antimicrobial committee) within the hospital was recommended strategy against the policy which might be helpful in finding whether guideline and policy was implemented properly or not.

Apart from above policy at Tertiary Care Hospital level and other recommendation from the experts for the National body and Government of Nepal are given below

1. Mandatory hospital pharmacy services: After extensive discussion among the experts, they recommended the inclusion of mandatory hospital pharmacy services in the all level of hospitals in the national level health policy. Further, they suggested involvement of DDA for effective implementation of policy.

2. National DTC: Experts recommended the formation of National level Drug and Therapeutics for effective co-ordination and functioning of DTC at the hospital. Further experts recommended, DDA should take the lead in formation of such committee.

3. National Standard Treatment Guideline: Although the Chief Drug Administrator from the Ministry of Health and Population shared his experience in the development of National Antibiotic Treatment Guideline which was under process of development, experts concerned about the formulation process and its implementation. Experts also recommended the formulation of National Antimicrobial Committee for the effective formulation and implementation. Experts also advocated the role of Ministry of Health and Population in formulation of National Antimicrobial Committee and implementation of Guideline.

4. Implementation of National Medicine Policy: National Medicine Policy drafted first time in 1995 was still to be implemented. The recent modified draft was prepared in 2010 that have the component of Prudent Use of Antibiotics. The experts recommended the formation of National Medicine Policy committee under Ministry of Health and Population for the effective implementation.

5 Restrictions of Over-the-counter (OTC) dispensing of Antibiotics: One major concern raised by the experts was OTC dispensing of antibiotics. Experts unanimously felt that OTC dispensing of antibiotics was the major cause of antibiotic misuse and resistance. Experts recommended the restriction of OTC antibiotic sale formulation of similar restriction policy as that of Narcotic and Psychotropic drugs. Experts suggested for the immediate action by the DDA.

6. Education and Training: Experts recommended the national educational program on antimicrobial for the healthcare professional as well as for the consumers separately. Further, Experts suggested the inclusion of National Medicine Policy in the pharmacy, nursing and medical education. Experts requested Ministry of Health to take the lead.

7. Monitoring: Experts suggested the centralized monitoring by the national body and collaboration among the hospital and ministry on the matter related to prudent use of antibiotics.

CHAPTER V

DISCUSSION, CONCLUSION AND RECOMMENDATION

5.1 Discussion: The research finding of this study is discussed in three different heading of Sturcture, Process and Outcomes (Antibiotic Utilization Pattern).

5.1.1Antibitic Utilization Pattern:

About 44% and 29% patients received antibiotics in WRH and MTH respectively. Indicating more number of patients in WRH were received antibiotics. The previous drug utilization study conducted in 1990,s found 72.4% (Joshi et al., 1992) and 84% (Rehana et al., 1998) which was very high compared to present study but previous study by Joshi et al. was conducted only in medicine department where as study conducted by only for one week in 98 patients which limit the comparison as this study was conducted in entire admitted patients over 4 months periods. However, antibiotics prescribed in WRH was higher than the study conducted in Caribbean developing county (Hariharan S et al., 2009) where it was 37% but similar to study from Ethiopia conducted in two hospitals found 47 and 46 % of prescription with antibiotics (Banja WD, 2007).

Mean number of antibiotics prescribed was 2.25 ± 1.14 in WRH which were significantly higher in than 1.84 ± 0.915 MTH (*P*=.000) indicating increase use of antibiotics in public hospital. Previous study conducted in pediatric inpatients (Palikhe, N., 2004) found that mean number of antibiotics was 2.41±1.02. Antibiotics use in present study was slightly lower which may be because present study was conducted in overall hospital patients in comparison only pediatric patients that limit comparison. Mean number of antibiotics prescribed in public hospital of our study was double compared to Ethiopian study (Banja WD, 2007) conducted in two Hospital found mean number of antibiotic per prescription was 1.04 and 1.13 suggesting increased use of antibiotics in present study.

About 45% and 40% of patients were treated with 2 antibiotics, 19% and 13% of patients treated with 3 antibiotics, 8% and 4% of patients were treated with 4 antibiotics in WRH and MTH respectively suggesting increased frequency of poly antibiotics case in

public hospital. Previous study conducted at MTH, the present study site found that 48%, 37%, 11%, 2% and % patients was treated with 1, 2, 3, 4 and 5 antibiotics respectively (Shankar RP, et al., 2003) which was more or less similar to present study but only limitation was that previous study was conducted only in internal medicine ward. A study conducted in tertiary care hospital in India (Gupta M, et al., 2004) found two anti-microbial per prescription were indicated in 43.88% of patients, three drugs in 22.5% and four drugs in 3%. Although pattern is similar, in present study few patients received up to 9 antibiotics during their treatment periods in WRH which is worrisome factors. This may be because of lack of process which was explained nicely in studying controlling system where one of clinician stated that they treat infection by hit and trial method and keep on adding antibiotics until patient responds (Interview 8)

Mean number of antibiotic used by departments and WRH were significantly higher than mean number of antibiotic use by departments and MTH (*P*=.000, .000). We could not find similar study to compare but significant higher use of antibiotics in the public hospital may be due to lack of structure and process in the in the public hospital which was also the finding of our controlling system study.

Most of the time antibiotics were prescribed for prophylactic purpose (34.11% in WRH and 53.46% in MTH), followed by respiratory tract infections (21.23% in WRH and 14.86% in MTH) in both of hospitals. Further, number of antibiotics used between the hospitals and co-morbid condition were significantly higher in WRH indicating overuse of antibiotics in public hospital. We could not find the similar study from Nepal to compare but one of the study conducted in Medicine department found common co-morbid condition where antibiotics were used include chronic obstructive pulmonary disease (COPD) 22.7%, lower respiratory tract infection (LRTI) 15.8%, Urinary Tract Infection (UTI) 13.3% and Pneumonia 8.9% A study from Libya conducted in Teaching Hospital found that, more number of times antibiotics were prescribed for respiratory infections (37%) followed by non-infectious condition (27%). Another study (Gupta M et al., 2004) conducted in tertiary care hospital in India found that antibiotics were prescribed in respiratory tract infections (22%), followed by CNS (20%), abdominal (18%) and 15% in

non-infectious condition like poisoning, snake bite, tetanus etc. The highest uses of antibiotics in respiratory tract infections were common. However, the increased use of antibiotics in non-infectious conditions presuming the chance of infections is worrisome factors.

DDD/100 bed-days of Azithromycin (10.21), Cloxacillin (6.9), Cefotaxime (5.49), Cefriaxone (11.57) and Metronidazole (P) [11.50] in WRH were 8, 8.6, 8.5, 2.2 and 4 folds higher than DDD/100 bed-days of MTH. Overall, antibiotic use in WRH (68.45 DDD/100 bed-days) was 3 fold higher than MTH (22.21 DDD/100 bed-days). Again this shows the over use of antibiotics in public hospital. Previous study which calculated DDD was conducted either in Medicine or ICU (Shankar RP, et al., 2003) where maximum antibiotics are utilized. However, we could not find the similar study conducted in entire hospital to compare. Similarly, a study conducted in 3 European University Hospital (Kiivet RA, et al., 1998) of Estonia, Sweden and Spain found that over all antibiotic use were 41, 47 and 51 DDD/100 bed-days respectively which is around two or more than two fold higher than private hospital but lower than public hospital. Increase use of antibiotics in WRH may be because of absence of structure and process like organization, policy and guideline and process of prescribing which was found during situation analysis. In addition, MTH is associated with the medical school and educational institute always try to teach rational use of medicine to their students.

In this study very less sample were tested in WRH and among tested sample only 28% showed growth. We found that Cephalexin, Nalidixic acid, Erythromycin, Cotrimoxazole and Tetracycline were 100% resistant to E. Coli in WRH whereas Amoxyclav, Carbenicillin were 100% resistance in MTH. Further, Piparacillin, Ampicillin, Cephalexin, Penicillin, Cefotaxime were 90, 88, 81, 89, and 76 percent resistance in MTH. Many antibiotics were not tested against E.coli in WRH. Similarly, resistance pattern of S. aureus suggest that Cephalexin, Norfloxacin in MTH were 100% resistant. Where as Piperacillin, Cotrimoxazole, Cloxacillin and Penicillin were 88, 86, 75 and 74 percent resistant to S. aureus in MTH respectively. Similarly, Cloxacillin, Gentamicin, Ampicillin, Ceftriaxone were 100, 60, 50 and 50 percent resistance in WRH. While comparing use and

resistance we found that cephalexin, Nalidixic acid, Erythromycin, Co-trimoxazole and Tetracycline in WRH was 100% resistance and similarly Piparacillin, Carbenicillin showed 100% resistances which were either not used or minimal used suggesting no relation between use and resistance. However, increased resistance to these antibiotics might be either due to rampant use of those antibiotics in that institution in past leaving resistant to those antibiotics or these antibiotics were widely used in community causing resistance. Increased use of antibiotics in the community was concern shown by the many interviews during situation analysis. Lack of previous data either from hospital or from community limits the comparison. Increased resistance in the public hospital might be partly because irrational prescribing without referring culture reports.

Significantly high total prescription cost in WRH compared to MTH. However, the mean cost of antibiotics 1007.78 ($14) in WRH and 892.88 ($12.8) in MTH were not significantly different in both the hospitals. A previous study conducted at MTH (Shankar RP, et al., 2003) found that mean cost of antibiotic was $16.5 which was higher than present finding. Higher antibiotic cost in the previous study might be because previous study was conducted only in Medicine department, specialties which use more antibiotics. A Study from Ethiopia (Banja WD, 2007) found that the costs of antibiotic per patient care day in two hospitals were $0.35 and $0.5 which was quite low. In Ethiopian study cost was calculated on outpatients which limit the comparison. In another study from Israel (Krivoy N, et al., 2007) found that mean antibiotic cost per patient was about $41 which is extremely high as compared to our study.

Appropriateness of the prescriptions were checked for the treatment of enteric fever patients using 10 different basic criteria using WHO guideline found that around 59.6% and 8.7% of the treatments were appropriate and marginally appropriate in MTH. In contrast, only 51% and 9.6% treatments were appropriate and marginally appropriate in WRH. Suggesting more appropriate use in MTH compared to WRH. We could not find similar study to compare. But a study assessing appropriateness of treatment of Community Acquired Pneumonia, Sinusitis, or Acute Exacerbations of Chronic Bronchitis using 10 point Medication Appropriateness Index (MAI) in Veterans (Tobia CC, et al.,

2008) found that 65% inappropriate antibiotic prescribing which was more than present study

5.1.2 Structure:

The relationship between structure-process-outcome is well explained by the Donabedian in terms of quality of care. He described “Good structure, that are a sufficiency resources and proper system design is probably the most important means of protecting and promoting the quality of care.”

In this study, structure components (Organizational, Personnel, Policy or guideline and Surveillance) were better in the private hospitals than public hospitals because of existence of organizations like DTC and Antimicrobial Committee and scattered policy and guideline like policy on promotion, antibiotic selection by DTC and interdepartmental guidelines. However, in terms of personnel there were no differences between two hospitals. In general in Nepal, clinicians in the public sector do not want to take responsibility and they are mostly focused towards private practice in the private clinics.

Although, 4 out of 5 hospitals were involved in national surveillance program, none of the clinicians were aware about existence of surveillance indicating huge communication gap which refers towards the non-existence of surveillance which needs to be addressed. This may be because of improper dissemination system and poor documentation by the NPHL who call the selected people for the dissemination seminar and do not compile the data in the form of publication. Hence clinician does not have access to the surveillance data.

5.1.3 Process:

Process components included in this study were knowledge, attitude, process of prescribing, process of procurement, and dispensing, process of monitoring, and evaluation, process of education and training. There were very poor knowledge on policy and existence of other structural components among the clinician, administrator and microbiologists in all hospitals. But overall, positive attitude was found towards the policy,

guideline and surveillance. The prescribing process were relatively better in private hospitals as prescriber in private hospital refer culture sensitivity repots before prescribing but it was poor in public hospitals which can be determined by the interview

"…we use high antibiotic and if it works then we think that the previous antibiotic is resistance but this is not the microbiologically determined." (Interview 32) and "*…we do hit and trial. If gram negative is to be cover we do accordingly… so, we go in such a way. We go on adding till the patient responded."* (Interview 8)

The process of dispensing was further weaken by the non-existence of hospital own pharmacy in the public hospitals. However, private hospitals have their own hospital pharmacy and antibiotics were not dispensed without prescriptions. Further there were lack of antibiotic evaluation and monitoring program in all hospitals. Also there were deficit of special educational and training program on antibiotics focused to clinician and to the public or patients. As like structure, process components were relatively better because of good prescribing process and existence of their own hospital pharmacy. But overall, again it was weaker process. Similarly, expert also noticed the poor process and recommended the need of education and training, good laboratory practice, regular CME and frequent seminar.

Considering Rational Use of Antibiotics in the hospital, study found that relatively more number of the clinicians and administrators of public hospitals admitted themselves that there was overuse of antibiotics in their hospital and was the major cause of resistance. However, very limited initiatives were taken in the past and hence clinicians themselves suggested the need of intervention in the form of education and enforcement. This proves that there was higher irrational use of antibiotics.

Donabedian suggested the presence of structure has salutary effect on quality of care (outcome) and it absence posses the deleterious effect leading to poor quality. Similarly, structural characteristics of setting in which care takes place have a propensity to influence process of care so that its quality is diminished or enhanced. Similarly

changes in the process of care on its quality will influence the effect of outcome. The finding of this study clearly explains relation of between Structure, Process and Outcomes of Donabedian model. Further it shows the relation of distinct effects of structure and process on outcomes at many instances.

- Relatively better structural components in MTH resulted into lower number of patients receiving antibiotics, lower mean number of antibiotics, lower DDD/100 bed-days of antibiotics and lower cost of drug therapy as compared to WRH showing salutary effects on utilization pattern of MTH and deleterious effects on utilization pattern of WRH.
- Relatively better process component of MTH has relatively effects on prescribing process and duplication of therapy with other antibiotics in enteric fever.
- Both structure and process posses' positive effects on rational use of antibiotics in MTH.

5.2 Conclusion:

Conclusively, study found that more number of antibiotics were prescribed in WRH (Public Hospital) compared to MTH (Private Hospital). Moreover, antibiotic use was more inappropriate in WRH compared to MTH. Similarly, study also found that there was poor controlling system in the public hospitals where there were lack of organizational structure (e.g. DTC, Antimicrobial Committee), Policy, guideline, good prescribing process and monitoring as compared to private hospitals. Surprisingly, there were huge communication gap between the clinicians in regards to national surveillance program and majority of healthcare professionals were unaware about the National Medicine Policy.

