Global
Antibiotic
Resistance
Partnership

SITUATION ANALYSIS AND RECOMMENDATIONS

Antibiotic Use and Resistance in Nepal

The GARP-Nepal National Working Group

Dr. Buddha Basnyat, Chairman

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GARP-Nepal National Working Group (NWG)

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Preface

Antibiotic resistance is a pressing issue, both globally and in Nepal. Overuse and misuse of antimicrobials have contributed to the emergence of resistance, at the same time, underuse through lack of access, inadequate dosing, and substandard antimicrobials also lead to resistance. Antibiotic resistance has lowered the ability to cure infectious diseases. As a part of global effort to preserve the effectiveness of antibiotics, the Global Antibiotic Resistance Partnership (GARP)-Nepal project was established by Nepal Public Health Foundation in collaboration with Centre for Disease Dynamics, Economics and Policy in 2013 with Dr. Buddha Basnyat as chairperson. Since its inception, GARP-Nepal has been actively supporting researches and studies related to antimicrobial resistance in institutions.
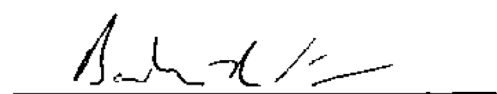
In this regard, I have a great pleasure in introducing this report "Situation Analysis and Recommendation: Antibiotic Use and Resistance in Nepal, " a first step in the GARP process, to create a baseline for identifying the important information gaps to be addressed in order to make responsible and effective recommendations for policymakers to consider. This report is an outcome of untiring effort of the GARP Nepal working group, a volunteer group of experts from different sphere of work. Nepal Public Health Foundation acknowledges the time and effort committed by the working group and is thankful to the group.

A series of effort has been made in this report to bring together all fragmented researches both in human and animal sector. Most prevalent bacterial diseases and antimicrobial resistance status of the pathogens towards most commonly used antibiotics are cited. Policies, related to antibiotics use and resistance, both human and veterinarian are reviewed and documented. Recommendations from experts as provided in dissemination workshop of 15 December 2014 have been included.

It assumes great importance in light of the recent resolution on global action plan on antimicrobial resistance during sixty-eighth World Health Assembly for member states to have in place national action plan on antimicrobial resistance within two years, aligning with the global action plan.

I firmly believe that this report provide evidence based input in formation of an effective country-specific policy to control antibiotic resistance and subsequently in preparation of national action.

Dr. Badri Raj Pande

Acting Executive Chair
Nepal Public Health Foundation

Government of Nepal

Ministry Of Health & Population

Ramshahpath, Kathmandu, Nepal

Ref :

Hon'ble Khaga Raj Adhikari
Minister for Health and Population
Date : ....
07ᵗʰ December 2014
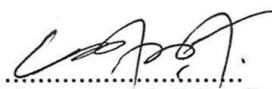
Foreword

In the developing country like ours, where the burden of treatable communicable diseases is very high and access to health facilities and laboratories not so easy, antibiotics have long worked as miracle drugs. Considering their effectiveness, antibiotics have for a long time been prescribed very regularly, and in many cases, randomly in the country. This has led to the emergence of antibiotic resistance as a silent epidemic in Nepal along with other countries of the world.   The World Health Organization has already warned of the global threat posed by antimicrobial resistance.   In the long run, AMR not only makes treatment difficult but also increases the health expenditure of people. In this regard, I am pleased to see that Global Antibiotic Resistance Partnership (GARP) Nepal, under Nepal Public Health Foundation has prepared this report "Situation Analysis and Recommendation: Antibiotic Use and Resistance in Nepal." This is a very important initial step towards bringing awareness on this issue.

The endeavor of GARP-Nepal to include the animal sector usage of antibiotics and publish this Situation Analysis is commendable as it also coincides with the "one health policy" of the Ministry of Health. Hence this document will bridge the information gap related to AMR in human and animal sector and will further serve as an important baseline document for developing plans, policies and programs in AMR for government and other allied agencies.

MOHP has recently endorsed "Antibiotic Treatment Guidelines, 2014" which aims to help with rational use of antibiotics in Nepal. In this context this Situation Analysis document will be important in helping to bring a clearer focus and hence strengthen the Guidelines.I thank the GARP Nepal team for their efforts in putting together this informative document and wish them every success in future AMR activities. MOHP looks forward to their continued hard work for Nepal in the field of antimicrobial resistance.

(Khaga Raj Adhikari)
Minister

Acknowledgement

This report on "Situation Analysis and Recommendations: Antibiotic Use and Resistance in Nepal" is developed by Global Antibiotic Resistance Partnership (GARP Nepal) under Nepal Public Health Foundation (NPHF). First of all, we are thankful to Center for Disease Dynamics, Economics and Policy (CDDEP) for their financial and technical support. Their expertise, knowledge and experience, has been very essential throughout the study.

We express our sincere gratitude to Honorable Minister Mr. Khaga Raj Adhikari, Ministry of Health and Population, for gracing the dissemination workshop of 15 December 2014 and motivating us with his wonderful speech. We are grateful to the honorable minister for writing immensely encouraging foreword for the report. We would like to express our sincere thanks to Dr. Ramanan Laxminarayan, Director of CDDEP for his valuable support; Ms. Hellen Gelband, Assistant Director and related experts of CDDEP for their guidance and technical support in completion of this report.

A sincere thanks to GARP-Nepal working group members who provided insight and expertise that greatly assisted the study. We highly acknowledge representatives from government, INGOs, NGOs, clinicians, academicians, veterinarians, microbiologist and journalist for attending our seminars and workshops; and providing invaluable suggestions and recommendations.

We would like to express our deep sense of appreciation to Dr. Badri Raj Pande, Acting Executive Chair of NPHF and entire NPHF team for continuous support. We wish to thank Ms. Santoshi Giri, Country coordinator for GARP Nepal and Program Officer Ms. Namuna Shrestha for their hard work in preparation and production of this report.

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Summary and Recommendations

Antibiotics are the 'miracle drugs' of the 20th century. They made possible great progress in turning many bacterial infections into illnesses rather than death sentences. Along with vaccines, they have transformed death in infancy and childhood from an ever-present danger into a rare event. Remarkably, Alexander Fleming, the discoverer of penicillin, warned of resistance eroding the drug's effectiveness in the year 1945. He made what may have been the first appeal for antibiotic stewardship: use penicillin only when necessary and do not 'under-dose'.

Unfortunately, the world has used penicillin and the rest of the available antibiotics, developed mainly in the 1940s and 1950s, at an ever-increasing rate, both when they are needed and when they are not, in human beings and in other animals. The result is that today, many antibiotics have lost their effectiveness against common bacterial infections, and antibiotic resistance is increasing in most countries before it is recognized as a major problem.

Antibiotic resistance is a natural evolutionary response to the exposure of bacteria to antibiotics. Every time an antibiotic is taken by a person or animal, bacteria come in contact with it and those that are naturally resistant, because of a mutation or natural variation have a survival advantage. When antibiotics are taken orally, a huge population of gut bacteria is exposed—pathogenic bacteria as well as bacteria living in equilibrium with the host, some of which may turn pathogenic at some point. Resistant strains of any of these bacteria may be selected for, and many exposed bacteria—both pathogenic and commensal—can pass on their resistant genetic material to other, even unrelated, bacteria.

Antibiotic resistance is no longer a concern for the distant future but is a pressing issue, both globally and in Nepal. As part of global effort to preserve the effectiveness of antibiotics, the Global Antibiotic Resistance Partnership (GARP)-Nepal was established to document the current state of antibiotic access, use and resistance in the country, and to identify policies and actions that could set a course for antibiotic sustainability.

This situation analysis is a first step in the GARP process, creating a baseline for what is known and identifying the important information gaps to be addressed in order to create responsible and effective recommendations for policymakers to consider.

ABOUT THE GLOBAL ANTIBIOTIC RESISTANCE PARTNERSHIP

Antibiotic resistance is a global concern strongly affected by local factors. Progress will be best made when national experts collaborate to understand all aspects of antibiotic access, use and resistance within their own country context, and then work together to craft policy solutions tailored to meet their own needs. With other health issues such as HIV/AIDS, tuberculosis, malaria, malnutrition and epidemics competing for global attention, antibiotic resistance has not been a priority in many low- and middle-income countries, though many scientists, clinicians and public health specialists are aware of and concerned about it.