5.3 Limitations

There were few limitations in this study. Firstly, the data of antibiotic utilization was taken only from two hospitals. This may not be representative to tertiary care hospital in Nepal which is the limiting factor for extrapolation of results. Secondly, the culture sensitivity was done in very less patients in WRH which dose not gives the actual figure

and hence cannot represent all tertiary care hospitals. Further, there were no representative hospitals from Eastern, Middle Western and Far-Western region of Nepal in studying the controlling system of antibiotics.

5.4 Recommendation

5.4.1 Policy recommendation: We strongly recommend the implementation of antibiotic policy recommended by the expert as national antibiotic policy.

5.4.2 Research recommendation: We recommend the intervention at the prescriber level in the hospitals in terms of educational, CME and workshop. We also recommend the proper data compilation and dissemination of national resistance surveillance program. Further, we recommend the similar research at the community, primary care level and secondary care level.

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APPENDICES

APPENDIX A

Studies suggesting the use antibacterial in developing countries

Authors	Country	Main objectives	Major findings
Dimri et al., 2009	India	• Drug use pattern in children	• A total of 254 patient prescriptions were analyzed for prescribing indicators • Antibiotic was prescribed in 29.1% of prescription
De Costa et al., 2008	India	• Patterns of drug use in the primary health centers	• A total of 1,051 patient prescriptions were analyzed for prescribing indicators • The proportion of consultations with antibiotics prescribed was 63.5%
Chatterjee et al., 2007	India	• Drug utilization study in a neonatology unit	• A total of 849 drugs were studied in 176 prescriptions • Antimicrobial constitute of 30.2% of the total drugs prescribed
Gupta et al., 2004	India	• Utilization of parenteral anti-infective agents in the medical emergency unit	• A total of 885 patients were screened • About 400 patients (45.2%) received parenteral anti-infective agents • Cephalosporins, aminoglycosides and metronidazole accounted for about 70% of total antimicrobial use
Ray et al., 2003	India	• Study of consumption, compliance and awareness about antibiotic utilization	• A cross-sectional survey was conducted upon 500 respondents • Antibiotic consumption without prescription was evident amongst 41.2% of adults in comparison to that of 8.4% in children ($P < 0.01$).
Maini et al., 2002	India	• Drug utilization study in dermatology	• Six hundred and six prescriptions of dermatology out-patients were analyzed • Percentage of encounters with an antibiotic was 46.86%
Ramesh et al., 2002	India	• Audit of aminoglycosides usage	• A total of 197 pediatric patients were evaluated • Majority of the patients were treated with gentamicin (53%) • The most frequent indication was respiratory tract infections (50%)

Authors	Country	Main objectives	Major findings
Rehan et al., 2001	India	• Study of drug utilization pattern in dental OPD	• A total of 491 prescriptions were collected randomly • 78.8% of all prescriptions contained antimicrobial agents. • Fixed dose combination of ampicillin and cloxacillin was most commonly prescribed antimicrobial agents
Thomas et al., 1996	India	• Monitoring of antibiotic use in a primary and tertiary care hospital	• Prophylactic and curative use of antibiotics was studied prospectively in 87 consecutive medical and surgical cases of a tertiary care hospital and in 98 cases of a primary care hospital • Antibiotic prophylaxis was found to be more inappropriate in the primary care hospital (49%) than in the tertiary care hospital (34%)
Hafeez et al., 2004	Pakistan	• Prescription and dispensing practices in public sector health facilities	• Documentation of 914 responses was completed from three provinces • More than half of the prescriptions contained antibiotics
Siddiqi et al., 2002	Pakistan	• Prescription practices of public and private health care providers	• Prescriptions were collected from 60 public and 48 private health facilities • General practitioners (GPs) who represent the private sector prescribed at least one antibiotic in 62% of prescriptions compared with 54% for public sector providers.
Das et al., 2001	Pakistan	• Prescribing practices of consultants at Karachi	• Prescribing practices of 354 consultants were analyzed • The antimicrobials, vitamins/minerals and injections were over-prescribed
Najmi et al., 1998	Pakistan	• Prescribing practices: an overview of three teaching hospitals	• Six hundred and one prescriptions from medical, paediatrics and psychiatry units of these hospitals were analyzed • Antimicrobials constituted 20.4% of the drugs prescribed • Antibiotic were prescribed frequently for cases of acute respiratory infections and gastroenteritis

Authors	Country	Main objectives	Major findings
Akter et al., 2004	Bangladesh	• Antimicrobial use in paediatric wards of teaching hospitals	• The treatment charts of 2171 admitted paediatric patients were reviewed • The most commonly used antimicrobials were ampicillin, gentamicin, amoxicillin, cloxacillin and ceftriaxone • The majority of the admitted paediatric patients (56.1%) included in this study received two or more antimicrobials in combination for their treatment • The percentages of appropriate antimicrobial treatment of pneumonia, and diarrhoea were 57.1% and 67.8% respectively
Mamun et al., 2006	Bangladesh	• A survey of antimicrobial prescribing and dispensing practices in rural	• This study was undertaken to determine the patterns of antimicrobial prescription by 64 Rural Medical Practitioners (RMPs) • All available antibiotics were prescribed in inappropriate doses and duration • In most cases, the RMPs initiated treatment with a parenteral form of antibiotic, and a different oral antibiotic usually followed.
Ahmed and Al-Saadi, 2005	Saudi Arabia	• A survey of multiple prescriptions dispensed	• Prescribing patterns of 200 doctors were surveyed • Multivitamins and antibiotics were the drugs most frequently prescribed
Angunawela et al., 1991	Sri Lanka	• Experimental evaluation of the effects of drug information on antibiotic prescribing	• Some 18,766 randomly selected outpatient drug prescriptions were studied. • Antibiotics (and sulphonamides) were prescribed to 33.2% of the patients • Penicillin was the most commonly prescribed antibiotic and tetracycline was only rarely prescribed to children
Boriboonhirunsarn, et al., 2007	Thailand	• Usage of prophylactic antibiotics in uncomplicated gynecologic abdominal surgery in Siriraj hospital	• The most common prophylactic antibiotics used were Cefazolin (41.9%), Cefoxitin (36.4%), and Augmentin (9.7%) • Rate of single dose of cefazolin usage were not significantly different between the two groups (10.1% and 12.4% respectively, $p = 0.482$)

Authors	Country	Main objectives	Major findings
Apisarnthanarak et al., 2006	Thailand	• Inappropriate antibiotic use in a tertiary care center	• The incidence of inappropriate antibiotic use was 25%. Admission to the surgical department (adjusted odds ratio, 2.0; P=.02) and to the obstetrics and gynecology department (adjusted odds ratio, 2.0; P=.03) were associated with inappropriate antibiotic use
Howteerakul et al., 2004	Thailand	• Antimicrobial use in children under five years with diarrhea	• Clinical audit of 424 cases treated by 38 physicians • Based on the presence of mucus and blood in stools, 27.4% of 424 cases received appropriate antimicrobial drugs • Cotrimoxazole was the most commonly prescribed drug (51%), followed by colistin sulfate (15.3%), norfloxacin (11%), and nalidixic acid (0.5%)
Zhang et al., 2008	China	• Antibiotic use in five children's hospitals during 2002-2006	• Total 56 different substances of systemic antibiotics were used. • The overall consumption of antibiotic drugs was 68.2, 58.4, 65.8, 65.6 and 49.9 DDD/100 bed-days for the years 2002-2006, respectively
Ding et al., 2008	China	• Antimicrobial usage in paediatric intensive care units	• Data were equally collected from 540 charts of PICUs in the three Chinese tertiary teaching • The main treatment started empirically in 387 (71.6%). The third-generation cephalosporins were the major antimicrobials used in all participating hospitals
Hanssens et al., 2005	Qatar	• Antibiotic prescribing pattern in a medical intensive care unit	• From the 71 eligible patients admitted, 54 (76%) were treated for presumed or proven infections and received antibiotics, corresponding with 280 (89%) of the 313 patient days • Ceftriaxone was prescribed in 31 patients (57%) as initial therapy
Hu et al., 2003	China	• Assessment of antibiotic prescription in hospitalised patients	• Clinical data on antibiotic prescriptions in 1025 inpatient cases chosen from 21,000 inpatients • Antibiotics were prescribed to 77.8% of inpatients, among which 55.2% were prescribed two or more kinds of antibiotics • In 58.5% of cases, antibiotic prescriptions were given therapeutically

Studies suggesting the use antibacterial in Nepal

Authors	Main objectives	Antibiotic utilization
Paudel et al., 2008	• Prevalence of antimicrobial therapy in hospitalized patients in the internal medicine department	• A total of 274 patients received antimicrobial chemotherapy out of 428 patients admitted during study period. • Intravenous AMA was significantly higher (55.48, P<0.01) Ceftriaxone (30.2%) is the most frequently prescribed cephalosporin
Giri et al. 2008	• Surgical site infection and antibiotics use pattern in a tertiary care hospital in Nepal	• E. coli was the most organism isolated from surgical site infection • Combination of ampicillin and cloxacillin was the most commonly used antibiotic regimen (138 patients) followed by combination of ampicillin, cloxacillin and metronidazole (26 patients)
Shankar et al., 2007	• Fluoroquinolone utilization among inpatients in a teaching hospital in Nepal	• Average 6.5 ± 3.3 drugs were prescribed in 263 prescriptions • Ciprofloxacin was the most commonly prescribed drugs (6.83 DDD/100 bed-days) • Fluoroquinolones utilization were 7.6 DDD/100 bed-days
Shankar et al,. 2006	• Morbidity profile and prescribing pattern and working of community drug program in Health post	• A total of 2289 drugs were studied in 1186 prescriptions • Antibiotics were found to be 41.3% • Amoxicillin (10.1%) and Sulphonamides (9.4%) were more frequently antimicrobials
Alam et al., 2006	• Rational drug prescribing and dispensing in outpatients	• A total of 720 drugs were studied in 247 prescriptions • Antibiotics were found to be 12.1%
Lamichhane et al., 2006	• Morbidity profile and prescribing patterns among outpatients	• A total of 3532 drugs were studied in 1772 prescriptions • Antibiotics were found to be 26.4%
Shankar et al,. 2006	• Prescribing patterns among surgical outpatients	• A total of 925 drugs were studied in 595 prescriptions • Antibiotics were found to be 31.4%
Shankar et al., 2006	• Prescribing patterns among pediatric inpatients	• A total of 1614 drugs were studied in 356 prescriptions • Antibiotics were found to be 69.9%

Authors	Main objectives	Antibiotic utilization
Shankar et al., 2005	• Cephalosporin utilization in the inpatient wards of teaching hospital in Nepal	• 252 patients were prescribed cephalosporin out of 9845 patients admitted during study period • Cephalosporin utilization was 4.6 DDDs /100 bed-days • Cephalosporin contributed to 51.56% of total drug cost
Shankar et al., 2005	• Intensive care unit drug utilization in a teaching hospital	• Out of 259 patients studied, 149 (57.5%) of patients were prescribed antibiotics • Antibiotic utilization were 118 DDD/100 bed -days
Dawadi et al., 2005	• Pattern of antimicrobial prescription in respiratory tract infection	• A total of 412 drugs were studied in 190 prescriptions • Antibiotics were found to be 46.12%
Shankar et al., 2005	• Drug utilization with special reference to antimicrobials in Subhealth post	• A total of 2198 drugs were studied in 1464 prescriptions • Antibiotics were found in 59.9% (877) encounter • Out of 2198 drugs prescribed, antibiotic alone account 46% (1011) total drugs
Das et al., 2005	• Antimicrobial utilization pattern in out patient services of ENT department of tertiary care hospital	• A total of 191 prescriptions were randomly audited which contain a total of 218 antimicrobials • AMAs were indicated therapeutically in 73.29% of patients & 19.37% patients for prophylaxis • Ciprofloxacin (23.85%) was preferred, followed by amoxycillin (20.06%), combination of ampicillin + cloxacillin (9.17%), doxycyclin (5.96%) • Erythromycin (4.58%) and cotimoxazole (4.58%). Expensive drugs i.e azithromycin (2.75%), roxithromycin (1.37%) and cephalosporins (3.21%) were also prescribed • The causative microbes were sensitive to amoxycillin (53.84%), cloxacillin (53.84%) ciprofloxacin (46.15%), gentamicin (46.15%), and cephalosporin (46.15%). But resistant to erythromycin, tetracycline, cotrimoxazole and norfloxacin)
Das et al., 2004	• Antimicrobial utilization pattern in a district hospital	• A total of 452 drugs were studied in 1o6 prescriptions • Antibiotics were found to be 36.5%

Authors	Main objectives	Antibiotic utilization
Palikhe, 2004	• Prescribing pattern of antibiotics in pediatric hospital	• Study found 5.01±1.36 drugs / prescription which studied 121 prescriptions • Antibiotics were found to be 2.41±1.02 / prescription
Sarkar et al., (2004)	• Prescribing habits of dentists	• A total of 3698 drugs were studied in 1820 prescriptions • Antibiotics were found to be 39 %
Shankar et al., 2003	• Investigation of antimicrobial use pattern in the intensive treatment	• Study found 3.4 ± 1.8 drugs / patients which studied 295 patients admitted during study period • About half of patients (50.2%) of patients received an antimicrobial
Palikhe et al., 2004	• Prescribing regimens of prophylactic antibiotic used in different surgeries	• Ampicillin + Cloxacillin was the most used regimen 12.4 in Western Regional Hospital (WRH) and 34% in Manipal Teaching Hospital (MTH) • Ciprofloxacin and Cefotaxime was used 12.4% of patient in WRH • Ciprofloxacin and Gentamicin in 12% of patient in WRH • Ampicillin + Cloxacillin and Gentamicin in 22.4%
Shankar et al., 2003	• Prescribing pattern of antibiotics and sensitivity patterns of common microorganism	• A total of 347 antibiotics were prescribed to 203 patients • Of the 203 patients receiving antibiotics, 1, 2 and ≥3 antibiotics were prescribed in 48, 37 and 15% of patients • Most frequently prescribed were Ampicillin (24.8%), Amoxicillin (16.7%) and Metronidazole (13.2%)
Rehana et al., 1998	• Prescribing pattern and use of antimicrobial	• A total of 495 drugs were studied in 94 patients • Antibiotics were found 84% of prescription constituting 42.8% of total drugs studied
Rauniar et al., 2001	• Use of antimicrobial in elective cholecystectomy in B.P. Koirala Institute of Health Science	• A total of 163 elective cholecystectomies performed • Ciprofloxacin alone was given in 76.1% of cases where as Ciprofloxacin + Metronidazole was given in 17.8% of cases
Joshi et al., 1992	• Prescribing trend at In-patient departments of teaching hospital	• A total of 30842 drugs were studied in 3786 prescriptions • Antibiotics were found to be 72.4 %

Authors	Main objectives	Antibiotic utilization
Kafle et al., 1992	• Antibiotic usage in the surgical wards	• Four hundred patients admitted during study was studied for antibiotic uses. • Among them 98.9% of the operated and 76% of non operated patients received antibiotics • Of the 368 patients receiving antibiotics, 1, 2 and ≥3 antibiotics were prescribed in 39.1, 25 and 35.87% of patients
Kafle et al., 1991	• Prescribing pattern in outpatient	• A total of 813 drugs were studied in 404 prescriptions • Antibiotics were found to be 28.4 %
Joshi et al., 1991	• Antibacterial usage Teaching hospital	• A total of 642 drugs were studied in 477 prescriptions • Antibiotics were found to be 19.8%

Antibiotic policies in the hospitals

Authors	Country/ setting	Main objectives	Policy Level	Policy Process	Outcomes
Arda et al., 2007	• Turkey • 1788 beded Tertiary Care hospital • Intensive Care Units	• To evaluate the effect of antibiotic control policy on usage of restricted antibiotics, their cost, overall mortality, bacterial resistance patterns and nosocomial infection rates	National	• Ministry of finance is responsible for payback of over 90% of the population's health expenditure, announces restriction on use of parenteral antibiotics inside and outside of the hospital with new budget • The payback of parenteral vancomycin, teicoplanin, meropenem, imipenem, pipracillin/tazobactam, ticarcillin/clavulanate restricted without prior approval of infectious diseases specialists (IDS) • Payback of ceftriaxone, cefotaxime, ceftizoxime, cefoperazone, ceftazidime, cefoperazone/sulbactam, cefepime, ciprofloxacin, levofloxacin, netilmicin, amikacin and isepermicin was unlimited, when prescribed for first 72 hr of treatment for all specialists (except general practitioners) but further uses required ISD approval • Other antimicrobials could be prescribed without any restriction	• Overall daily defined dose/1000 patients/day of restricted drugs decreased, whereas unrestricted drugs increased significantly after the instruction • The cost of drugs decreased by 19.6% • Nosocomial infection rates in ICUs decreased significantly ($p < 0.05$). • Resistance to amoxycilline/clavulanate, ciprofloxacin, cefuroxime, cefotaxime, piperacilline/tazobactam and ESBL rate in Klebsiella pneumoniae decreased significantly ($p < 0.05$). • Amikacin resistance in Escherichia coli and Acinetobacter baumannii increased significantly ($p < 0.05$).

Antibiotic policies cont…

Authors	Country/ setting	Main objectives	Policy Level	Policy Process	Outcomes
Erbay et al., 2003	• Turkey • 1100 beded Tertiary Care hospital	• To evaluate rational antibiotic use in relation to diagnosis and bacteriological findings with an antibiotic restriction policy	Hospital	• Hospital antibiotic control committee impose antibiotic restriction policy on the purchase of antibiotics to the hospital pharmacy based on cost and annual resistance rates • A prior consultation with an infectious disease specialist (IDS) is required for ceftazidime, cefepime, imipenem, meropenem, ticarcillin-clavulanate, pipracillin-tazobactum and intravenous formulations of quinolones, vancomycin and teicoplanin	• The most frequently requested were first generation cephalosporins (19.9%), ampicillin-sulbactam (19.1%) and aminoglycosides (11.7%) • Inappropriate antibiotic use was significantly higher among unrestricted antibiotics than restricted ones (P<0.001). Irrational antibiotic use was high for unrestricted antibiotics
Mamdani et al., 2007	• Canada • Entire Ontario residents • Use of administrative healthcare database	• To study the impact of fluoroquinolone restriction policy elderly individuals	State	• The province of Ontario instituted a fluoroquinolone restriction policy in March of 2001	• Immediately after the introduction of the fluoroquinolone policy, fluoroquinolone prescription rates decreased to approximately 70% of expected rates (P < .01) • Approximately 30% higher than expected use of sulfonamide (P = .01) and urinary anti-infectives (primarily nitrofurantoin and trimethoprim; P < .01) were observed within 1 year after policy implementation • No significant changes in the use of any other groups of antibiotics were observed. Although no significant changes in the rates of overall infection-related hospital admissions among antibiotic users were observed

Antibiotic policies cont…

Authors	Country/ setting	Main objectives	Policy Level	Policy Process	Outcomes
Ho et al., 2004	• Taiwan • National Health Research Institute Database	• To study changes before and after a policy to restrict antimicrobial usage in upper respiratory infections	National	• Taiwan has a universal health insurance system • The Bureau of National Health Insurance (BNHI) of Taiwan issued a new reimbursement regulation effective from 1 February 2001 forbidding the use of antimicrobials in ambulatory patients with upper respiratory infections (URI) without evidence of bacterial infection	• Between 1999 and 2001, antimicrobials for respiratory infections decreased from 18.0 to 9.97 DDD/1000 per day or by 44.6% (P=0.0000+) • Antimicrobials for URI decreased from 8.32 in 1999 to 3.28 DDD/1000 per day in 2001 or by 60.6% (P=0.0000+); from 2000 to 2001 the decrease was 55.8%. • Reduction of antimicrobials for URI from 1999 to 2001 accounted for 62.8% of the reduction of antimicrobials in respiratory infections or 51.3% of the total reduction of antimicrobials.
O'Connor et al., 2004	• United Kingdom	• To establish whether changing an antibiotic policy with the aim of reducing the use of injectable cephalosporins leads to a reduction in the incidence of C. difficile diarrhoea in elderly patients	Hospital	• In July 2000, in the light of increasing numbers of cases of C. difficile diarrhoea, restrictions were made on the indications for third-generation cephalosporins. Ceftriaxone was the only intravenous third-generation cephalosporin in use in the department throughout the study period. As a principle of the new policy, the use of all intravenous second- and third-generation cephalosporins was discouraged if alternatives were available.	• Intravenous cephalosporin use fell from 210 to 28 defined daily doses ($p < 0.001$) following the change in antibiotic policy, with a corresponding increase in piperacillin-tazobactam ($p < 0.001$) and moxifloxacin ($p < 0.001$) use. • The new policy led to a significant reduction in C. difficile diarrhoea cases. The relative risk of developing C. difficile infection with the old policy compared to the new policy was 3.24 (95%CI 1.07-9.84, $p = 0.03$)

APPENDIX B

Ethical Approval Letter from Nepal Health Research Council

Nepal Health Research Council

Estd. 1991

NHRC

Ref. No. 463

30 November 2010

Mr. Kadir Alam
Principal Investigator
Department of Pharmacology
Manipal College of Medical Sciences
Pokhara, Nepal

Ref: Approval of Research Proposal entitled **Utilization pattern and controlling system of antibiotic in tertiary care hospital in Nepal**

Dear Mr. Alam,

It is my pleasure to inform you that the above-mentioned proposal submitted on dated 1 August 2010 has been approved by NHRC Ethical Review Board on 28 November 2010 (2067-08-12).

As per NHRC rule and regulation, the investigator has to strictly follow the protocol stipulated in the proposal. Any change in objective(s), problem statement, research question or hypothesis, methodology, implementation procedure, data management and budget that may be necessary in course of the implementation of the research proposal can only be made so and implemented after prior approval from this council. Thus, it is compulsory to submit the detail of such changes intended or desired with justification prior to actual change in the protocol.

Further, the researchers are directed to strictly abide by the National Ethical Guidelines published by NHRC during the implementation of your research proposal.

As per your research proposal, your research is self-funded and NHRC processing fee is US$ 100.

If you have any questions, please contact our research section.

Thanking you.

Sincerely Yours,

Dr. Shanker Pratap Singh
Member Secretary

Tel.+977-1-4254220, 4227460, Fax: +977-1-4262469, RamShah Path, P.O. Box 7626, Kathmandu, Nepal.
Website: http://www.nhrc.org.np, Email : nhrc@healthnet.org.np

Ethical Approval Letter from Manipal Teaching Hospital

MANIPAL COLLEGE OF MEDICAL SCIENCES
POKHARA, NEPAL

(AFFILIATED TO KATHMANDU UNIVERSITY)

MEMG/NHRC/GA

12 March 2010

Manipal College of Medical Science Pokhara Nepal

Mr Kadir Alam
Lecturer
Department of Pharmacology
Manipal College of Medical Sciences,
Pokhara, Nepal

Subject : **Permission to Carry out Research Work at MTH.**

Dear Mr Kadir Alam,

1. Reference your application dated 12 Feb 2010.

2. Permission is hereby accorded for carrying out research work on "Utilization Pattern and Controlling System of Antibiotics in Tertiary Care Hospital in Nepal", on the following conditions :-

(a) The research work has to be completed within the specified period.

(b) You have to report to the undersigned before commencing the research work.

(c) You have to submit a monthly progress report to IRC, MCOMS on the status of your research work.

Dr VM Alurkar
Member Secretary
IRC, MCOMS, Pokhara

Copy to

Dr Archana Saha - for information please.
Prof &Head
Department of Pharmacology
MCOMS, Pokhara

/niure

Ethical Approval Letter from Western Regional Hospital

नेपाल सरकार
स्वास्थ्य तथा जनसंख्या मन्त्रालय
पश्चिमाञ्चल क्षेत्रीय अस्पताल बिकास समिति
रामघाट, पोखरा ।

प.सं.२०६६/०६७
च.न. ११५५

मिति: २०६६।११।४

विषय: सोधकर्यका लागी अनुमती दिइएको ।

श्री सम्पूर्ण बिभाग
प.क्षे.अस्पताल, पोखरा ।

मणिपाल कलेज अफ मेडिकल साईन्सेज फर्माकोलोजिका लेक्चरर कदिर आलम लाई त्यस बिभागमा "Utilization pattern and controlling system of abtibiotics in tertiary care hospital in Nepal" विषयमा सोधकार्य गर्न अनुमति दिइएको व्यहोरा अनुरोध छ ।

बोधार्थ
श्री कदिर आलम
मणिपाल कलेज अफ मेडिकल साइन्सेज

.....
डा. बुद्धि बहादुर थापा
नि.मे.सु.
मेडिकल सुपरिन्टेन्डेण्ट

Ethical Approval Letter from Bir Hospital

Government of Nepal
Ministry of Health and Population
National Academy of Medical Science
Bir Hospital

Ref. No.: 1775

Mahabouddha, Kathmandu

Date: .....२०६७।१०।३.....

Subject: अनुसन्धान कार्यमा सहयोग गरिदिने वारे ।

श्री प्रमुख ज्यु, मेडिकल विभाग
श्री प्रमुख ज्यु, सर्जरी विभाग
श्री प्रमुख ज्यु, अर्थोपेडिक विभाग
श्री प्रमुख ज्यु, ई. एन. टि. विभाग
श्री प्रमुख ज्यु, माईक्रोवायोलोजी युनिट ।

प्रस्तुत विषयमा Utilization pattern and controlling system of Antibiotics in tertiary care Hospital in Nepal विषयमा अनुसन्धान कार्यमा संलग्न मनिपाल मेडिकल कलेजमा कार्यरत सहायक प्राध्यापक श्री कादिर आलमलाई आवश्यक सहयोग गरिदिनु हुन अनुरोध छ । निजले पेश गरेको Nepal Research Council को मिति 30 Nov 2010 को Research Approval letter को प्रतिलिपि यसैसाथ संलग्न छ ।

निर्देशक
प्रा.डा. बुलन्द थापा
निर्देशक

बोधार्थ :

श्री कादिर आलम

Ph. No.: 977-1-4221800, 977-1-4221119, 977-1-4221988, Fax: 977-1-4222864

Ethical Approval Letter from KIST Hospital

Regd. No. : 38970/062/063

किष्ट मेडिकल कलेज
KIST MEDICAL COLLEGE
Imadol VDC-6, Lalitpur, Nepal, Tel. : 977-1-5201682, Fax: 977-1-5201496
Email: kistmc@wlink.com.np ● Web: www.kistmcth.edu.np
GPO Box: 14142, Kathmandu, Nepal

Ref. No : KISTMC – BS/067-068/191

To
Mr. Kadir Alam
PhD student
Chulalangkorn University
Thailand.
Asst. Professor
Department of Pharmacology
Manipal College of Medical Sciences
Pokhara.

Sub: Approval of research proposal

Dear Mr. Kadir Alam

With reference to your application for carrying out your study titled **'Utilization pattern and controlling system of antibiotic in tertiary care hospital in Nepal'** for the award of PhD degree at KIST Medical College I am pleased to inform you that permission has been granted based on your research proposal and approval letter of the study by the Nepal Health Research Council (NHRC). You are requested to submit a soft copy of your completed research proposal to the IRC of KIST Medical College. You are requested to kindly coordinate with the Program Coordinator, Dr. Ravi Shankar and the Clinical Coordinator, Dr RM Piryani regarding the conduct of your research at KIST Medical College.

Wishing you best of luck in the research

25th Jan 2011
Prof. BMS Karki
Chairperson
IRC, KIST Medical College

CC File

Ethical Approval Letter from Dhulikhel Hospital

To
Dr. Rajendra Koju
Chief Administrative officer
Dhulikhel Hospital
Dhulikhel, Kavre, Nepal

Subject: Permission to carryout research work

Respected Sir,

This is to inform you that I am Kadir Alam, Assistant Professor in department of pharmacology, Manipal college of Medical sciences, Pokhara, Nepal. I am doing PhD from Chulalongkorn University, Bangkok, Thailand. My research topic is "Utilization pattern and controlling system of Antibiotic in tertiary care hospital in Nepal." In this regard, I need to interview some of Clinician, Microbiologist Pharmacists, Nurses & related healthcare professionals on controlling system of antibiotics.

My research proposal is already ethically approved by Nepal Health Research council (NHRC). A copy of approval letter is attached with this. Hence, I humbly request you to allow me to conduct the research work in your esteemed reputed hospital.