This was the rationale for establishing GARP, a project of the Center for Disease Dynamics, Economics & Policy (CDDEP), a non-profit research and policy organization with offices in Washington, DC and New Delhi and funded by the Bill & Melinda Gates Foundation. GARP was created to enable local experts to occupy the multidisciplinary space to understand local conditions and identify policy opportunities related to antibiotics, especially (but not limited to) those affecting antibiotic resistance, and ultimately, to play a role in global deliberations.

GARP began in 2008 in Kenya, India, South Africa and Vietnam, where working groups continue to develop a deeper understanding of antibiotic issues and have become trusted sources of information for all sectors. The working groups are becoming largely independent of CDDEP for financial support, but they continue to collaborate and now serve as a resource for new members. After a successful initial 3-year phase culminating in the First Global Forum on Bacterial Infections, held in New Delhi in October 2011, the Gates Foundation supported the establishment of GARP in a second group of countries: Nepal, Tanzania, Mozambique, and Uganda.

Antibiotic Access

Despite GARP's emphasis on reducing the excessive use of antibiotics, we must keep in mind that in Nepal, as in so many countries, many people have little or no access to antibiotic treatment when it is needed. Pneumonia is still the leading cause of death for children under five and most of these children will have had no effective antibiotic treatment. These children—mankind—would clearly benefit from proper use. Although we are mainly concerned about resistance, the desire to preserve antibiotics must be balanced with the absolute need to get antibiotics to as many people who actually need them as possible. No saving of antibiotic resistance is worth losing lives that could have easily been saved with a few tablets.

DISEASE BURDEN AND ANTIBIOTIC RESISTANCE

Humans

As in many countries, no adequate surveillance system for tracking antibiotic resistance rates or documenting antibiotic use currently exists in Nepal. However, a number of individual studies have been carried out and are reviewed in detail in Chapter 4. These studies are summarized here, grouped by bacterial diseases that contribute to the morbidity and mortality burden in Nepal. These include respiratory infections, diarrheal infections, bloodstream infections, urinary tract infections, sexually transmitted infections and tuberculosis.

All of the studies identified reported relatively high rates of resistance. This is not surprising, as many studies worldwide tend to focus on patients with stubborn infections that are very likely to be antibiotic resistant. This body of literature is, therefore, unlikely to represent the situation in the general population. Nonetheless, it provides the only information available for assessing current levels of antibiotic resistance. Going forward, it will be important to establish some type of surveillance in order to reliably monitor antibiotic resistance trends in the population. In particular, if interventions to mitigate resistance are put in place, evaluating their effects will require tracking antibiotic resistance levels.

Burden of bacterial infections

The leading causes of premature mortality from infectious diseases in Nepal in 2010, were lower respiratory infections (pneumonia), diarrheal diseases, neonatal encephalopathy (birth asphyxia and birth trauma), preterm birth complications, and tuberculosis (GBD, 2010). Bacterial infections are implicated in all but the neonatal and preterm birth complications.

Rates of acute respiratory tract infections, diarrheal diseases, and bloodstream infections remain high. Diarrhea, pneumonia, and sepsis are major health risks for neonates and children under five, in spite of a significant decrease in infant mortality in Nepal of almost 70 percent over the past twenty years (World Bank, 2013).

Respiratory Infections

Infections of the respiratory tract are a major cause of death in Nepal, and are the most common cause of morbidity and mortality in children under five years of age. Most common are upper respiratory tract infections (ARIs), which are primarily caused by viruses, with some bacterial infections. More serious are lower respiratory tract infections, including pneumonia, a leading cause of death of infants, children and the elderly. Lower respiratory tract infections are also caused by viruses and other organisms, in addition to bacteria.

The most common bacterial causes of pneumonia in Nepal (and worldwide) are several species of *Streptococcus, Staphylococcus aureus*, *Klebsiella pneumoniae*, *Haemophilus influenzae* type b, and *Pseudomonas aeruginosa*. Some bacteria, such as methicillin-resistance *S. aureus*, the well-known MRSA, are more likely to be acquired in hospitals or other healthcare facilities and are known as healthcare acquired infections (HAIs).

Eight studies were identified, all conducted between 2004 and 2011, reporting antibiotic resistance of *Streptococcus pneumoniae* and *K. pneumoniae* isolates from respiratory infections in Nepal. In all studies, more than half of all isolates were resistant to the commonly-used antibiotics cotrimoxazole and ciprofloxacin, with resistance increasing to both drugs from 2000 through 2008 (G. Shakya & Adhikari, 2012).

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Diarrheal Infections

Diarrheal infections are also common, especially among children, and are the third leading cause of under-five mortality in Nepal. As with respiratory infections, most are caused by viruses (especially the genus *Rotavirus*), but an important minority are caused by bacteria, most commonly species of *Shigella*, *Campylobacter,* and *Salmonella* (including typhoid), *Escherichia coli*, and *Vibrio cholerae* (cholera). Most cases of viral and bacterial diarrhea can be treated with oral rehydration (and zinc, in some cases) and do not require antibiotics or other drugs for full recovery, with the exception of complicated, bloody diarrhea, or dysentery. However, antibiotics are often used to treat diarrheal infections, regardless of severity or cause.

Three studies were identified documenting antibiotic resistance among *Shigella* spp. and three among *V. cholerae* in Nepal, all published since 2007. In the *Shigella* studies, most isolates were resistant to one or more of the antibiotics tested, which included ampicillin, nalidixic acid, cotrimoxazole and ciprofloxacin. In the largest study, out of 118 isolates, one-third were resistant to all four antibiotics (Kansakar, Malla, & Ghimire, 2007). Almost all *V. cholerae* isolates were resistant to nalidixic acid, cotrimoxazole, and furazolidone, the three drugs for which resistance levels were sought.

Bloodstream Infections

Major blood stream infections (often referred to as bacteremia) include neonatal sepsis, typhoid and meningitis. These infections are often very serious and require antibiotic treatment. These infections are prevalent in Nepal.

Neonatal Sepsis*:* Three out of the four sepsis studies, though all fairly small, reported resistance rates to antibiotics in bacteria that were responsible for neonatal infections in hospitals. Resistance rates of *S. aureus*, *K. pneumoniae*, *Pseudomonas* spp., *Acinetobacter* spp., and Gram-negative *Enterobacteriaceae* ranged from 50 to 100 percent for some drugs. Common drugs reported in these studies were ampicillin, cefotaxime, ceftriaxone, imipenem, ceftazidime, and piperacillin.

Typhoid and Paratyphoid (enteric fever): A comprehensive meta-analysis analyzed 32 antibiotic resistance studies conducted over 18 years (1993-2011) of *Salmonella* Typhi and *Salmonella* Paratyphi A, the main bacteria responsible for causing typhoid and paratyphoid.

Resistance of *S*. Typhi to ciprofloxacin increased from 2 percent in the 1998-2002 period to 11 percent in the 2008-2011 period. Resistance of *S*. Paratyphi A to ciprofloxacin increased from 4 percent between 1998 and 2002 to 14 percent between 2008 and 2011. From 2008-2011, resistance to nalidixic acid was 91 percent (Karki, Shakya, Cheng, Dumre, & Leder, 2013). In actual fact, nalidixic acid resistance better reflects ciprofloxacin resistance, hence this is staggering resistance to ciprofloxacin and calls into question treatment of enteric fever with ciprofloxacin.

Urinary Tract Infections

Urinary tract infections are common and can be appropriately treated with antibiotics, but resistance levels to first-line antibiotics can be very high. *E. coli* is the most common bacterial cause of these infections.

Nepal's National Public Health Laboratory reported on resistance rates from 2006 to 2010. Resistance rates were well above 50 percent for all the drugs tested, which included, in order of those with the most to least resistance; amoxicillin, cefixime, amoxicillin-clavulanic acid, nalidixic acid, ceftazidime and cefotaxime. Resistance to all drugs increased from 2006 to 2010 (Shakya et al., 2012).

Sexually Transmitted Infections

Antibiotic resistance studies on sexually transmitted infections remain limited in Nepal. The two identified studies reported expectedly high rates of resistance of *Neisseria gonorrhoeae* to penicillin, tetracycline and ciprofloxacin (Bhargava, Shakya, Mondal, & Rijal, 2010; Bhatta et al., 2012).

Healthcare Acquired Infections (HAIs)

Many patients acquire infections in hospitals and other healthcare facilities around the world, triggering heavy antibiotic use. These facilities are, thus, a potent breeding ground for antibiotic resistance. Most of the HAI studies in Nepal have reported a high prevalence of methicillin-resistant *S. aureus* (MRSA) and other resistant bacteria in patient isolates and on equipment. MRSA was frequently highly resistant to one or more of the common drugs used for treatment, such as cotrimoxazole, chloramphenicol and erythromycin. MRSA prevalence of up to 7 percent was also detected in studies looking at bacterial carriage

rates (Shakya, Shrestha, & Mitra, 2010). The relatively few studies and lack of ongoing surveillance point to an under reporting of HAIs in Nepal.

Tuberculosis

Mycobacterium tuberculosis, the bacterial causative agent of tuberculosis in humans, is treated primarily with five first-line drugs: isoniazid, rifampin, ethambutol, pyrazinamide, and streptomycin. Reports of resistance to first-line drugs are discrepant, with some reporting relatively low resistance rates (3 and 18 percent, respectively for new and retreated cases) and others reporting rates that are quite high (35 percent and higher for each drug individually and up to 23 percent resistant to all first-line drugs. With increasing *M. tuberculosis* resistance to isoniazid and rifampin, two of the most powerful first-line drugs, MDR-TB is becoming more prevalent in Nepal.

World Health Organization Reported Antibiotic Resistance in Nepal

A recent World Health Organization report provided the first comprehensive review of the current state of global AMR surveillance (WHO, 2014). The report includes data from Nepal on antibiotic resistance rates for six combinations of bacterial pathogens and antibiotics. The bacteria were *E. coli*, *S. aureus*, non-typhoidal *Salmonella*, *Shigella* spp., *K. pneumoniae*, and *N. gonorrhoeae*.

Out of 140 isolates, 64 percent of *E. coli* isolates were resistant to fluoroquinolones and 38 percent were resistant to third-generation cephalosporins. Smaller data sets showed resistance rates of *S. aureus* to methicillin ranging from 2 to 69 percent. *K. pneumoniae* showed resistance to third-generation cephalosporins of 0 to 48 percent, while no resistance to carbapenems was detected (WHO, 2014).

Agricultural Animals

Animals are susceptible to infections just as humans are, and bacterial diseases in animals can require antibiotic treatment to prevent morbidity and to halt disease transmission. The livestock sector in Nepal is responsible for 11 percent of the total GDP, and animal health is important for sustaining productivity in this sector. However, inappropriate antibiotic use in animals can

contribute to antibiotic resistance in humans. Epidemic investigations and disease surveillance of this industry are the charge of the Central Veterinary Laboratory.

The major diseases impacting animals in Nepal are foot and mouth disease, peste des petits ruminants, highly pathogenic avian influenza, and classical swine fever. The bacterial diseases of bovine and small ruminants are mastitis, black quarter disease and hemorrhagic septicemia, and common bacteria detected include Coagulase Negative *Staphylococci, Streptococcus* spp., *Staphylococcus* spp., and *E. coli*. The major diseases in poultry are salmonellosis, fowl typhoid and colibacillosis, while common bacteria detected include *Salmonella* spp. and *E. coli* (Thakuri, 2012).

In many countries, antibiotics are, or were in the past, used as growth promoters in food animals. The main reason for phasing out this practice (either voluntarily or by law) is to reduce the generation of antibiotic-resistant gut flora. Antibiotics are used both for growth promotion and as a disease preventive in Nepal, with low doses mixed with animal feed, with much the same result.

Very few studies of antibiotic resistant organisms in food animals and animal products have been carried out in Nepal, but those few do report a high prevalence of resistant organisms.

Consumption data can serve as a useful indicator for the potential overuse of antibiotics for therapeutic or sub-therapeutic purposes. Very few studies present such data, but their findings establish the need for stronger surveillance of antibiotic use in animals and the development of regulatory measures. A survey of distributors of veterinary medicine and feed supplements, reported in 2003, in six Nepali districts reported annual sales of NRs. 492 million (USD 6,739,726). Antibiotics represent 13 percent of the total expenditure on veterinary drugs (Bhandari and Singh, 2003). In a recent survey, the volume of veterinary antibiotic sales rose more than 50 percent between 2008 and 2012. In that survey, 71 percent of veterinary drug sales were based on prescription by retailers, not veterinary professionals (Khatiwada, 2012).

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INTERVENTIONS TO CONTAIN ANTIBIOTIC RESISTANCE AND THE NEPALI SITUATION

Antibiotics should be used whenever they might save a life or cure an infection that is unlikely to be self-limited, but even those appropriate uses lead eventually to antibiotic resistance emerging. In those cases, mankind (or animal kind) has benefited from the use. Equally, however, resistance emerges from inappropriate use. The ideal would be to use antibiotics only when a person or animal benefits. In practice, that is a difficult ideal to meet, because diagnoses are difficult to make and many suspected bacterial infections are caused by viruses or other conditions.

Reducing resistance requires limiting antibiotic use while ensuring access for those who need treatment. The six primary strategies to improve antibiotic use are to:

1. Reduce the need for antibiotics by improving public health;
2. Improve hospital infection control and antibiotic stewardship;
3. Rationalize antibiotic use in the community;
4. Reduce antibiotic use in agriculture;
5. Educate health professionals, policy makers and the public on sustainable antibiotic use; and
6. Ensure political commitment to meet the threat of antibiotic resistance.

1. Reduce the need for antibiotics by improving public health

The best way to reduce the need for antibiotics is to reduce the burden of bacterial disease treated with antibiotics which, ultimately, reduces resistance levels. The main benefit, of course, is a healthier populace. Vaccination is the most powerful engine of disease prevention available worldwide. Clean water, improved sanitation and adequate and safe food are also priorities. All of these have strong constituencies related to their main aims of improving the health of the population.

Situation in Nepal

The National Immunization Program in Nepal has achieved coverage rates of over 80 percent for most diseases, and remains a government priority. By 2009, the program included routine immunizations for children and pregnant women against 10 diseases: tuberculosis, polio, diphtheria, pertussis, tetanus, hepatitis B, *H. influenzae* type b, measles, tetanus and Japanese encephalitis. The government has added a childhood pneumococcal vaccine to the national immunization schedule in 2015, but has not yet scheduled addition of *Rotavirus* vaccine. Other national prevention programs include control of malaria, tuberculosis, leprosy, and HIV.

2. Improve hospital infection control and antibiotic stewardship

Improving infection control in hospitals and other healthcare facilities can also reduce the need for antibiotics by reducing the spread of healthcare associated infection and therefore, the need for antibiotics. This also benefits patients immensely and at least in some instances, is cost-saving. Antibiotic stewardship programs in hospitals are designed to improve antibiotic prescribing through a number of mechanisms, which should be tailored to the facility. These can include guidelines for appropriate treatment, with consultations required for treatment outside of the guidelines, required cultures when antibiotics are started without a firm diagnosis and step down antibiotics to narrow-spectrum when appropriate, among others. Finally, the establishment of sentinel surveillance or point prevalence systems for antibiotic resistance can a provide data to guide clinical decisions and policies at the hospital level.

Situation in Nepal

National infection control and antibiotic stewardship guidelines have not been established in Nepal. Some hospitals have developed manuals on nosocomial infection control and have appointed infection control committees and others have done neither (Ohara, Pokhrel, Dahal, Mishra et al., 2013). This is an area with great potential for improvement.

Evidence of inappropriate prescribing in Nepal has been shown in several studies across different healthcare facilities, particularly for ampicillin, amoxicillin, ceftriaxone and gentamicin. In 13 studies of prescribing practices, nearly all found that antibiotics were the most frequently prescribed type of medication and most patients were

prescribed more than one antibiotic at a time, usually without bacterial confirmation or susceptibility testing. Antibiotics were prescribed inappropriately in 10 to 42 percent of patients, and were prescribed for both therapeutic and prophylactic purposes.

There is also evidence that, especially in lower level health facilities, healthcare workers often do not give the correct dosages of antibiotics and often advise patients incorrectly on how to take them.