Thanking you

Sincerely
Kadir Alam
Asst. professor
Dept of pharmacology
Manipal Medical college
Pokhara, Nepal

approved

APPENDIX C

Combination of antibiotics used in the treatments

Antibiotics	Alone	Aminoglycoside	Cephalosporin	Chloramphenicol	Co-amoxyclav	Cotrimoxazole	Macrolide	Penicillin	Quinolone	Tetracycline	Miscellaneous
WRH											
Aminoglycoside	12		651	5	31	6	155	375	69	11	276
Cephalosporin	519	651		8	32	12	308	151	88	9	373
Chloramphenicol	0	5	8		0	1	7	2	5	2	6
Co-amoxyclav	16	31	32	0		3	78	7	10	0	30
Cotrimoxazole	0	6	12	1	3		9	9	7	7	12
Macrolide	10	155	308	7	78	9		156	52	7	84
Penicillin	91	375	151	2	7	9	156		54	2	296
Quinolone	60	69	88	5	10	7	52	54		7	449
Tetracycline	2	11	9	2	0	7	7	2	7		14
Miscellaneous	21	276	373	6	30	12	84	296	449	14	
MTH											
Aminoglycoside	12		173	2	4	1	7	84	22	1	83
Cephalosporin	276	173		0	11	3	62	51	61	2	291
Chloramphenicol	0	2	0		0	0	0	2	1	0	2
Co-amoxyclav	25	4	11	0		0	9	7	2	2	15
Cotrimoxazole	0	1	3	0	0		0	1	0	0	1
Macrolide	14	7	62	0	9	0		10	4	1	18
Penicillin	183	84	51	2	7	1	10		12	2	59
Quinolone	84	22	61	1	2	0	4	12		0	206
Tetracycline	5	1	2	0	2	0	1	2	0		4
Miscellaneous	37	83	291	2	15	1	18	59	206	4	

* Other antibiotic: Metronidazole (P), Nitrofurantoin, Vancomycin, Piperacillin + Tazobactam, Polymyxin B

Group of Antibiotics in various Co-morbid conditions

Source of Infection (Co-morbid condition)	Aminoglycoside		Cephalosporin		Amoxyclav		Penicillin		Macrolide		Quinolone	
	WRH	MTH	WRH	MTH	WRH	MTH	WRH	MTH	WRH	MTH	WRH	MTH
Respiratory Tract Infection	0.55	.22	0.5	.52	0.13	.15	0.67	.33	0.38	.19	0.04	.11
Urinary Tract Infection	0.48	.14	0.8	.52	0.02	-	0.11	.16	0.29	.07	0.23	.43
Sepsis	0.87	.83	0.81	.53	0.01	-	0.28	.50	0.04	.11	0.03	.03
Intraabdominal Infection	0.2	.11	0.57	.93	0.02	.02	0.2	.05	0.18	.04	0.43	.25
Prophylaxis	0.23	.15	0.53	.58	0.02	.04	0.59	.30	0.1	.04	0.26	.25
Soft tissue infection	0.33	-	0.65	.75	0.05	-	0.48	.25	0.12		0.16	-
Surgical site infection	0.33	-	0.67	-	-	-	0.33	-	0.17		0.17	-
Pelvic Infection	0.5	-	-	.25	-	-	-	-	-	.25	-	.75
Ear-nose-throat Infection	-	.09	0.5	1.07	-	.05	1	.09	-	.04	-	.08
CNS infection	0.19	.50	0.89	.34	0.04	-	0.37		0.11		-	-
Gastroenteritis	0.16	.05	0.81	1.05		-	0.08	.09	0.2	.01	0.27	.72
Bone and Joint infection	0.19	.42	0.95	.31	0.03	.05	0.3	.05	0.08	.06	0.13	.14
Other	0.38	.15	0.45	.25	0.05	.08	0.67	.69	0.09		0.19	.08

DDD distribution of Antibiotics

Antibiotics Class	ATC Code	Antibiotic	ATC code	DDD *	DDD/100 bed-day (MTH)	DDD/100 bed-days (WRH)
Penicillins	J01C	Ampicillin	J01CA01	2 g	0.59	2.64
		Amoxicillin	J01CA04	1 g	1.74	1.13
		Cloxacillin	J01CF02	2 g	0.77	**6.59**
		Cumulative DDD of penicillin			**3.1**	**10.36**
Cephalosporin	J01D	Cefadroxil	J01DB05	2 g	0.063	
		Cefazolin	J01DB04	3 g	0.202	0.24
		Cefuroxime (P)	J01DC02	3g	0.033	0.28
		Cefuroxime (O)	J01DC02	0.5 g	0.046	0.23
		Cefotaxim	J01DD01	4 g	1.198	**5.49**
		Ceftazidime	J01DD02	4 g	0.031	0.07
		Ceftriaxon	J01DD04	2 g	**5.279**	**11.57**
		Cefixime	J01DD08	0.4 g	0.924	1.29
		Cefpodoxime	J01DD13	0.4 g	0.405	0.18
		Cumulative DDD of Cephalosporin			**8.181**	**19.35**
Combinations of β-lactum, incl. beta-lactamase inhibitors	J01CR	Co-amoxiclav (O)	J01CR	1 g	0.40	0.84
		Co-amoxiclav (P)	J01CR	3 g	0.45	1.84
		Ampi.+ Sulbatum	J01CR01	2g		0.38
		Piperacillin and enzyme inhibitor	J01CR05	14g	0.77	0.04
		Cumulative DDD for combination of β-lactum and β-lactamase inhibitors			**1.62**	**3.1**
Macrolides	J01F	Clarithromycin	J01FA09	0.5 g	0.13	0.35
		Azithromycin	J01FA10	0.3 g	1.28	**10.21**
		Cumalative DDD for Macrolides			**1.41**	**10.56**
Aminoglycoside	J01G	Amikacin	J01GB06	1 g	0.83	2.56
		Tobramycin	J01GB01	0.24g	0.08	0.31
		Gentamicin	J01GB03	0.24g	0.88	3.42
		Cumalative DDD for Aminoglycoside			**1.79**	**6.29**
Quinolones	J01M	Ofloxacin	J01MA01	0.4 g	0.03	1.28
		Ciprofloxacin (O)	J01MA02	1 g	1.08	0.93
		Ciprofloxacin (P)	J01MA02	0.5 g	**1.43**	**4.58**
		Norfloxacin	J01MA06	0.8 g	0.20	
		Levofloxacin (O)	J01MA12	0.5 g	0.07	0.08
		Cumulative DDD for Quinolones			**2.81**	**6.87**
Tetracycline	J01A	Doxycycline (O)	J01AA02	0.1 g	0.35	0.42
Others	J01X	Metronidazole (P)	J01XD01	1.5 g	**2.90**	**11.50**
		Vancomycin	J01XA01	2g	0.05	
Total Cumulative DDD/100 bed days in hospital					**22.211**	**68.45**

Mean cost of treatments in different co-morbid conditions

Co-morbidity	Hospitals	Total Cost		Cost of Antibiotics		% cost share of Antibiotic
		Mean	Std. dev	Mean	Std. dev	
Respiratory Tract Infection	MTH	1242.72	1738.71	996.78	1699.99	80.21
	WRH	1561.08	1712.82	917	1148.69	58.74
Urinary Tract Infection	MTH	1162.14	2018.42	799.73	1627.71	68.82
	WRH	1573	1331.17	1169.28	886.81	74.33
Sepsis	MTH	808.43	814.3	707.63	747.21	87.53
	WRH	1011.63	1224	678.9	494.3	67.11
Intraabdominal Infection	MTH	1465.79	913.93	1050.65	754.94	71.68
	WRH	2286.88	2361.99	1303.09	1261.97	56.98
Prophylaxis	MTH	1255.76	1837.32	841.85	1346.71	67.04
	WRH	1521.49	2821.47	949.76	1661.24	62.42
Soft tissue infection	MTH	218.4	127.38	126.3	52.88	57.83
	WRH	1762.64	2856.88	1230.71	2301.83	69.82
Surgical site infection	MTH					
	WRH	1501.7	1118.39	1322.55	1101.22	88.07
Pelvic Infection	MTH	1244.11	843.62	991.24	780.94	79.67
	WRH	801.76	568.17	686.34	637.9	85.60
Ear-nose-throat Infection	MTH	1302.43	773.95	848.81	559.74	65.17
	WRH	4400.78	6195	1864.53	2612.96	42.37
CNS infection	MTH	13876.9	4893.77	12790.7	4987.66	92.17
	WRH	1785.18	1852.33	1285.44	1444.82	72.01
Gastroenteritis	MTH	879.52	835.41	639.41	775.64	72.70
	WRH	930.61	1308.62	678.75	907.96	72.94
Bone and Joint infection	MTH	1687.94	1621.88	1237.39	1321.57	73.31
	WRH	1519.59	1961.62	1117.47	1630.08	73.54
Other	MTH	887.12	758.71	630.81	717.65	71.11
	WRH	1680.08	5270.12	659.31	672.51	39.24

Cost of treatment in different departments

Departments	Hospitals	Total Cost (NRs)		Cost of Antibiotics (NRs)		% cost share of Antibiotic
		Mean	Std. dev	Mean	Std. dev	
Medicine	MTH	1438.03	2177.47	1016.15	1865.77	70.66
	WRH	2112.99	2317.92	1250.27	1246.13	59.17
OBG	MTH	779.12	753.65	524.81	525.54	67.36
	WRH	925.07	1223.1	688.09	893.44	74.38
Orthopedics	MTH	1766.16	1661.51	1351.9	1342.35	76.54
	WRH	1837.67	2206.34	1354.8	1794.6	73.72
Pediatrics	MTH	1080.7	1768.7	805.41	1342.93	74.53
	WRH	994.54	1162.83	730.27	930.33	73.43
Surgery	MTH	1337.37	1632.39	940.93	1259.57	70.36
	WRH	2490.83	3858.8	1314.37	2080.08	52.77
ICU	MTH	2973.48	3764.2	2444.83	3018.86	82.22
	WRH	5225.71	7076.84	2912.84	6500.95	55.74
Neurosurgery	MTH	2451.47	2256.49	1640.17	1734.63	66.91
	WRH	2491.38	1554.31	1466.73	1280.46	58.87
Neonatal ICU	MTH	621.61	449.73	522.1	351.65	83.99
	WRH	763.95	656.45	602.16	569.74	78.82
Post Operative	MTH					
	WRH	4874.49	5879.02	1595.23	886.01	32.73
Dental	MTH	1655.08	1079.61	970.27	452.44	58.62
	WRH					
Dermatology	MTH	569.02	429.04	267.14	362.36	46.95
	WRH					
Emergency	MTH	1297.81	976	717.34	456.81	55.27
	WRH					
ENT	MTH	1580.62	1321.89	948.27	801.98	59.99
	WRH	440.11	430.39	337.24	311.28	76.63
Oncology	MTH	5037.79	4031.35	4129.78	3535.28	81.98
	WRH	8598.98	6604.24	4015.89	2050.6	46.70
Missing	MTH	1134.5	1433.12	830.24	1106.53	73.18
	WRH	1588.36	2180.44	1127.58	1649.78	70.99

Isolated organism

Organism	Specimen in Manipal Teaching Hospital					Specimen in Western Regional Hospital				
	Blood (n=209)	**Urine** (n=1238)	**Pus** (n=386)	**Body fluid** (n=360)	**Sputum** (n=274)	**Blood** (n=101)	**Urine** (n=30)	**Pus** (n=16)	**Body fluid** (n=7)	**Sputum** (n=3)
Gram Negative										
H. influenzae			1		5					
E. coli		205	42	2	3	1	3	2		
K. pneumoniae		17	12		7					
Enterobactor spp	1	5	8	1	4					
S. typhi	2								1	
Acinetobacter spp		10	5	1	7	2				
Citrobactor spp		3	6		2		2	4		
Proteus		6	5		1					
Pseudomonas		6	17		23		5	1		
Neisseria gonnorrhoea			2							
Moraxella Catterhalis					1					
Shigella flexhen				2				1	2	
Gram –ve bacteria						1				1
Gram Positive										
S. aureus	2	4	77	2	1	5		5		
Streptococcus pyogen			8	1	6					
Streptococcus pneumoniae			2		10	2				
Coag –ve. staph		3	3			3				
Enterococus		26	15			2				
Others										
Candida spp		3	3		13					
yersiinia								1		
Insignificant bacteriurea		166								
Noramal flora			64		168					
Multiple organism growth		72								
Contaminated growth	5	19		1	1					
No Growth	199	691	116	350	22	85	20	2	4	2

Resistance of various organisms

Antibiotic / Hospitals	Amikacin	Ampicillin	Amoxicillin	Azithromycin	Cefazolin	Ceftriaxone	Cefotaxim	Cephalexin	Chloramphenicol	Ciprofloxacin	Cloxacillin	Co-Amoxyclav	Co-trimoxazole	Gentamycin	Imipenem	Nitelmycin	Nitrofurantoin	Norfloxacin	Ofloxacin	Penicillin	Piperacillin	Tetracycline	Tobramycin	Vancomycin
H. influenza																								
MTH (n=6)	-	50	-	0	-	0	0	100	100	0	-	60	100	-	-	-	-	-	-	-	-	100	-	-
WRH (n=0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
K. pneumonia																								
MTH (n=36)	0	80	100	-	66.6	40	58	75	-	37.5	-	-	42.8	17.6	-	-	27.2	10	0	100	100	0	0	0
WRH (n=0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Streptococcu (Pneumonia+Pyogen)																								
MTH (n=27)	50	0	0	-	0	14.3	0	14.3	-	33.3	0	0	25	25	0	-	-	-	33.3	9	0	0	0	50
WRH (n=2)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Acinetobacter																								
MTH (n=23)	40	75	100	-	0	50	0	50	0	66.7	-	-	75	66.6	0	0	66.6	66.6	80	50	75	-	85.7	0
WRH (n=2)	0	100	-	0	-	50	-	-	-	0	-	-	-	0	-	-	-	-	0	-	-	-	-	-
Proteus sp.																								
MTH (n=12)	0	80	50	-	50	0	0	100	-	16.7	-	-	50	0	-	-	75	0	50	100	0	100	-	-
WRH (n=0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Antibiotics used in the treatment of Enteric Fever

Antibiotics	Alone	Aminoglycoside	Cephalosporin	Chloramphenicol	Co-amoxyclav	Macrolide	Penicillin	Quinolone	Tetracycline	Miscellaneous
WRH										
Aminoglycoside	1		30	0	0	15	2	3	0	6
Cephalosporin	16	30		1	2	49	3	4	1	15
Chloramphenicol	0	0	1		0	1	0	0	0	2
Co-amoxyclav	0	0	2	0		2	1	1	0	1
Macrolide	0	15	49	1	2		3	3	0	8
Penicillin	0	2	3	0	1	3		0	0	1
Quinolone	1	3	4	0	1	3	0		0	2
Tetracycline	0	0	1	0	0	0	0	0		0
Miscellaneous	2	6	15	2	1	8	1	2	0	
MTH										
Aminoglycoside	0		23	0	0	3	1	7	0	6
Cephalosporin	33	23		0	0	11	4	19	13	16
Chloramphenicol	0	0	0		0	0	0	0	0	0
Co-amoxyclav	0	0	0	0		0	0	0	0	0
Macrolide	0	3	11	0	0		1	1	1	1
Penicillin	0	1	4	0	0	1		2	0	1
Quinolone	2	7	19	0	0	1	2		5	3
Tetracycline	0	0	13	0	0	1	0	5		3
Miscellaneous	0	6	16	0	0	1	1	3	3	