Appropriate antibiotic treatment requires trained staff and well-equipped facilities to ensure a correct diagnosis as well as surveillance for resistance. While there are a number of public and private laboratories located across Nepal, the availability of well-trained microbiologists, pathologists, and other higher level specialists and technicians to manage these labs remains limited (Mishara, Tiwari, & Yadav, 2012).

Nepal has made some progress in establishing AMR surveillance for infections in humans. The Ministry of Health ran an AMR surveillance program from 1998-2003 and the Nepal Public Health Laboratory and the Epidemiology and Disease Control Division took over these efforts in 2004. The AMR surveillance network has grown to include 13 participating public laboratories. Their most recent report, with results from 1999 to 2012, includes *V. cholerae*, *Shigella* spp., *S. pneumoniae*, *H. influenzae*, *N. gonorrhoeae*, *Salmonella* spp. and *E. coli*. MRSA and other HAI-related bacteria are not included in the surveillance program. No private sector laboratories contribute to the network.

3. Rationalize antibiotic use in the community

Antibiotics may be prescribed by physicians and other healthcare workers inappropriately (e.g., without confirmation or for a common cold, usually caused by a virus and self-limiting) or they may be purchased directly by consumers without recourse to the healthcare system. Many patients self-treat with antibiotics, including prior to hospital admission, which can contribute to increased resistance rates.

Situation in Nepal

Antibiotics can be purchased routinely in the community, from pharmacies, drug shops and informal drug sellers. It

is likely that healthcare providers also prescribe antibiotics unnecessarily for coughs, colds and diarrhea.

The Community Based Integrated Management of Childhood Illness (CB-IMCI) program addresses major diseases that affect children from 2 months to 5 years old in all 75 districts of the country. The program aims to cover all children under 5 years old. Acute respiratory infections, pneumonia, and diarrhea are the most prevalent conditions, and each of these has important bacterial causes (in addition to viral and parasitic causes). However, neonatal mortality remains high, and the CB-IMCI program could be expanded to include detection and care for neonatal sepsis infections. This program should be improving antibiotic use in Nepal, but formal evaluation for this purpose has not been conducted.

4. Reduce antibiotic use in agriculture

Antibiotics are needed to treat bacterial infections in animals, just as they are in humans. However, it has become common practice to use antibiotics in food animals for two other purposes: 1) growth promotion and 2) to prevent disease. These two practices may be indistinguishable, as both rely on "sub-therapeutic" doses—small amounts of antibiotics are usually mixed with animal feed at the retail level. Farmers have also been using antibiotics to prevent disease in animals in place of improved sanitation and conditions for raising animals for decades. Use of antibiotics for growth promotion has been banned in Europe and some other countries, and has been deemed an inappropriate use of antibiotics.

Situation in Nepal

Although there is a great deal of anecdotal evidence of antibiotic use in animals, few studies have documented the specific formulations and quantities used. Therefore, the quality and quantity of veterinary antibiotics being used are difficult to assess. Antibiotics for animals are commonly bought from informal vendors with no training, and usually inadequate storage conditions.

Since the early 1990s, veterinary medicines and vaccines have been supplied by the private sector but the field suffers from lack of availability, high cost, poor quality, low awareness and poor distribution.

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No veterinary AMR surveillance network exists. The Central Veterinary Laboratory provides conducts epidemic investigation and some disease surveillance. Nepal currently lacks veterinary drug use regulations and guidelines.

5. Educate health professionals, policy makers and the public on sustainable antibiotic use

In spite of the seriousness of the issue, antibiotic resistance is still not widely recognized as a problem, even within the health community. Raising awareness about resistance and educating health professionals, policy makers and the public on the diverse roots of resistance will support efforts to improve practices and build policies that improve rational antibiotic use.

Health professionals can be targeted through updates to curricula and to treatment guidelines, as well as through the implementation of hospital antibiotic stewardship programs, as mentioned previously. Policy makers can be engaged through the dissemination of relevant research and participation in national and regional meetings. Finally, the public can be educated through awareness campaigns. Effective education should have an impact on many other areas, including improving rational use at the hospital and community level, reducing use in agriculture and building political commitment for the issue.

Situation in Nepal

Antibiotic resistance has received little attention in the education of professionals from community workers to physicians, and including nurses, pharmacists, veterinarians and the associated professions.

6. Ensure political commitment to meet the threat of antibiotic resistance

Addressing antibiotic resistance is a shared responsibility of health professionals, the private sector and the public. Ensuring a comprehensive response requires political commitment as well. Government cannot solve all the problems, but they can legislate, regulate and take a variety of other actions to lay the groundwork for action and

represent the public interest.

Situation in Nepal

GARP-Nepal is the first multi-sectoral group working on antibiotic resistance in the country, and has engaged with key stakeholders from human, animal and environmental health. Further efforts to raise awareness and build cooperation between experts have the potential to improve antibiotic use as they engage in advocacy and take action in their respective sectors. In addition, increasing collaborative research will strengthen the knowledge base on which policies can be built. Creating policies to guide antibiotic use is the most sustainable way to ensure that changes are implemented and maintained. At present, though there are laws that guide drug purchasing, distribution and use, and a national formulary that outlines essential medicines and the type of health providers that may prescribe them, no national policies are in place to guide antibiotic use.

With this situation analysis and these recommendations, GARP-Nepal has the tools to begin building political and popular support to address this important issue.

Box 1-1 : From the situation analysis launch: participant observations and recommendations

The executive summary of this situation analysis was the focus of discussion at a launch meeting held in Kathmandu on December 15, 2014. More than 60 stakeholders and interested professionals from various sectors in Nepal, including the Minister of Health and Population spoke or were in attendance. The reactions and recommendations offered by participants are summarized below.

Raise awareness about the public health crisis
Antibiotic resistance is a huge public health challenge and could quickly become a crisis if no action is taken to ensure the sustainability of these life-saving drugs. It should be of concern to clinicians, patients, government and the public at large. The dissemination of critical information on resistance to all audiences is important in building behavior change. The media can play a significant role in this process and should be involved in awareness

raising campaigns. Efforts should be made to appeal to the public and policy makers by demonstrating the economic impact of antibiotic resistance in addition to the impact on human and animal health.

Collaborate with the government to improve guidelines and policies
Some national guidelines and policies are not sufficient to curb antibiotic resistance in their current form. For instance, the "National Treatment Guideline" is not consistent with technical standards for the treatment of infectious diseases and should be reviewed and updated in line with scientific evidence.

In addition, some policies currently in place may conflict with policies designed to encourage rational antibiotic use. For instance, female community health volunteers were authorized to distribute cotrimoxazole when treating respiratory infections at community level. While this policy may decrease the disease burden of ARI in children, treating infections without a laboratory diagnosis or clinician consultation may encourage the overuse of and resulting increase in resistance to cotrimoxazole. This policy should be revised and updated to promote the rational use of antibiotics.

Focus on antibiotic use and resistance in animals
Antibiotic use in livestock is currently uncontrolled, and the threat imposed by the irrational use of veterinary antibiotics is quite significant. It is important that activities to investigate and curb antibiotic use in animals be implemented.

Consistent with the recommendations of the International Federation for Animal Health, there should be a separate policy and agency responsible for regulating the use of veterinary antibiotics in country.

Ensure access
Many rural areas of Nepal lack access to healthcare, and increasing access to health services and personnel should be a major national focus to improve and safeguard human health.

Take an ecological approach
Antibiotic resistance is a multi-sectoral issue that requires the participation of many diverse partners and sectors. Efforts should target the individual all the way up to the societal level.

RECOMMENDATIONS AND NEXT STEPS

Recommendations

Considering the information in this situation analysis and the pressing global need, the overarching recommendation of the GARP-Nepal Working Group is:

> **A national strategic plan for the use of antibiotics that preserves their effectiveness into the future and gains the maximum health benefits from their appropriate use.**

Developing and implementing such a plan will require the collaboration of all relevant sectors, including private and public sectors, and those involved with both human and veterinary health.

At the global level, the development of new antibiotics, alternatives to antibiotics and new diagnostics for bacterial and other infectious diseases is an important aspect of curbing antibiotic resistance, and these efforts should be increased.

Next steps

The development and implementation of a strategic plan will take time, and some activities can and should be implemented while this process is ongoing, providing more information and impetus. Financial and human resource limitations dictate that activities have to be staged. GARP-Nepal will initially focus on the development of curricula for healthcare workers and the implementation of studies to assess antibiotic use and resistance in animals. Concurrently, working group members will continue to use this situation analysis and other information to generate interest in and action on antibiotic use and resistance.