Common drug-drug interactions

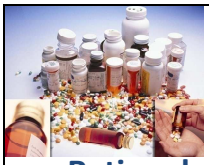
Drug	Drug	Interaction	Severity	Documentation	WRH	MTH
Amitryptaline	Metoclopramide	Concurrent use may result in an increased risk of extrapyramidal reactions or neuroleptic malignant syndrome.	Contraindicated	Fair	-	√
Ibuprofen	Ketorolac	Concurrent use may result in enhanced GI adverse effects (peptic ulcers, GI bleeding and/or perforation).	Contraindicated	Fair	-	√
Amitryptaline	Chloroquine	Concurrent use of may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).	Major	Good	√	-
Amikacin	Furosemide	Concurrent use may result in increased amikacin plasma & tissue concentrations & additive ototo and/or nephrotoxicity	Major	Fair	√	√
Ketorolac	Norfloxacin	Concurrent use may result in an increased risk of seizures	Moderate	Fair	√	-
Ampicillin	Pantoprazole	Concurrent use may result in loss of ampicillin efficacy	Moderate	Fair	√	√
Furosemide	Ibuprofen	Concurrent use may result in decreased diuretic & antihypertensive efficacy.	Moderate	Good	√	√
Chloroquine	Ciprofloxacin	Concurrent may result in increased ciprofloxacin urinary excretion	Moderate	Good	√	-
Antacid	Ciprofloxacin	Concurrent use may result in decreased ciprofloxacin effectiveness	Moderate	Good	-	√
Ciprofloxacin	Diclofenac	Concurrent use may result in increased ciprofloxacin plasma concentrations	Moderate	Excellent	-	√
Doxycycline	Ferrous sulphate	Concurrent use may result in decreased tetracycline and iron effectiveness.	Moderate	Good	-	√

APPENDIX D

Interviews categorization

Category of interviews	Academic qualification (Degree)	Number
Pharmacist	Master of Pharmacy	5
	Diploma of Pharmacy	2
Pharmacologist	Pharmacology (M.D.)	1
Microbiologists	Doctor (Ph.D)	1
	M.D. Microbiology	1
	M.Sc. Microbiology	4
Clinician	Paediatician (M.D)	3
	Medicine (M.D.)	12
	Gynecologist (M.D.)	2
	Orthpedician (M.D)	2
	Surgeon (M.D.)	4
	Dental Surgeon (MDS)	1
	E.N.T Specialist (M.D)	2
Hospital Administrator/ DTC chairman /Antibotic committee chairman	Medical Doctor (M.D)	6
Other	Nurse (B. Nursing)	1

Presentation on Rational Use of Antimicrobial



Rational use of antimicrobials: The Nepalese perspective

- Dr. P. Subish MPharm, PhD

College of Medical Sciences, Bharatpur

E-mail: subishpalaian@gmail.com

- Dr. P. Ravi Shankar MD

KIST Medical College, Lalitpur

E-mail: ravi.dr.shankar@gmail.com

Friday, 22nd April (3.15 -3.30 pm)

2

Areas which will be covered in next 15 mins.

- Antimicrobial resistance
- Implications of antimicrobial resistance
- Rational use of medicines
- Problems with use of antimicrobials in Nepal

3

Antimicrobials

- Antibiotics
- Antivirals
- Antifungals
- Anthelminthics

4

Problem of antimicrobial resistance

- High percentage of resistance among shigella and E. coli
- Typhoid fever
- Intensive care units
- Neonatal intensive care units
- Recovery rooms

Problem of antimicrobial resistance

- Community infections
- TB
- HIV/AIDS
- TB and HIV/AIDS
- Higher cost
- Increased morbidity & mortality

6

Nepal report

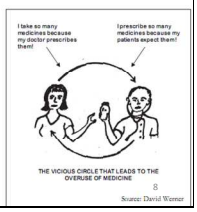
Year	Initial Any Resistance	Initial MDR	Acquired Any Resistance	Acquired MDR
1999	13.32%	3.74	28.20%	11.96%
2002	10.99%	1.32%	40.93%	20.46%
2007	14.71%	2.86%	25.3%	11.72%

Sharat C Verma, National TB Center

7

Rational use of medicines

- Patients receive medicines appropriate to their clinical needs, in doses that satisfy their own individual requirements and at the lowest cost to them and their community
- Different RIGHTS



8

Are antimicrobials used rationally in Nepal?

- Over-use
- Availability OTC
- Lack of standard treatment guidelines
- Guidelines if available non-adherence
- Newer antibiotics freely available

Are antimicrobials used rationally in Nepal?

- Use of antibiotics for SAP
- Compliance (concordance)
- Stopping antibiotics on feeling better
- Cost of medicines (antimicrobials)
- Resistance to anti-TB drugs
- MDR-TB, XDR-TB
- HIV and TB (Resistance to antiretrovirals)

10

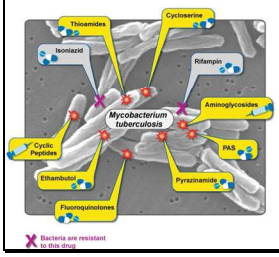
Improving antibiotic use in tertiary hospitals

- Medicine (drug) and Therapeutics Committee
- Regulating pharmaceutical promotion
- Antibiotic use guidelines
- Restricting use of newer and reserve antimicrobials
- Lack of microbiological support should not be taken as excuse for over-use of antimicrobials

11

Comments from experts

- How do we improve antimicrobial use in tertiary care hospitals?



3 mins.

12

Presentation on National Antibiotics Treatment Guidelines

National Antibiotics Treatment Guidelines (Draft, June 2010)

Bhupendra B.Thapa
Ministry of Health and Population

1

Introduction

- Guidelines initially drafted by Alliance for Prudent Use of Antibiotics, Nepal Chapter (APUA-Nepal)
- Submitted to Ministry of Health and Population for Implementation
- Ministry consulted experts, organised workshop and finalised the draft in June , 2010

2

World Health Day 2011

- Antimicrobial Resistance :
  No action today – No cure tomorrow
- AMR addressed by WHA 58.27
- ARM Strategy SEAR 2010 -2015

3

General chapters (from APUA)

- Relative Safety of Antimicrobial Agents in Pregnancy and Breast-feeding
  - Pregnancy: safety scale A (Safe)– D (Risky)
  - Breast-feeding : Safe; uncertain; avoid
- Antibiotic Prophylaxis in Surgery
- Topical Antibiotics
- Antimicrobial Combinations

4

Guidelines

- No detailed guidelines (as treatment protocol, STG)
  (Guidelines for various programes developed and used)
- Disease: symptom and signs – treatment
- Prevention and referral where appropriate
- Categorization of health facilities
- SHP/HP/PHCC/District Hospital (District hospital separate class in certain case)
- Zonal and above or referral centre

5

Disease classification

- GENERAL MEDICINE
- OPHTHALMOLOGY
- Obstetrics and Gynaecology
- SEXUALLY TRANSMITTED INFECTION
- ENT
- SURGERY
- Dentistry

6

Antibacterials included in Treatment Guidelines
(compared to EDL2011)

- Amoxicillin +clavulanic acid tablet (Not in EDL, except for DR-TB)
- Ampicillin Inj
- Azithromycin tablet
- Benzathine Penicillin Inj
- Benzyl penicillin G Inj
- Cefaclor capsule (Not in EDL)
- Cefixime tablet
- Cefotaxime Inj (Not in EDL)

7

Antibacterials Continued....

- Cefpodoxime capsule (Not in EDL)
- Ceftazidine Inj. (Not in EDL)
- Ceftriaxone Inj
- Cefuroxime axetil capsule (Not in EDL)
- Cephalexin capsule (Not in EDL)
- Chloramphenicol capsule
- Chloramphenicol ear drop
- Chloramphenicol eye ointment

8

Antibacterials Continued...

- Ciprofloxacin ear drops
- Ciprofloxacin eye ointment
- Ciprofloxacin Inj.& tablet
- Clarithromycin tablet (Not in EDL)
- Clotrimazole tablet
- Clotrimazole ear drops
- Clotrimazole vaginal pessary
- Cloxacillin capsule
- Cotrimoxazole tablet
- Doxycycline tablet/capsule
- Erythromycin tablet & syp.

9

Antibacterials Continued...

- Fluconazole tablet
- Gentamicin Inj
- Gentamycin eye drops and ointment
- Gentian Violet (ear drop?)
- Meropenem injection (Not in EDL)
- Metronidazole Inj.
- Metronidazole tablet
- Nitrofurantoin tablet
- Norfloxacin tablet (Not in EDL)

10

Antibacterials Continued...

- Ofloxacin tablet (Not in EDL, except for DR-TB)
- Piperacillin +Sulbactam (Not in EDL)
- Procaine penicillin Inj.
- Silver suphadiazine cream
- Spectinomycin Inj (Not in EDL)
- Teicoplanin inj (Not in EDL)
- Tertracycline capsule
- Tinidazole tablet
- Vancomycin Inj. (Not in EDL)
- Variconazole (Not in EDL)

11

Included in EDL 2011, but NOT in treatment protocol

- Phenoxymethyl penicillin (Penicillin V) tablet
- Cefazolin injection
- Nalidixic acid tablet
- Nystatin lozenges
- Diloxanide furoate tablet

(Hence, before finalisation of Treatment Protocol, it has to be harmonsied with EDL, so that only antibacterials included in EDL would be used for treatment)

12

Presentation on International Antibiotic Policy

International Antibiotic Policy

Niyada Kiatying-Angsulee, Ph.D.
Pranaya Mishra, Ph.D.
Kadir Alam, M.S.
22 April 2011

1

'it is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body …..'

Alexander Fleming 1945

2

World Health Day 2011

- 7 April 2011
- Combat Drug Resistance: No Action Today No Cure Tomorrow (WHO)
- Use Antibiotic Rationally (SEARO)
- Save the Pill for the Really Ill (ReAct)

3

WHO Global Strategy for Containment of Antimicrobial Resistance

- Part A. Introduction and background
- Part B. Appropriate antimicrobial use and emerging resistance: issues and interventions
- Part C. Implementation of the WHO Global Strategy

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Part A. Introduction and background

- Introduction
- Antimicrobial resistance is a global problem that needs urgent action
- A global problem calls for a global response
- Implementation of the WHO Global Strategy
- Background
- What is antimicrobial resistance?
- Appropriate use of antimicrobials
- Surveillance of antimicrobial resistance
- The prevalence of resistance
- Conclusion

5

Part B. Appropriate antimicrobial use and emerging resistance: issues and interventions

- Chapter 1. Patients and the general community
- Chapter 2. Prescribers and dispensers
- Chapter 3. Hospitals
- Chapter 4. Use of antimicrobials in food-producing animals
- Chapter 5. National governments and health systems
- Chapter 6. Drug and vaccine development
- Chapter 7. Pharmaceutical promotion
- Chapter 8. International aspects of containing antimicrobial resistance

6

Part C. Implementation of the WHO Global Strategy

- Introduction
- Prioritization and implementation
- Implementation guidelines
- Monitoring outcomes
- Summary
- Recommendations for intervention
- Suggested model framework for implementation of core interventions

7

Regional Strategy on Prevention and Containment of Antimicrobial Resistance

2010-2015

Situation

- Neglected problem of antimicrobial resistance with profound impact on health and economy.
- Inadequate visibility at the decision-making level in spite of WHA resolutions.
- Absence of a national approach/direction to combat the emerging problem of antimicrobial resistance.
- Lack of education among prescribers and users.
- Weak collaboration between stakeholders.
- Poor or no systematic surveillance of resistance and consumption of antimicrobial agents.
- Ineffective regulatory mechanisms.
- Lack of economic potential/incentives for pharmaceuticals to invest in the development of new drugs.
- Abysmal infection control practices.

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Regional Strategy on Prevention and Containment of Antimicrobial Resistance

2010-2015

Objectives

- To establish a national alliance for prevention and control of antimicrobial resistance.
- To institute a surveillance system that captures the emergence of resistance, trends in its spread and utilization of antimicrobial agents in different settings.
- To promote rational use of antimicrobial agents at all levels of healthcare and veterinary settings.
- To strengthen infection control measures to reduce the disease burden.
- To support research to develop and/or improve use of antimicrobial agents.

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Objective 1: To establish a national alliance for the prevention and control of antimicrobial resistance

- Establish a national alliance against antimicrobial resistance
- Strengthen national networks
- Collaborate with stakeholders

10

Objective 2: To institute a surveillance system that captures the emergence of resistance, trends in its spread and utilization of antimicrobial agents in different settings

- Monitor resistance in microorganisms
- Monitor use of antimicrobials
- Monitor disease and economic burden due to resistant organisms

11

Objective 3: To promote rational use of antimicrobial agents at all levels of health-care and veterinary settings

- Promote optimal prescription
- Make available quality laboratory data in real time
- Rationalize use in veterinary sector
- Promote compliance and proper public use

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Objective 4: To strengthen infection prevention and control measures to reduce the disease burden

- **Strengthen disease control programes**
- **Augment infection-control practices in hospitals**
- **Promote infection control practices in communities**
- **Promote and strengthen disease prevention interventions**

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Objective 5: To promote research in the area of antimicrobial resistance

- Encourage basic research
- Support operational research
- Support the development of new antimicrobial agents and vaccines

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Countries known to set up AMR policy and / or programmes

EU = Sweden, Belgium, France

Asia and Pacific = South Korea, Taiwan, Australia, India, Thailand, Nepal,

America = USA, Chile,

Africa = ?