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Chapter **2**:
Population Health and Background

HUMANS

2.1 Population

Nepal is a landlocked country with an area of 147,181 square kilometers. It shares an open border with India to the south, east and west and with China to the north. Topographically Nepal has three distinct ecological zones: mountain, hill and terai. The Mountain Region is situated at 4,000 meters or more above sea level. Windy climatic conditions and rugged topography limit human habitation and economic activities in this region, which is sparsely populated. The Hill Region lies mainly between 1,000 and 4,000 meters in altitude. Although agriculture, supplemented by livestock farming, is the predominant economic activity in the hill region, it is a food deficit area. The Terai Region is a lowland tropical and subtropical belt of flat, alluvial land stretching along the Nepal-India border. This region is the most inhabited, and is home to 50 percent of the population (CBS, 2012). The geography of Nepal is a serious challenge to delivering health services to all. In the Mountain Region, 4 of 10 individuals have to travel 1-4 hours to reach the nearest health or sub-health post. In the Hill Region, 3 of 10 individuals have to travel 1-4 hours to reach the nearest health or sub-health post (NHSP, 2010). Administratively, Nepal is divided into 5 development regions—including eastern, central, western, mid-western, and far-western—14 zones and 75 districts.

Nepal has a population of 26,454,904, with a population growth rate of 1.35 percent per annum in 2011 as compared to 2.25 percent per annum in 2001 (CBS, 2012). This decline in the growth rate is attributed to the increased proportion of youths living abroad (about 1.92 million). National gender ratio (males per 100 females) decreased from 99.8 in 2001 to 94.2 in 2011. Men outnumber women in urban areas, while the reverse is true in rural areas. This is largely due to the migration of males from rural to urban areas for employment and other purposes. Population density at national level has increased from 157 people per square kilometer in 2001 to 180 in 2011. The highest population density is in Kathmandu district, with 4,416 people per square kilometer, and the lowest is in Manang district, with 3 people per square kilometer (CBS, 2012).

The working-age population (ages 15-54) has increased, from 54 percent of the total population in 2001 to 57 percent in 2011. Out of the total population, in 2011, 17 percent resided in an urban setting compared to 14 percent in 2001. This increase reflects the rapidly increasing urbanization taking place in Nepal. Kathmandu is the fastest growing metropolitan area in South Asia, with 4 percent population growth per annum. Nepal has an adult literacy rate of 57 percent, with a huge disparity between males and females. While the male literacy rate is 72 percent, the female literacy rate is just 45 percent (CBS, 2012).

2.2 Economy

Nepal is one of the poorest countries in the world. The 2013 UNDP Human Development Report ranked Nepal in 157th position, with a Human Development Index of 0.463. The Third National Living Standards Survey (NLSS-III) (2010-11) reported that the percentage of the population living below the poverty line decreased from 42 percent in 1995-96 to 25 percent in 2010 (NLSS, 2010-11). This significant change in poverty is attributable to the Government of Nepal's focus on poverty reduction. The report also recorded a 6 percent decline in absolute poverty in between 2003-04 and 2009-10. Absolute poverty refers to a condition where a person does not have income needed to meet the minimum requirements for one or more basic living needs, such as food, safe drinking water, health, education, sanitation facilities, shelter and information, over an extended period. The survey also indicate that Nepal is experiencing a 2 percent annual decline in poverty. Eastern Nepal has the lowest poverty level (21 percent), while far west has the highest (46 percent) (NLSS, 2010-11). According to the 2013 UNDP Human Development Index, 25 percent of the population lives in absolute poverty (income of less than USD 1.25 per day in 2010) and about 57 percent of the population lives in a slightly lower level of poverty (income less than USD 2 per day in 2010) (UNDP, 2013).

Nepalese economy is based largely on agriculture. According to the Central Bureau of Statistics Report 2011, about 76 percent of households are involved in agricultural activities. The gross domestic product (GDP) annual growth rate increased from 3.8 percent in 2011 to 4.6 percent in 2012 (CBS, 2012).

2.3 Health system

Health remains a high priority for Government of Nepal. The interim constitution, which came into force on January 15,

2007 declared free basic health services as a fundamental right for every Nepalese citizen. The constitution is part of the transformation process which began with the massive people's movement against Monarchy in April 2006. Government of Nepal has enforced many other plans and policies to strengthen the health sector. Government policies such as Drug Act 1978, National Health Policy 1991, and National Drug Policy 1995 promise universal access to essential medicines and health services. Government of Nepal has also formulated long-term plans to promote health of its citizens and increase access to and utilization of essential health services. Ministry of Health and Population (MoHP) has adapted universal and targeted free care approaches to health. In accordance with the universal free care policy, government has distributed selected essential drugs free of charge since 2006, including 40 drugs to all district hospitals (DHs)—as well as a recent addition of 20 more—35 drugs to primary health care centers (PHCCs) and 25 drugs to health posts (HPs). In addition, in response to the Interim Constitution, MoHP/GoN decided to provide essential health care (emergency and in-patient services) free of charge to targeted groups, including the ultra-poor, poor, helpless, senior citizens, people living with physical and psychological disabilities, and Female Community Health Volunteers (FCHVs) at the level of

Box 2-1: Operational definition of ultra-poor, poor, senior citizens, helpless senior citizens and FCHVs

Ultra-poor: Those people who receive less than 80 percent of the minimum calorie intake while spending 80 percent of their income on food.

Poor: Those people who do not have enough income to buy food items worth 2,124 calories per person per day plus some non-food items.

Senior citizen: A citizen of Nepal 60 years or older.

Helpless senior citizen: A senior citizen who has no income source or property; no family members to support him or her; or who is being compelled to live a neglected life.

Female Community Health Volunteer (FCHV): FCHVs are the frontline local health resource in Nepal, providing community based health education and services in rural areas, with a special focus on maternal and child health and family planning.

sub-health posts (SHPs), health posts (HPs), primary health care centers (PHCCs) and district hospitals (DHs).

The main health related goal of Nepal's Three-Year Plan (Approach Paper: 2010–2013) is to establish the right of every citizen to free basic health care services. According to this plan, preventive, promotional and curative health services will be provided according to the principles of primary health care services. Providing free services generally increases the utilization of quality health services by ensuring availability and accessibility of health services to the citizens of all the geographical regions, classes, genders and ethnicities, helping to alleviate disparities in access to health services. Health access and utilization is poor among Dalits (untouchable caste), Muslims and disadvantaged Janajatis. Private sector health services are unaffordable for majority of Dalits, who are also unable to utilize low-cost public health services due to caste discrimination (Bhattachan, Sunar, & Bhattachan, 2009). Women in these marginalized groups have the lowest levels of access to pre and postnatal care, family planning services and knowledge on HIV/AIDS (Bennette, 2005). Other studies have reported disparities in utilization of health services.

In a study of 40 village development committees (VDCs) from 10 districts (Solukhumbu, Jhapa, Parsa, Lalitpur, Mustang, Kaski, Surkhet, Dang, Doti and Kanchanpur) interviews were conducted with 800 mothers with children under two years of age, 40 health service providers, 145 key informants and 40 exit clients; Focus Group Discussions were held and health records reviewed. Health service access and use varied according to ethnicity, with the highest utilization of services reported in Brahmin/Chettri (47 percent) followed by Janajati (24 percent), Dalits (17 percent) and Muslims (4 percent) (Devkota B, 2008).

Another study conducted in Biratnagar sub-metropolitan city demonstrated discrimination in vaccination. Among 69 children of Janjatis, 9 (13 percent) did not receive vaccines, while of 115 Muslim children, 49 (43 percent) were not vaccinated. Similarly, among 81 Dalit children, 27 (33 percent) were not vaccinated. Ethnic discrimination also prevails in family planning service and contraceptive use. The study also found that home delivery was high for Janajatis, Muslims and Dalits, while most upper castes have an institutional delivery (Bakhundol & Tiwari, 2008).

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Organization and distribution of health services

Government of Nepal provides health services at national, regional, zonal and district levels. Services are also provided below the district level in primary health care centers, health posts, sub-health posts, and at the community level. GoN has established an organizational structure for delivering health services in Nepal (figure 2-1).