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Sweden

STRAMA (Swedish Strategic Programme against Antibiotic Resistance)

SMI (Swedish Institute for Infectious Disease Control)

Swedish plan of action against antibiotic resistance (2000)

Strategy to prevent antibiotic resistance and healthcare associated infection (2006)

Strategy for Sweden's cooperation with the World Health Organization (WHO) 2011 – 2015

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Sweden

Strategy for Sweden's cooperation with the World Health Organization (WHO) 2011 – 2015

- **five areas have been selected**
  - **1) WHO as an efficient institution,**
  - **2) Strong and sustainable health systems,**
  - **3) Health promotion and the prevention and control of non-communicable diseases,**
  - **4) Serious health threats focusing on antibiotic resistance,**
  - **5) Sexual and reproductive health and rights.**

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Objective: WHO has taken on global leadership aimed at achieving rational antibiotics use and reducing resistance to them

- ***Measures,* Sweden shall**
- **• work to ensure WHO establishes a plan of work to combat antibiotics resistance, including an appropriate organizational structure and division of responsibilities,**
- **• support the establishment of a global system for monitoring resistance trends and the disease burden linked to measures on the global, regional and local level,**
- **• work to ensure WHO monitors the effects of measures on global, regional and local level aimed at more rational antibiotics use.**
- **Division of responsibilities: The Ministry of Health and Social Affairs has the main responsibility for achieving this objective.**

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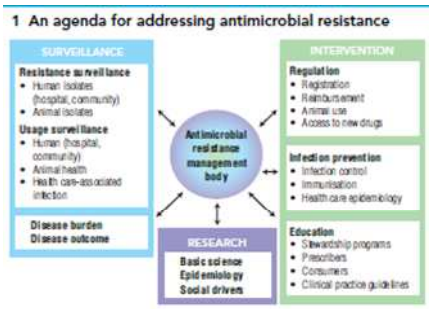
Australia: The Antimicrobial Resistance Summit plan for action



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Australia

- **Antimicrobial Resistance Management Body**
- **Intervention**
  - **Surveillance**
    - **Antimicrobial resistance surveillance**
    - **Antibiotic usage surveillance**
    - **Disease burden and outcome**
  - **Education and stewardship**
  - **Infection prevention and control strategies**
- **Future research agenda** (Basic science, Epidemiology, Social drivers)
- **Regulation** (registration, reimbursement, animal use, access to new drugs)

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NATIONAL POLICY FOR CONTAINMENT OF ANTIMICROBIAL RESISTANCE INDIA

Aims of the National Antimicrobial Policy

- **Understanding emergence and spread of antimicrobial resistance and the factors influencing it**
- **Establish a nationwide well coordinated antimicrobial program with well defined and interlinked responsibilities and functions of different arms of the program**
- **Rationalizing the usage of available antimicrobials**
- **Reducing antibiotic selection pressures by appropriate control measures**
- **Promotion of discovery of newer and effective antimicrobials based on current knowledge of resistance mechanisms**
- **Rapid and accurate diagnosis of infections and infectious diseases**

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Indian Implementation

- **Establish government commitment and support for nation-wide antimicrobial program and within it the policy & set up national focal point for collaborations & compilation.**
- **Establish a National Alliance for prevention and control of antimicrobial resistance**
- **Institute a surveillance system that captures the emerging resistance, seeks and envisions trends in it's spread and correlates with utilization of antimicrobial agents in community as health care set ups**
- **Promote rational usage of antimicrobial agents**
- **Strengthen infection prevention and control measures-healthcare associated and community based**

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Indian Implementation (cont.)

- **Support research in developing newer antimicrobial agents and improving usage of available ones, based on pharmacological properties**
- **Educate, train and motivate all stake holders in rational and appropriate usage of antimicrobials and its regulation**
- **Establish a Quality System and a National registry for Antimicrobial resistance for bacteria, fungi and viruses at national focal point.**
- **Co-development of antimicrobial agents with pharmaceuticals and leaving the distribution, sales and promotion with the government**

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Thailand

- **National Drug Policy just approved 14th March 2011 with 4 arms**
- **Rational Use of Medicine with 7 strategies**
- **AMR strategy**

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Nepal National Drug Policy -1995

- **Prudent Use of Antibiotics** (added by amendment in 2001)
  - Prevailing antibiotics used in food products, animal feeds and agriculture substances will be managed properly.
  - Supervision and monitoring on use of antibiotics will be carried out. Misuse will be controlled and proper recording system will be developed.
  - Antibiotic will be classified into different groups for prescribing purposes by medical Doctors, veterinary doctors and other health personnel.
  - GoN will constitute a national antibiotic control committee comprising of experts from human and animal health, agriculture and representation from professional organizations/councils and organizations involved in consumers right and other sectors for prudent use of antibiotic.
  - GoN will constitute a national antibiotics therapeutics advisory committee (NATAC) comprising of experts from relevant sectors to advice a prudent use of antibiotics.

25

Nepal National Medicines Policy 2007

- **Prudent Use of Antibiotics:**
  - Prevailing antibiotics use in food products, animal feeds and agriculture substances will be managed properly.
  - Supervision and monitoring on use of antibiotics will be carried out. Misuse will be controlled and proper record keeping system will be developed.
  - Treatment protocols for antibiotics use will be developed for different level of recognized health workers.
  - A sub committee comprising of experts from relevant sector to advice on prudent use of antibiotics will be constituted to advice the Drug Advisory Committee and Government of Nepal.

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Nepal

- **Implementation ?**
  - **What's Next?**

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Nation wide survey on Utilization Pattern and Controlling System of Antibiotics in Tertiary Care Hospital in Nepal

Utilization Pattern and Controlling System of Antibiotics in Tertiary Care Hospital in Nepal

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Antibiotics in Nepal

- Consumption of allopathic drugs was Rs.9 billion 61 million (2005/2006)
- About 30% of total consumption of drugs was covered by antibiotics
- Amoxicillin (9.7%) with the highest individual consumption in Nepal
- Ciprofloxacin (4.1%), Ofloxacin (2.7%), Cefixime (2.4%), Ampicillin + Cloxacillin (2.3%), co-trimoxazole (2.3%) & metronidazole (2.2%)

2

Antibiotic resistance in Nepal

- Increasing resistance of first line drugs
  - Drugs like co-trimoxazole, amoxicillin, norfloxacin against common organism like E.coli, Klebsiella species Pesudomonas aureginosa, staphylococcus aureus etc.
  - Emerging multi-drug resistance and extended spectrum penicillin

3

Problems

- Around 30% of drug consumed is antibiotic in Nepal
- Data on Rational Use of Antibiotics are lacking
- National Drug Policy (NDP) mentioned about the prudent use of antibiotic
- Situation of antibiotic control mechanism at tertiary care unknown

4

Objectives of the study

General objectives:

- To study the situation, utilization and policy related to antibiotics in tertiary care hospital in Nepal

Specific objectives:

- To study the antibiotic utilization pattern in pubic and private tertiary care hospitals in Nepal
- To study the system control related to antibiotic use in tertiary care hospitals
- To propose antibiotic policy for tertiary care hospital implementation in Nepal

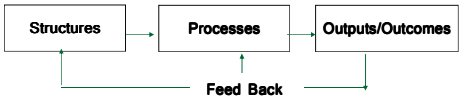
5

Conceptual Framework

6

Total Quality Management (TQM)

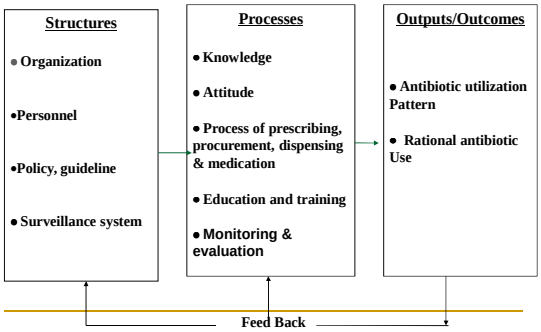
- Management philosophy
- Avedis Donabedian - quality standard of medical care



Donabedian model for quality of medical care

7

Conceptual Framework



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Global Scenario of AMR

- World Health Day 2011 on combating antimicrobial resistance
- AMR is no longer local problem
- About 440 000 new cases of multidrug-resistant tuberculosis (MDR-TB) emerge annually, causing at least 150 000 deaths
- A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci.

9

Global Scenario Cont…

- Ciprofloxacin is the only antibiotic currently recommended by WHO for the management of bloody diarrhoea due to Shigella organisms, now that widespreadresistance has developed to other previously effective antibiotics.
- New antibiotics suitable for oral use are badly needed.
- New resistance mechanisms, such as the beta-lactamase NDM-1, have emerged among several gram-negative bacilli. This can render powerful antibiotics, which are often the last defence against multi-resistant strains of bacteria, ineffective.

10

Methodology

11

Study Design

S. No.	Objectives	Research Design
1	To study the antibiotic utilization pattern	▸ Prescription survey
2	To study the system control related to antibiotic use	▸ Documentation ▸ Observation ▸ Interview
3	To propose antibiotic policy for tertiary care hospital	▸ Expert-panel discussion

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1. Antibiotic utilization pattern

- Prospective
- Setting: One private (Manipal Teaching Hospital) and one public (Western Regional Hospital)
- Duration: 4 months
- Admitted patients prescribed with at least one antibiotic

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Method of data collection

- Patient file of admitted patients referred before discharge
- Data on antibiotic utilization were recorded in Data collection form
- Recorded data were entered in SPSS for analysis
- Descriptive statistic were used in characterization of patients demography where as independent sample t-test for comparison between two hospital and univariate analysis for comparison between more than two variable.

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Data collection cont…

- Enteric fever was pointed as most common disease
- Appropriateness data was collected from 100 different enteric fever patients from each hospital
- Appropriateness of treatment were analyzed comparing indication, effectiveness, correct dosage, correct direction, drug-drug interaction, practical directions, least expensive alternative, duplication with other drug and duration of therapy with WHO Guideline.

15

In this section

- Demography of the patients
- Medicine use
- Antibiotics use
- Cost of antibiotics
- Antibiotic Resistance

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Demography of patients

Demographic	Groups	WRH (n=3034)	MTH (n=1534)
Age of the patients	Mean	24.36 ± 28.017	26.83 ± 37.370
Gender of Patients (%)	Male	47.33	41.97
	Female	49.77	54.77
	Missing	2.50	3.26
Races of Patients (%)	Brahman	29.41	36.28
	Chhetri	14.28	16.18
	Mangolian	15.96	15.78
	Newar	5.11	2.62
	Others	31.52	20.76
	Missing data	3.73	8.38

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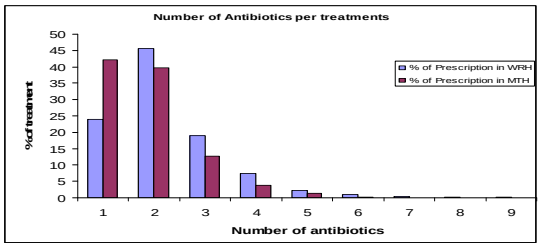
Antibiotic use

• Mean number of medicine in MTH (5.75 ± 2.64) significantly higher than WRH (5.59 ± 3.06)
• Mean number of antibiotics use in WRH (2.25 ± 1.14) significantly higher than MTH (1.84 ± .915)



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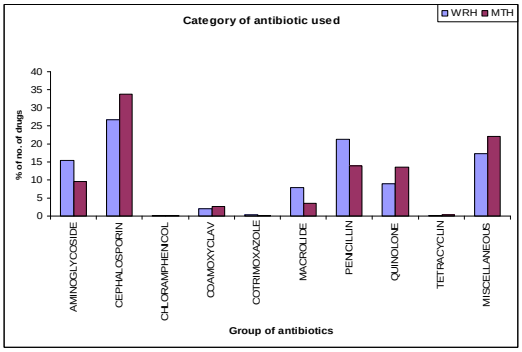
Category of antibiotic used



Others: Metronidazole (P), Nitrofurantoin, Vancomycin, Piperacillin + Tazobactam

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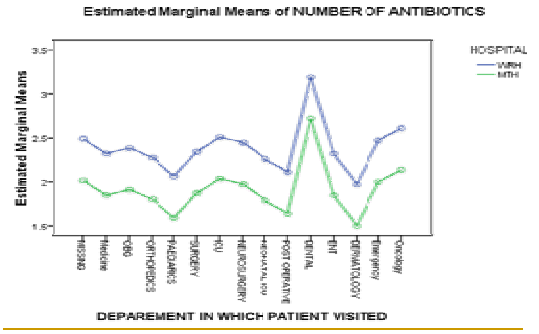
Antibiotics Vs Departments



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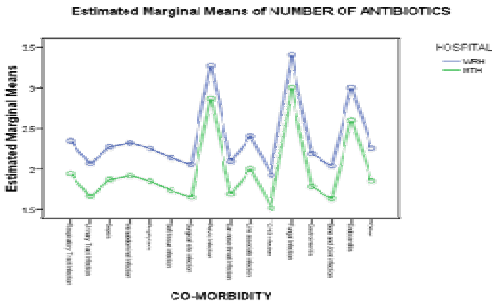
Antibiotics Vs Co-morbid conditions



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Defined Daily Dose (DDD) of Antibiotics for per 100 bed-days

Antibiotics Class	ATC Code	Antibiotic	ATC code	DDD*	DDD/100 bed-day (MTH)	DDD/100 bed-days (WRH)
Penicillins	J01C	Ampicillin	J01CA01	2 g	0.59	2.64
		Amoxicillin	J01CA04	1 g	1.74	1.13
		Cloxacillin	J01CF02	2 g	0.77	6.59
		Cumulative DDD of penicillin			**3.1**	**10.36**
Cephalosporin	J01D	Cefadroxil	J01DB05	2 g	0.063	
		Cefazolin	J01DB04	3 g	0.202	0.24
		Cefuroxime (P)	J01DC02	3g	0.033	0.28
		Cefuroxime (O)	J01DC02	0.5 g	0.046	0.23
		Cefotaxim	J01DD01	4 g	1.198	5.49
		Ceftazidime	J01DD02	4 g	0.031	0.07
		Ceftriaxon	J01DD04	2 g	5.279	11.57
		Cefixime	J01DD08	0.4 g	0.924	1.29
		Cefpodoxime	J01DD13	0.4 g	0.405	0.18
		Cumulative DDD of Cephalosporin			**8.181**	**19.35**

22

DDD cont…

Antibiotics Class	ATC Code	Antibiotic	ATC Code	DDD*	DDD/100 bed-days (MTH)	DDD/100 bed-day (WRH)
Combinations of β-lactum. Incl. beta-lactamase inhibitors	J01CR	Co-amoxiclav (O)	J01CR	1 g	0.40	0.84
		Co-amoxiclav (P)	J01CR	3 g	0.45	1.84
		Ampi.+ Sulbatum	J01CR01	2 g		0.38
		Piperacillin and enzyme inhibitor	J01CR05	14 g	0.77	0.04
		Cumulative DDD for combination of β-lactum and β-lactamase inhibitors			**1.62**	**3.1**
Macrolides	J01F	Clarithromycin	J01FA09	0.5 g	0.13	0.35
		Azithromycin	J01FA10	0.3 g	**1.28**	**10.21**
		Cumulative DDD for Macrolides			**1.41**	**10.56**

23

DDD cont…

Antibiotics Class	ATC Code	Antibiotic	ATC Code	DDD*	DDD/100 bed-days (MTH)	DDD/100 bed-day (WRH)
Aminoglycoside	J01G	Amikacin	J01GB06	1 g	0.83	2.56
		Tobramycin	J01GB01	0.24g	0.08	0.31
		Gentamicin	J01GB03	0.24g	0.88	3.42
		Cumalative DDD for Aminoglycoside			**1.79**	**6.29**
Quinolones	J01M	Ofloxacin	J01MA01	0.4 g	0.03	1.28
		Ciprofloxacin (O)	J01MA02	1 g	1.08	0.93
		Ciprofloxacin (P)	J01MA02	0.5 g	**1.43**	**4.58**
		Norfloxacin	J01MA06	0.8 g	0.20	
		Levofloxacin (O)	J01MA12	0.5 g	0.07	0.08
		Cumulative DDD for Quinolones			**2.81**	**6.87**