In addition to government health services and facilities, there are a number of private hospitals and non-governmental organizations that provide health services in Nepal.

Health work force
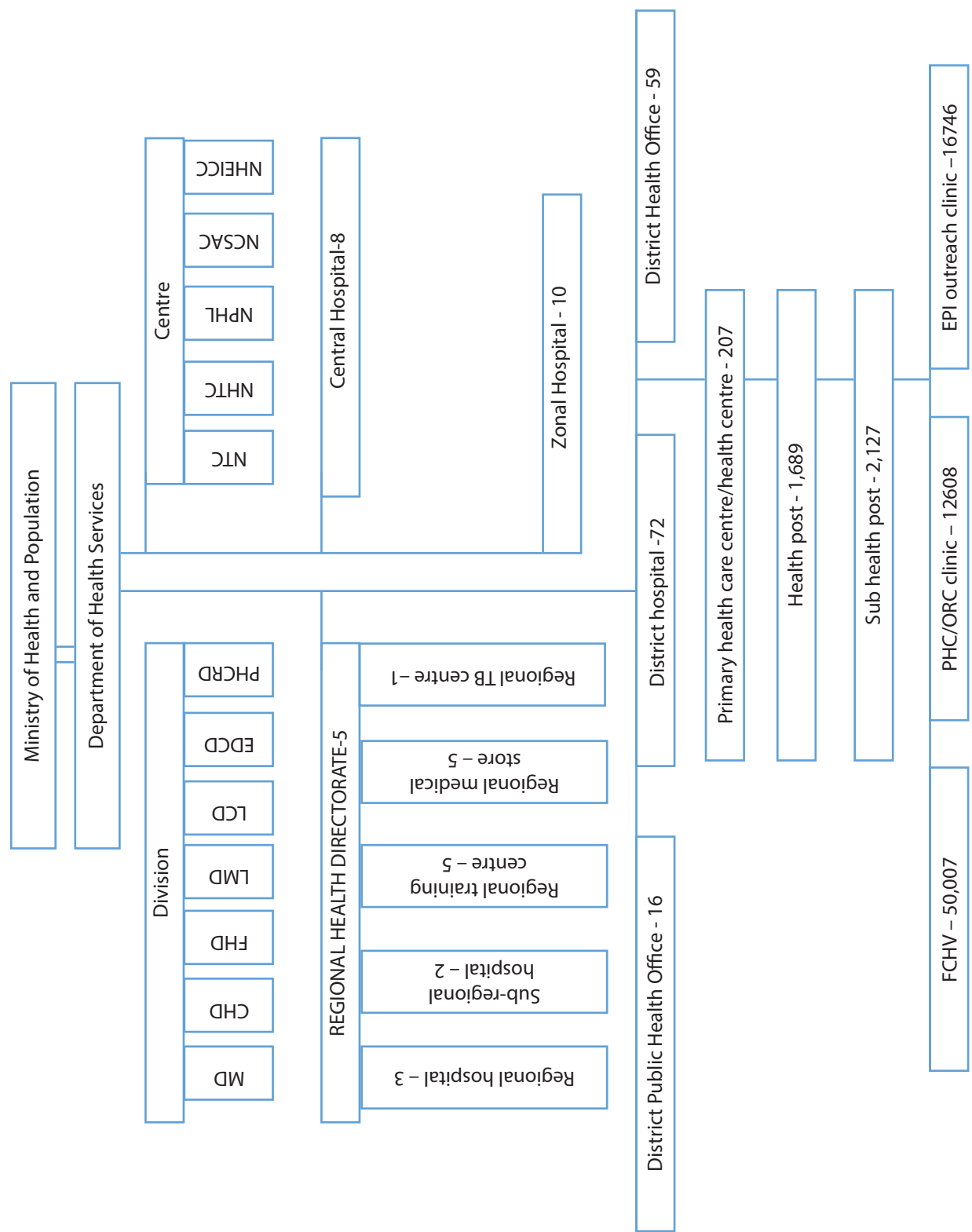
With the increasing number of private academic institutions in Nepal, there are increasing numbers of health worker, including medical doctors, nurses and other health professionals. There are fewer highly skilled health workers such as doctors of general practice (MDGPs), anesthetists, and surgeons. According to a human resource analysis report from 2011-12, there are 0.09 General Medical Practitioners per 1,000 people (46 percent of total General Medical Practitioners (n=2,450) are in public health facilities and 54 percent in private health facilities), 0.07 specialist medical practitioners per 1,000 (33 percent of total (n=1,915) in public and 67 percent in private health facilities) and 0.27 nurses per 1,000 (48 percent of total (n=7,054) in public and 52 percent in private health facilities).

Only 22 percent of medical officer positions are filled at primary health care center level (Mehata et al., 2013). Retention of medical doctors is a major challenge for health sector. There are just 16 registered health workers per 10,000 people, including public and private sectors. Due to the migration and shifting of registered health professionals to private practice, public sector has a ratio of only 2.9

health workers (doctors, nurses, and midwives) per 10,000 people, far below the 23 health workers per 10,000 people recommended by World Health Organization (WHO) in order to achieve health-related Millennium Development Goals (Poudyal, 2012).

There is a similar shortage of pathology professionals in Nepal. A study conducted by Mishra and colleagues in 2012 in Kathmandu showed that there were unauthorized workers in approximately half of the laboratories. Only 30 percent of 373 laboratories employed officer level pathologists (eligible to work independently). Similarly, there was lack of intermediate level pathology workers in 66 percent of laboratories. Of the specialist level (MD/MSc) workers, according to the guidelines of the National Medical Council (NMC), Nepal Health Professional Council (NHPC) and National Public Health Laboratory (NPHL), 43 (11 percent) work in histocytopathology, 10 (3 percent) in clinical microbiology and 3 (1 percent) in cytopathology & hematology (Mishara, Tiwari, & Yadav, 2012).

Figure 2-1: Organization and Distribution of Health Services

- Ministry of Health and Population
- Department of Health Services

Centre
- NTC
- NHTC
- NPHL
- NCSAC
- NHEICC

Central Hospital-8

Division
- MD
- CHD
- FHD
- LMD
- LCD
- EDCD
- PHCRD

REGIONAL HEALTH DIRECTORATE-5
- Regional hospital – 3
- Sub-regional hospital – 2
- Regional training centre – 5
- Regional medical store – 5
- Regional TB centre – 1

- Zonal Hospital - 10
- District hospital -72
- District Public Health Office - 16
- District Health Office - 59
- Primary health care centre/health centre - 207
- Health post - 1,689
- Sub health post - 2,127
- EPI outreach clinic –16746
- PHC/ORC clinic – 12608
- FCHV – 50,007

Source: (DoHS, 2012-13)

Health Indicators

Life expectancy is a significant indicator of population health. Nepal observed an increase in life expectancy at birth between 1990 and 2011. In 2011, WHO reported the life expectancy at birth as 67 for males, 69 for females and 68 overall (table 2-1) (WHO, 2013).

Table 2-1: Life expectancy at birth and at 60 years

	LE at Birth		LE at 60 years	
	1990	2011	1990	2011
Male	54	67	14	16
Female	55	69	15	18
Both	55	68	15	17

Source: (World Health Statistics, 2013)

The statistics reported by WHO differ from those reported by the Central Bureau of Statistics (CBS), but both reports showed that life expectancy is increasing. According to the 2011 CBS report, life expectancy at birth is 64.6 for males, 67.1 for females and 65.8 overall, compared to 60.2 for males, 60.8 for females and 60.5 overall in 2001 (table 2-2) (CBS, 2012).

Table 2-2: Life expectancy at birth

	LE at Birth	
	CBS 2001	CBS 2011
Male	60.1	64.6
Female	60.7	67.1
Both	60.4	65.8

Source: (CBS, 2012)

Infant mortality rate (IMR) (deaths per 1,000 live births during the first year of life) is another important indicator of population health. IMR in Nepal decreased slightly from 48 in 2006 to 46 in 2011. Similarly, under-five mortality (death before age 5 per 1,000 live births) decreased from 61 in 2006 to 54 in 2011 (table 2-3) (NDHS, 2006, 2011). IMR in urban areas is 38 compared to 55 in rural areas (NDHS, 2011).