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DDD cont…

Antibiotics Class	ATC Code	Antibiotic	ATC Code	DDD*	DDD/100 bed-days (MTH)	DDD/100 bed-day (WRH)
Tetracycline	J01A	Doxycycline (O)	J01AA02	0.1 g	0.35	0.42
Others	J01X	Metronidazole (P)	J01XD01	1.5 g	**2.90**	**11.50**
		Vancomycin	J01XA01	2 g	0.05	
Total Cumulative DDD/100 bed days in hospital					**22.211**	**68.45**

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Cost of drug therapy

- Cost of NRs 4889166.84 ($67769.08) and 1937959.18 ($26862.19) of medicine were used for the treatment in WRH and MTH respectively over 4 months of times
- About 63 and 70 percent of total cost of all medications were antibiotics in WRH and MTH respectively
- Cost of medicine [1611.55 ($22.54) ± 2454.81] in WRH with the range of 40309.02 (Min-7.4, Max-40316.42) were significantly higher compared to mean cost medicine [1266.33 ($17.67) ± 1741.72] with the range of 21991.3 (Min-5.27, Max-21996.57) in MTH

27

Cost

cont…

- Mean cost of antibiotics was not statistically different in WRH [1007.52 ($14.09) ± 1509.83] and MTH [892.88 ($12.49) ± 1405.56]
- Mean cost of antibiotics was significantly different among the co-morbid conditions (p = .000) but not significantly different between two hospitals (p = .194)
- Cost of antibiotics in different departments and hospitals was highly significant in WRH than MTH (P-value = .000, .001)

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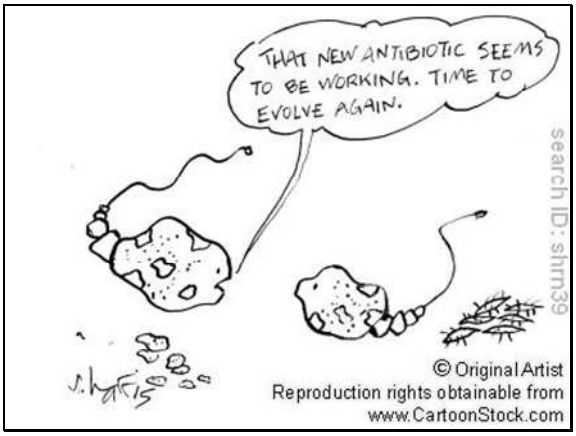

Isolate Organism

Organism	Specimen in Manipal Teaching Hospital					Specimen in Western Regional Hospital				
	Blood (n=209)	Urine (n=1238)	Pus (n=386)	Body fluid (n=360)	Sputum (n=274)	Blood (n=101)	Urine (n=30)	Pus (n=16)	Body fluid (n=7)	Sputum (n=3)
Gram Negative										
H. influenzae			1		5					
E. coli		20	42	2	3	1	3	2		
K. pneumoniae		17	12		7					
Enterobactor spp	1	5	8	1	4					
S. typhi	2								1	
Acinetobacter spp		10	5	1	7	2				
Citrobactor spp		3	6		2		2	4		

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Cont…

Organism	Specimen in Manipal Teaching Hospital					Specimen in Western Regional Hospital				
	Blood (n=209)	Urine (n=1238)	Pus (n=386)	Body fluid (n=360)	Sputum (n=274)	Blood (n=101)	Urine (n=30)	Pus (n=16)	Body fluid (n=7)	Sputum (n=3)
Gram Negative										
Proteus		6	5		1					
Pseudomonas		6	17		23		5	1		
Neisseria gonnorrhoea			2							
Moraxella Catterhalis					1					
Shigella flexhen				2				1	2	
Gram –ve bacteria						1				1

31

Cont…

Organism	Specimen in Manipal Teaching Hospital					Specimen in Western Regional Hospital				
	Blood (n=209)	Urine (n=1238)	Pus (n=386)	Body fluid (n=360)	Sputum (n=274)	Blood (n=101)	Urine (n=30)	Pus (n=16)	Body fluid (n=7)	Sputum (n=3)
Gram Positive										
S. aureus	2	4	77	2	1	5		5		
Streptococcus pyogen			8	1	6					
Streptococcus pneumoniae			2		10	2				
Coag –ve. staph		3	3			3				
Enterococus		26	15			2				

32

Cont…

Organism	Specimen in Manipal Teaching Hospital					Specimen in Western Regional Hospital				
	Blood (n=209)	Urine (n=1238)	Pus (n=386)	Body fluid (n=360)	Sputum (n=274)	Blood (n=101)	Urine (n=30)	Pus (n=16)	Body fluid (n=7)	Sputum (n=3)
Others										
Candida spp		3	3		13					
yersiinia								1		
Insignificant bacteriurea		166								
Noramal flora			64		168					
Multiple organism growth		72								
Contaminated growth	5	19		1	1					
No Growth	199	691	116	350	22	85	20	2	4	2

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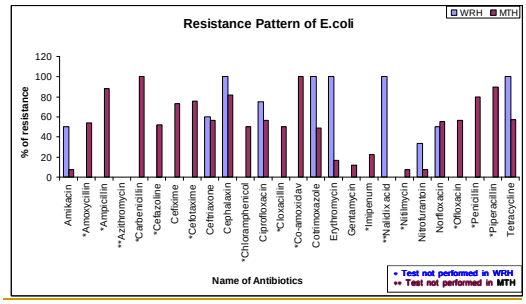
Sensitivity pattern of *E. coli*



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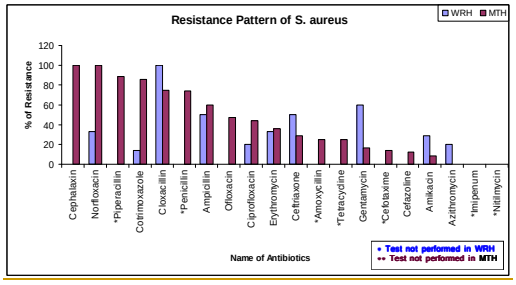
Sensitivity pattern of *S. aureus*



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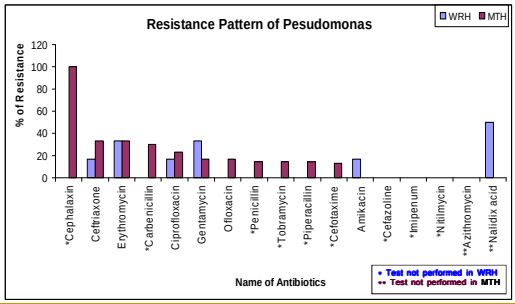
Sensitivity pattern of *Pseudomonas*



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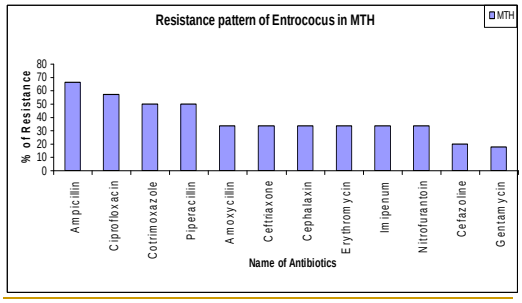
Sensitivity pattern of *Enterococcus*



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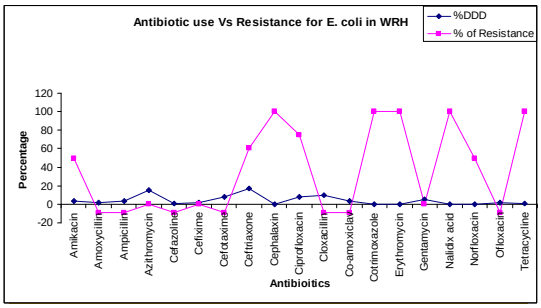
Comparing use and resistance in WRH



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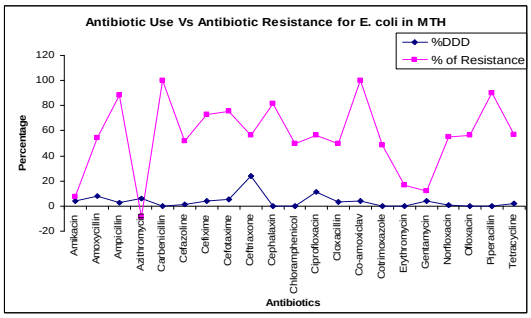
Comparing use and resistance in MTH



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Assessing Appropriateness

- Demography of patients suffering from enteric fever
- Medicine used in the treatments
- Antibiotic use
- Appropriateness of treatments
- Cost of therapy

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Demography of patients

Demography	Parameter	WRH	MTH
Age	Mean	22.81 ± 20.52	29.13 ± 17.84
Gender	Female	45	46
	Male	55	54
Races	Brahman	54	47
	Chhetri	10	22
	Mangolian	13	6
	Newar	0	8
	Others	15	17
	Missing	8	0
Duration of stay	Mean	3.74 ± 1.58	5.64 ± 2.34
Departments	Medicine	63	84
	Pediatrics	36	15
	ICU	1	1

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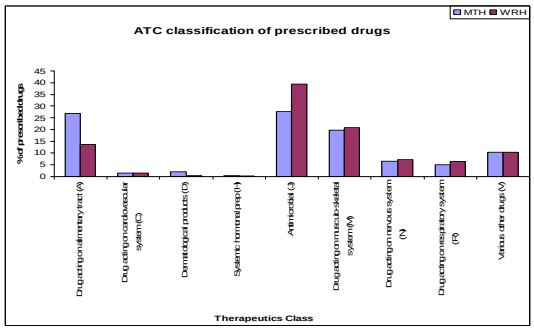
Medicine used in the treatments



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Antibiotics in enteric fever treatment

- A total of 218 and 213 antibiotics were prescribed for the treatment of 100 patients in WRH and MTH respectively
- Mean use of antibiotics in WRH (2.18 ± .87) was not significantly different (p = .015) from MTH (2.13 ± 1.11)
- Study found that more than 20% of case was treated with 3 antibiotics both the hospitals. Similarly 7% in WRH and 8% case in MTH were treated with 4 antibiotics
- Cephalosporin group of antibiotics were used widely to treat enteric fever in both the hospital (1.12 Cephalosporin in MTH and 0.93 Cephalosporin in WRH per treatments)

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Appropriateness of Antibiotics in Enteric Fever

Criterion	Appropriate		Marginally appropriate		Inappropriate	
	MTH	WRH	MTH	WRH	MTH	WRH
Indication	12	4	8	7	80	89
Effectiveness	12	1	44	47	44	52
Correct dosage	95	98	1	1	4	1
Correct direction	95	97	2	0	3	3
Drug-drug interactions	89	89	0	1	11	10
Drug-disease interaction	100	100	0	0	0	0
Practical directions	65	45	18	22	17	33
Least expensive alternative	7	7	3	1	90	92
Duplication with other drug	46	18	1	0	53	82
Duration of therapy	75	50	10	17	15	33
Average Score	59.6	50.9	8.7	9.6	31.7	39.5

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Cost of treatment of enteric fever

Parameter	WRH	MTH	p-value
Cost of prescribed Medication	1428.98 ± 1178.35	2279.07 ± 1533.49	.029
Cost of Antibiotics	1228.49 ± 840.28	1523.86 ± 1054.19	.422

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2. Controlling system of antibiotics

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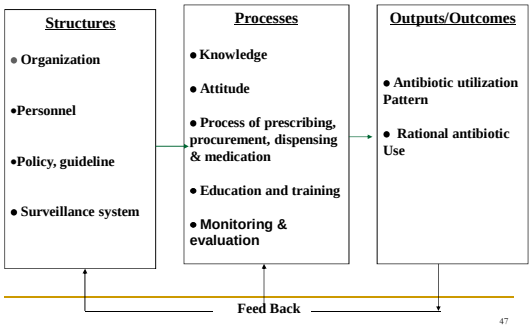
Conceptual Framework



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Methods

- Study Method
  - Documentation Analysis
  - Observation
  - Interview (Qualitative)
- Study Site
  - Manipal Teaching Hospital, Pokhara (Private)
  - Western Regional Hospital, Pokhara (Public)
  - Dhulikhel Hospital, Dhulikhel (Community/private)
  - Bir Hospital, Kathmandu (Public)
  - KIST Hospital, Lalitpur (Private)

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Interviews Chararacteristics

Category of interviews	Academic qualification (Degree)	Number
Pharmacist	Master of Pharmacy	5
	Diploma of Pharmacy	2
Pharmacologist	Pharmacology (M.D.)	1
Microbiologists	Doctor (Ph.D)	1
	M.D. Microbiology	1
	M.Sc. Microbiology	4
Clinician	Pediatrician (M.D)	3
	Medicine (M.D.)	12
	Gynecologist (M.D.)	2
	Orthpedician (M.D)	2
	Surgeon (M.D.)	4
	Dental Surgeon (MDS)	1
	E.N.T Specialist (M.D)	2
Hospital Administrator/ DTC chairman /Antibotic committee chairman	Medical Doctor (M.D)	6
Other	Nurse (B. Nursing)	1

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Structure Component

- Organization
- Personnel
- Policy, guideline
- Surveillance system

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Organization

- Antimicrobial Committee (AC) /Infectious Control Committee (ICC)/Drug and Therapeutics Committee (DTC)

Name of Hospital	DTC	Antimicrobial Committee
Manipal Teaching Hospital (MTH)	Yes	Yes
Western Regional Hospital (WRH)	No	No
Bir Hospital	No	No
Dhulikhel Hospital	Yes	Yes
KIST Hospital	Yes	Yes

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Cont…

"... no committee and no mechanism to monitor, we use antibiotic by hit and trial method." (Interview 30)

"… we have not formulated any committee as such but we have culture sensitivity testing facility and our clinician prescribe antibiotic based on culture report." (Interview 15)

- Structure of DTC include 15-20 members, including member from all clinical departments, administration, pharmacy and nursing
- Similarly, Antimicrobial committee includes the 5-7 members from various departments like Medicine, Pharmacy, Microbiology, Surgery, Pediatrics, Orthopedics, Obstetrics and gynecology.

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Performance of Organizations

Parameter	MTH		Dhulikhel		KIST Hospital	
	DTC	AC	DTC	AC	DTC	AC
Document that indicates its functions and membership	Yes	Yes	Yes (Not shared)	Yes (Not shared)	Yes (Not shared)	Yes (Not shared)
Budget allocation	No	No	No	No	No	No
% DTC members who attend > 50% of meetings	100%	100%	>90%	>90%	100%	100%
No. DTC meetings per year	2-3	2	1-2	1 (As per need)	6	Not fixed (As per need)
Are the meeting minutes recorded	Yes	Yes	Yes (Not shared)	Yes (Not shared)	Yes (Not shared)	Yes (Not shared)
Have STGs been developed/adapted and implemented?	No	No	Developed for few disease		In the process	
Has the committee organized any educational activities?	No	No	No	Yes	No	Yes

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Cont…

- Antimicrobial committees are mainly focused on the formulation of antibiotic treatment guidelines
- DTC has major role in the selection of antibiotics
- Initiative like banning of the irrational combination of antimicrobial

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Personnel

- No concept of Infectious Disease Specialist (IDS) working on antimicrobial use and resistance
- The personnel involved in antibiotic controlling system were clinicians, microbiologists and pharmacists
- In absences of IDS, clinicians seek the advice of either microbiologists or pharmacists in case of any problem related to antimicrobial use or resistance.