Table 2-3: Infant mortality rates, under-five mortality rates and neonatal mortality rates

	1996	2001	2006	2011
Neonatal mortality rate (per 1,000 live births)	50	39	33	33
Infant mortality rate (per 1,000 live births)	79	64	48	46
Under-five mortality rate (per 1,000 live births)	118	91	61	54

Source: (NDHS, 2011)

Maternal mortality ratio (MMR) also helps to assess the current state of health. MMR is the annual number of female deaths per 100,000 live births from any cause related to or aggravated by pregnancy or its management (excluding accidental or incidental causes). Maternal mortality ratio decreased from 539 in 1996 to 229 in 2009, and further decreased to 170 in 2011 (NDHS, 2006; WHO, UNICEF, UNFPA, & World Bank, 2012). The dramatic drop in MMR is attributed to the effective implementation of many health sector programs focused on maternal, neonatal and child health.

The 2013 World Health Statistics Report shows age standardized mortality rates (per 100,000 people) among adults aged 30-70 years by different disease categories in 2008. For communicable diseases, the rate was 338 per 100,000 population, while for non-communicable diseases it was 620, and for injury, 58. Total number of deaths among children less than 5 years of age was 67,000 in 2000 and 35,000 in 2010. In 2010, 30 percent of deaths of children under 5 were due to infectious diseases including diarrhea, pneumonia and sepsis (table 2-4) (WHO, 2013).

Table 2-4: Distribution of the causes of death among children aged less than 5 years

Disease	Deaths (percent of total)		Disease	Deaths (percent of total)	
	2000 (N=67,000)	2010 (N=35,000)		2000 (N=67,000)	2010 (N=35,000)
HIV	0	0	Birth asphyxia	10	12
Diarrhea	11	6	Neonatal sepsis	7	8
Measles	2	0	Congenital anomalies	3	5
Malaria	0	0	Others	16	15
Pneumonia	19	16	Injuries	5	5
Prematurity	26	32			

Source: (World Health Statistics, 2013)

Outpatient morbidity

The top five reported causes of outpatient morbidity are gastritis (APD) (5.8 percent), upper respiratory tract infection (5 percent), headache (4.9 percent), lower respiratory tract infection (4.7 percent) and pyrexia of unknown origin (3.6 percent). Other major reported causes for outpatient morbidity include impetigo-boils-furunculous (3.2 percent), intestinal worms (3.2 percent), presumed non-infectious diarrhea (2.8 percent), typhoid (2.5 percent) and falls, injuries or fractures (2.5 percent). Of all the outpatients, 85 percent visited OPD for non-communicable diseases and 15 percent for communicable diseases (DoHS, 2012-13).

Inpatient Morbidity

Of 427,436 total inpatients recorded in 2012-13, single spontaneous delivery was the most common cause of inpatient stay, followed by diarrhea, gastroenteritis of presumed infectious origin and single delivery by caesarean section (table 2-5) (DoHS, 2012-13).

Table 2-5: Top ten causes of hospitalization

S. N	Cause of patients hospitalization	Number	Percent
1	Single spontaneous delivery	83,861	28.7
2	Diarrhea and gastro-enteritis of presumed infectious origin	11,008	3.8
3	Single delivery by caesarean section	10,836	3.7
4	Pneumonia, organism unspecified	10,019	3.4
5	Typhoid and paraty-phoid fevers	9,422	3.2
6	Other chronic obstruc-tive pulmonary diseases	9,382	3.2
7	Unspecified acute lower respiratory infection	8,804	3.0
8	Other disorders of urinary system	8,090	2.8
9	Others maternal diseas-es classifiable elsewhere but complicating preg-nancy, childbirth and the puerperium	6,060	2.1
10	Injury of unspecified body region	4,735	1.6
	All other reasons	130,301	44.5
	Total number of discharged patients	292,518	100

Source: (DoHS, 2012-13)

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Causes of mortality in central level hospitals

Death rate for inpatients with communicable diseases is higher than for those with non-communicable diseases among hospitalized cases. Five leading causes of morbidity and mortality among inpatients in Nepal's seven central level hospitals vary based on each hospital's specialty (table 2-6).

Table 2-6: Five leading causes of mortality in different hospitals of Nepal

Name of central hospital	Five leading causes of mortality (N)				
	I	II	III	IV	V
National Academy of Medical Sciences (NAMS), Bir Hospital	Chronic Obstructive Pulmonary Disease (COPD)	Chronic Lung Disease	Pneumonia	Diabetes Mellitus	Cancer Lung
Kanti Children's Hospital	Neonatal sepsis	Pneumonia	Coronary Heart Diseases	Malnutrition	Encephalitis
Paropakar Maternity and Women's Hospital	Amniotic Fluid Embolism	Pulmonary Edema	Septicemia	Primary Pulmonary hypertension	-
Sukraraj Tropical & Infectious Disease Hospital	PLHA	Tetanus	Rabies	Enteric Fever	Hepatitis
Shahid Gangalal National Heart Centre	Coronary Artery Diseases	Rheumatic Heart Diseases	Congenital Heart Diseases	Heart Failure	Arrhythmia
Nepal Police Hospital	COPD	Chronic Kidney Diseases	Hypertension and Diabetes Mellitus	Surgery	-
TU Teaching Hospital	Pneumonia	Septicemia	Stroke	COPD	Hypertension

Source: (DoHS, 2012-13)

Nutritional status

Malnutrition seriously affects child survival, growth and development. Approximately one quarter of infants in Nepal are born with low birth weight (less than 2.5 kg at birth), and among children under 5 years of age, 41 percent are stunted, 29 percent are underweight and 11 percent are wasted (table 2-7) (NDHS, 2011).

Table 2-7: Nutritional status of children under five years

	2001	2006	2011
Stunting	57	49	41
Wasting	11	13	11
Underweight	43	39	29

Source: (NDHS, 2011)

Box 2-2: Operational definition of wasting, stunting and underweight

Wasting: Weight below minus two standard deviations from median weight for height of reference population.

Stunting: Height below minus two standard deviations from median height for age of reference population

Underweight: Weight below minus two standard deviations from median weight for age of reference population

Source: (Unicef, 2014)

Percentage of children under five years old classified as malnourished decreased by 1.3 percent, from 4.7 in 2008-09 to 3 in 2012-13 (DoHS, 2010-11; DOHS, 2012-13).
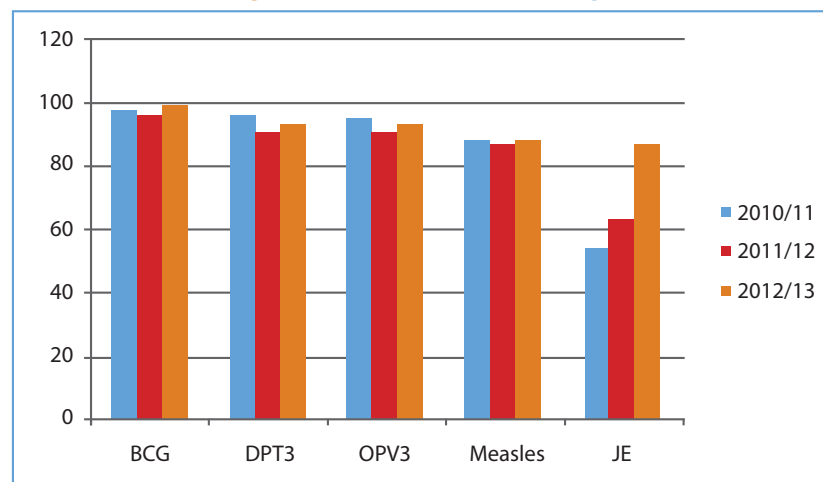
Immunization coverage

Immunization coverage is defined as having received the following:

- One dose of Bacillus Calmette-Guérin (BCG) vaccine for tuberculosis;
- Three doses each of diphtheria, pertussis and tetanus (DTP), hepatitis B and *Haemophilus* influenzae typeb (Hib) vaccines;
- Three doses of the polio vaccine;
- One dose of measles vaccine;
- Two doses of tetanus toxoid (TT) vaccine for pregnant women; and
- One dose of Japanese encephalitis vaccine.

National immunization coverage has increased each year from 2010 through 2013 (figure 2-2) (DoHS, 2012-13).