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Cont…

- One of the private hospital has antibiotic treatment guideline for certain disease like pneumonia, UTI, Enteric fever, sepsis. where other two are in the process
- In absence of guideline, majority of clinician follow standard textbooks as guideline

"…no, we don't have any policy but it is a necessary thing… we go through the literature and books like Davidson, Harrison." (Interview 26)

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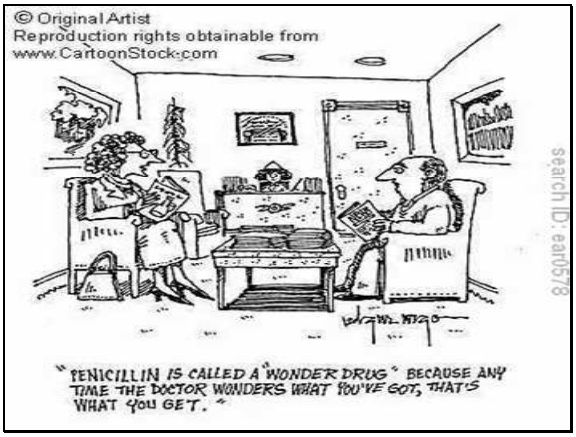

Policy and Guidelines

- No written antibiotic policy in any hospitals
- In certain department of hospitals of private hospitals work on understanding

"…we discuss within the department and senior faculty members before starting fourth generation cephalosporin (Cefepime)." (Interview 2)

- One private Hospital Guideline has guideline on certain disease

"…*Guideline for common diseases likes pneumonia, enteric fever, sepsis*." (Interview 19)

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Surveillance system

- Four out of 5 study hospitals are enrolled in national antibiotic resistant surveillance program conducted by Nepal Public Health Laboratory
- Surveillance include common 7 organism like Salmonella, Shigella, N. gonorrhea, H. influenza, S. pneumonia, ESBL- E.coli and Vibrio
- Disseminate information 3 times in year by conducting workshop

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Process Component

- Knowledge and Attitude
- Process of prescribing
- Process of procurement and dispensing
- Process of monitoring and evaluation
- Process of education and training

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Knowledge and Attitude

- Knowledge and Attitude on antibiotic policy / guideline / surveillance / intervention / promotion
- Except pharmacists, most of interviews were unaware about the National Medicine Policy and the antibiotic component of the policy
- Almost all the interview feel the need of antibiotic policy and guideline in the hospital as well as at the national level and were unaware about the guideline

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Cont..

- Reason Behind lack of policy implementation,
  - Country situation, Medicine is not in the priority list, funding problem, lack of manpower, lack of coordination, lack of commitments

"…regulatory body should do this... not blame but is universal… policy not implemented due to effective governance." (Interview 8)

"…in the Health care so that medicine is not in priority. Since medicine is not in the priority then automatically antibiotic is also not in the priority." (Interview 45)

- Although, 4 out of 5 study hospitals were involved in National Antibiotic Surveillance, none of the clinicians were aware about such surveillance indicating communication huge communication Gap

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Process of prescribing

- In public hospital, rarely see culture sensitivity result before prescribing, prescribe based on clinical sign and symptom but was relatively higher in private hospital

"…rarely see culture sensitivity report before prescribing" (Interview 15)

- Reasons behind not looking for culture sensitivity, Either, patient has already consumed antibiotic before visiting them or patient cannot afford

"…it is difficult to see in all case because patient has already taken antibiotic as antibiotics are available over-the-counter." (Interview 29)

"…If the patient is affordable I will do definitely other wise no. If the patient is educated I definitely do the culture." (Interview 3)

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Process of procurement and dispensing

- No separate policy for the procurement of antibiotics in the hospital
- However, antibiotic selection is done by either DTC or Antimicrobial Committee
- Although public hospital do not have their own hospital pharmacy as like private hospital but antibiotics are dispensed base on prescription inside the hospital pharmacy

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Process of monitoring and evaluation

- Monitoring of use/resistance/promotion
- No system of monitoring either use or resistance in any hospitals
- However, two private hospitals have policy to monitor the promotion where MR can not meet the clinicians individually.

"…MR are not allowed to meet the doctors individually but they can present in the group of doctors in every Tuesday." (Interview 40)

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Process of education and training

- No separate regular education and training program related to antibiotic
- However, student training as a part of course, sometime presentation in clinical meeting, some guest lecture are the type of education run by the hosptials

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Outcome

- Antibiotic utilization pattern
- Rational use of antibiotics

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Rational use of antibiotics

- Most of the clinician believe that antibiotic use and resistance both is problem in the hospital.
- Most of them agreed that antibiotic is over used in the hospital and reason for the increase in the resistance

"…overuse, All get azithromycin. It is easy also because the therapy is of 3 day and patient already take the one so it is also easier for us to treat."

- Majority advocate the immediate intervention. Further, suggested that educational only will not be effective, enforcement of policy will be required.

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3. Antibiotic policy recommendation

- Expert-panel discussion
- Experts from hospital and Department of Drug Administration
- Experts (10-20)
  - Stake-holder from different hospital
  - Infectious disease specialists
  - Microbiologists
  - Pharmacists
  - Expert from Ministry of health and DDA

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Policy recommendation Cont…

- Policy to Tertiary Care Hospital Management
  - Feasible policy
  - Strategy to implement
  - Policy and recommendation to Government

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Acknowledgement

- Dr. Niyada
- Dr. Pranaya Mishra
- All Committee member
- All Friends

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Little is known
Lot to be done……

Thank you

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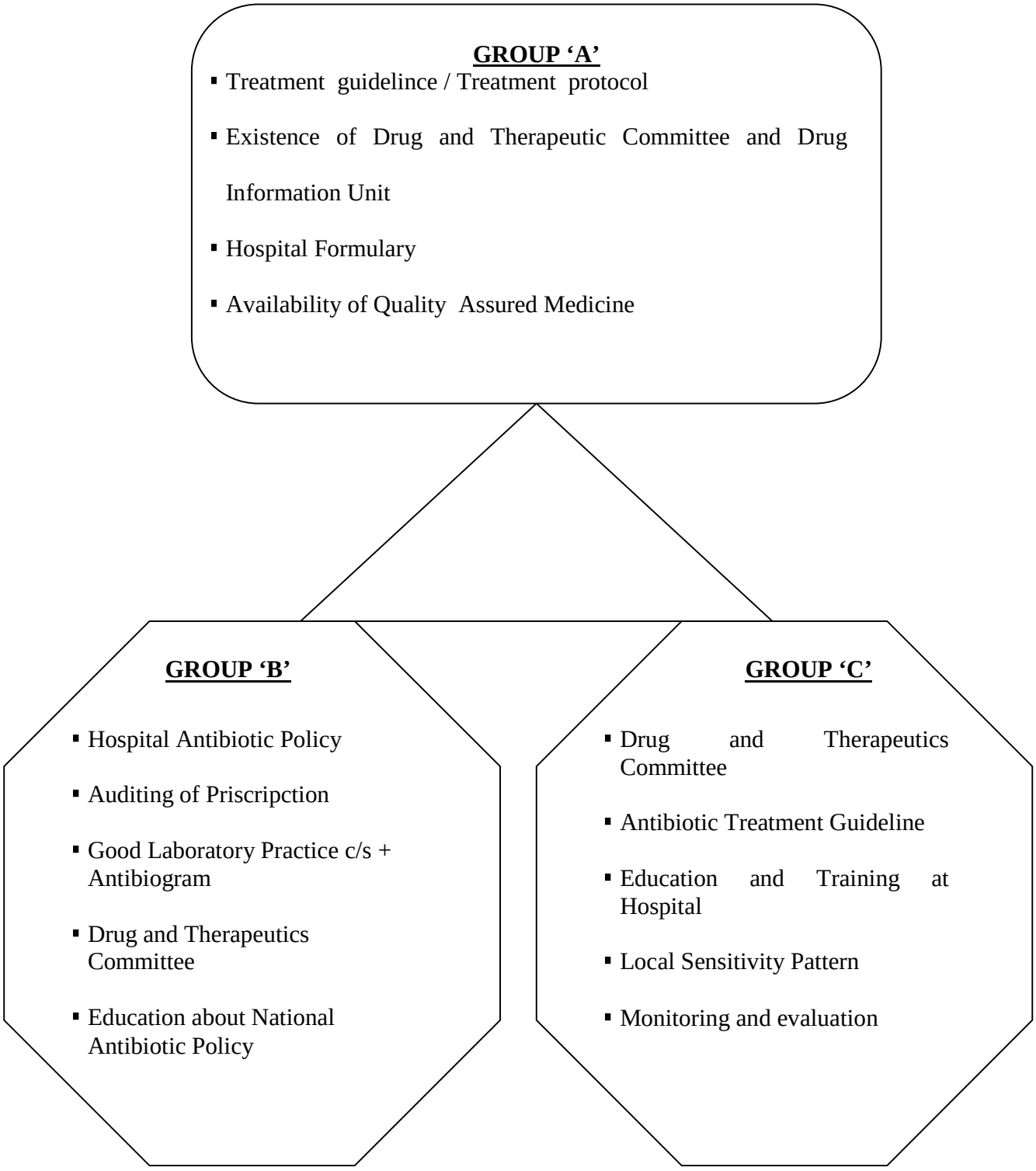
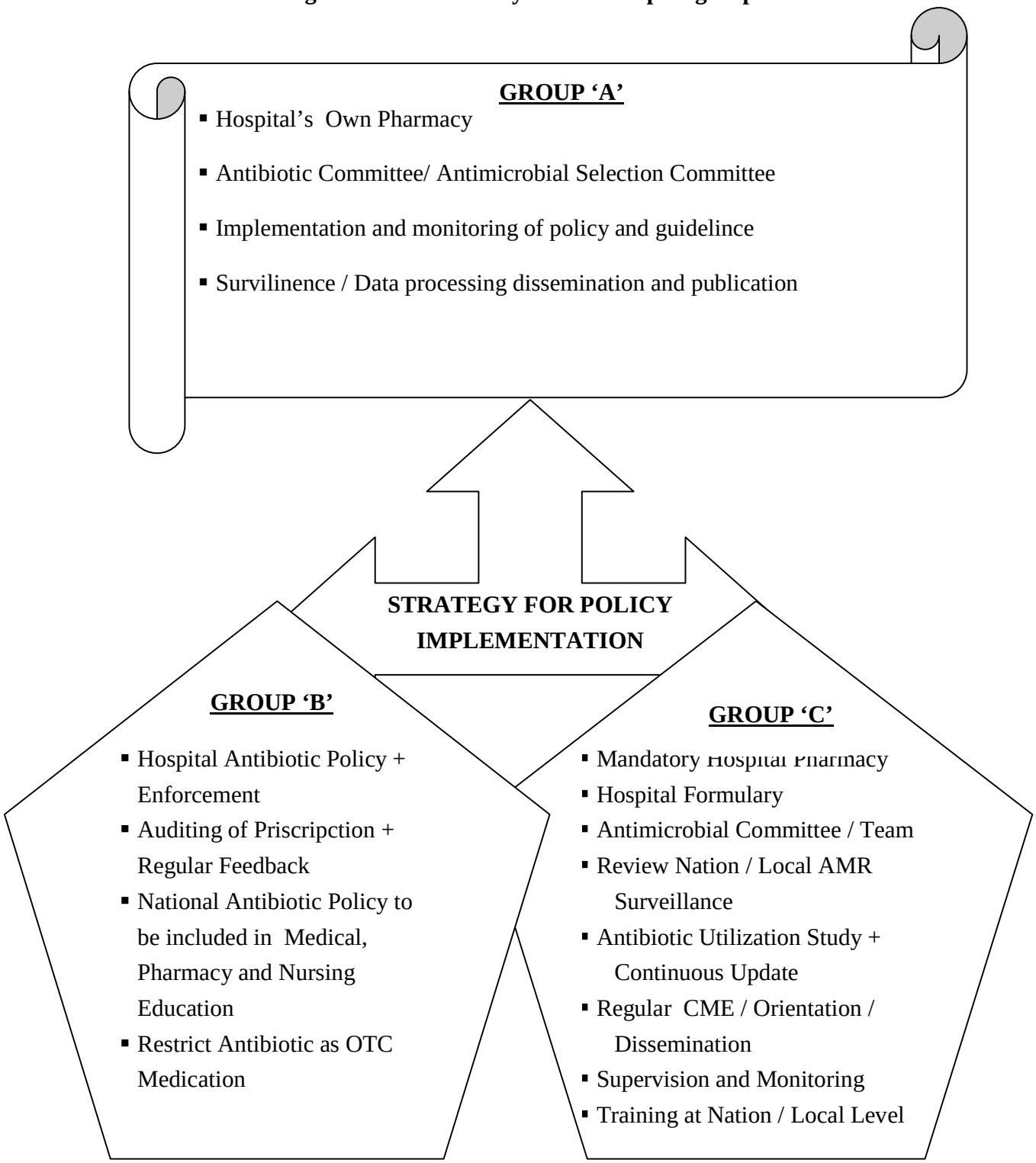
Policy Recommended by the different expert groups



Strategies recommended by different expert groups



VITAE

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Education

Course	Board/ University	Year of passing	Marks (%)
M. Pharm	Kathmandu University, Dhulikhel, Nepal	2006	CGPA 3.42
B. Pharm	Rajiv Gandhi University of Health Sciences, Bangalore, India	2000	62.20
SSLC+2	Bihar Intermediate Education Council, Patna, India	1995	88.44
SSLC	His Majesty's of Government of Nepal, Ministry of Education and Cultural.	1993	54.71

Work Experience

April 2010 – Present	Assistant Professor, Department of Pharmacology Manipal College of Medical Sciences, Pokhara, Nepal
September 2006- Present	Incharge, Pharmacy Unit Department of Hospital and Clinical Pharmacy Manipal Teaching Hospital, Pokhara, Nepal.
September 2006- March 2010	Lecturer, Department of Pharmacology Manipal College of Medical Sciences, Pokhara, Nepal
2003 - September 2006	Incharge, Bulk Pharmacy Unit, Department of Hospital and Clinical Pharmacy Manipal Teaching Hospital, Pokhara, Nepal.
July 2001- September 2003	Hospital and Clincal Pharmacist, Department of Hospital and Clinical Pharmacy Manipal Teaching Hospital, Pokhara, Nepal.