Figure 2-2: Immunization coverage

Source: (DoHS, 2012-13)

Overall, national vaccination coverage is high, and in 2012-13 coverage rates were above 91 percent for all routine childhood immunizations in all regions. Over reporting is a potential issue, as some rates were reported as over 100 percent. Some disparities in coverage between regions exist, with the western region reporting lowest coverage rates in all consecutive years 2010-11 and 2011-12, 2012-13 whereas highest coverage rates were reported in mid-western region in 2010-11 and 2011-12 and in far-western region in 2012-13 (DoHS, 2010-11 ; DoHS, 2012-13).

2.4 Availability of and Access to Essential Medicines

In accordance with the decisions of the Popular Movement (Jana Aandolan, 2006) essential health care services (emergency and in-patient) are provided free of charge to the ultra-poor, poor, helpless, senior citizens, people living with physical and psychological disabilities and FCHVs at the level of sub-health post, health post, primary health care centre and district hospital.

In addition, government provides 60 essential drugs free of charge to all district hospitals, 35 drugs to primary health posts and 25 drugs to health posts. The government aims to ensure the availability of essential drugs year round in all health facilities by 2017.

2.5 Government Policies and Regulatory Environment

Restoration of monarchy in 1951 and establishment of international airport in Kathmandu in 1955 opened the door for foreign assistance to Nepal. Traditionally, medical care was provided by indigenous practitioners such as homeopathic doctors, tibetan medical doctors, herbalists or ayurvedic doctors. Until 1954 there were very few allopathic medical doctors, trained health workers, and missionary or government hospitals. Beginning in 1954, with aid support from WHO, India and the U.S., health care services expanded.

Government of Nepal's first five-year plan, created in 1956, initiated planned development of health sector. Between early 1950s and late 1970s, the sector expanded to include approximately 70 hospitals with 15-300 beds, 450 medical doctors, 350 nurses and 550 health posts.

During this period government of Nepal also launched malaria, small pox, leprosy and tuberculosis control program and established Integrated Basic Health Services Division within the Department of Health Services. In 1974, WHO regional office for South East Asia (SEARO) introduced country health programs to its members, and asked each ministry to form a planning department in

order to gather data and provide information to National Planning Commission, enabling Nepal to organize its own health planning bureaucracy. In response, Ministry of Health and Population formed Health Planning Unit and developed fifth five-year development plan and the first long term health plan for Nepal (WHO, 2007).

National policies

Antibiotic Treatment Guidelines-2014

Antibiotic Treatment Guidelines, 2014 provides antibiotic treatment protocol for various diseases at different level of health institutions. The guideline categorized health institutions in three levels on the basis of infrastructure and availability of healthcare providers: sub-health posts (SHPs) and health posts (HPs); primary health care centers and district hospitals; and tertiary level and specialized hospitals. According to the guideline, for the use of antibiotic in sub health post and health post level, choice of antibiotics is entirely based on the list of essential drugs. Antibiotics that are not included in the essential list are prohibited at SHP/HP level whereas for primary health care center and district hospital level, doctors make judgments for the use of some antibiotics that are not included in the national list of essential drugs. At tertiary level and specialized hospitals priority is given to the essential drugs, although other antibiotics can also be used depending upon the need of the patients. However, reserve antibiotics are prescribed only by faculty, specialist and consultant. Hospitals should develop their own policies for the use of such antibiotics. The guideline details the antibiotics that should be prescribed for the diseases: general medicine (enteric fever, ARI, Gastritis and Peptic Ulcer, Bronchitis, Pneumonia, Acute Bacterial Meningitis, UTI); surgery (Cellulitis, Lymphadenitis, Abscess, Wound Infection, Burn, Trauma, Pancreatitis, Acute Cholecystitis/ Acute Appendicitis, Obstructed or Strangulated Hernia, all surgeries); paediatrics (Pneumonia, Bacillary Dysentery, Acute Ear Infection, Acute Osteomyelitis and Septic Arthritis, Acute Post-streptococcal Glomerulonephritis, Acute Rheumatic Fever); obstetrics and gynaecology (UTI, Puerperal Sepsis, Post Abortion Infection), STI (Urethral Discharge Syndrome, Scrotal Swelling Syndrome, Genital Ulcer Disease Syndrome (GUD), Inguinal Swelling (bubo) Syndrome, Vaginal discharge Syndrome (cervicitis & vaginitis), Lower Abdominal Pain Syndrome, Neonatal Conjunctivitis (Ophthalmia neonatorum); Dental etc. (Antibiotic Treatment Guidelines, 2014).

Drugs Act–1978

The Drugs Act, 1978 was formulated for two main purposes:

- "To prevent the misuse or abuse of drugs and allied pharmaceutical substances and false or misleading information relating to the efficacy and use of drugs"; and
- "To control the production, sale, distribution, export, import, storage and consumption of those drugs which are not safe for public consumption, efficacious and of standard quality."

The act formed Drug Consultative Council and Drug Advisory Committee, and established Department of Drug Administration and Royal Drug Research Laboratory (Now called National Medicine Laboratory) for the quality control of drugs. The act also permitted the establishment of new research laboratories by a person or an institution that had received approval from government of Nepal. Finally, the act provided foundations for establishing a drug industry by setting mechanisms for obtaining licenses for the production, import and export of drugs and drug quality standards (Drugs Act, 1978).

National Health Policy–1991

The National Health Policy, 1991 aimed to extend primary health care system to rural areas and to improve overall health of the Nepalese population. The policy established a system to allow rural populations access to modern medical facilities and allopathic care providers. The national policy addressed several areas to improve the health system, targeting deliverables at national, local and sub-local levels.

Policies included the creation of preventive health care services devoted to reducing infant and child mortality; health promotion services; curative health care services focused on expanding the number of regional and district hospitals based on population density and patient loads; development of specialist and referral care; expansion of basic primary health care services; and promotion of ayurvedic and other traditional health services. Other policies were the improvement of organization and management of health facilities and the development of District Health Offices; encouragement of community participation through community health workers, birth attendants, and others; strengthening of training centers, academic institutions,

and human resources necessary for health care expansion; mobilization of national and international resources; and coordination of the participation of private and non-governmental health services. Finally, policies focused on strengthening of District Health Offices to support decentralization; centralization of blood transfusion services in Nepal Red Cross Society; establishment of a National Drug Policy to promote procurement and upgrading the quality of essential drugs; and encouragement for research on improved management of health services (National Health Policy, 1991).

National Drug Policy–1995

The National Drug Policy, 1995 was formed to fulfill the objectives of National Health Policy and to ensure the effective implementation of National Drug Act. It aimed to make Nepal self-reliant in drug production in order to ensure the availability of safe, standard, and quality drugs at affordable prices throughout the country. The policy covered the management of all drug-related activities including production, import, export, storage, sale, supply and distribution. It emphasized on rational use of drugs at both prescriber and consumer level. Following points on rational antibiotic use were covered in the policy, including the amendment in 2001 (National Drug Policy, 1995):

- Management of antibiotics in food, animal feed and agricultural substances.
- Supervision and monitoring of antibiotic use.
- Classification of antibiotics according to therapeutic effectiveness.
- Establishment of a National Antibiotic Control Committee including experts from the human and animal health sectors, professional organizations and consumer groups.
- Establishment of a National Antibiotic Therapeutic Advisory Committee to advice on the prudent use of antibiotics.
- Strengthening of the quality assurance system.

National Health Insurance Policy–2013

As outlined in the Three Year Plan (2010-13) and the Health Sector Program II (2010–2015), National Health Insurance Policy addresses issues pertaining to the finance and administration of health services through the following mechanisms: a universal coverage insurance program; an output-oriented expenditure system; service integration; and promotion of health-seeking behaviors (through the use

of entitlement procedures, awareness raising, and behavior change communication). Through these mechanisms, the policy aims to build a health system that is accessible, equitable, affordable and efficient in terms of both quality and cost.

The policy outlines three methods to achieve the universal insurance program. First, to increase public financial protection for health sector by encouraging systems of prepayment and risk pooling, second, to mobilize financial resources equitably, and third, to improve the effectiveness, efficiency, accountability and quality of care in healthcare service delivery (National Health Insurance Policy, 2013).

Implementation Plans

Long Term Health Plan–1976 to 1992

The first 15-year long-term health plan (LTHP) was implemented in 1976 with the purpose of promoting physical, mental and social health of the population; producing human resources needed to ensure availability of basic health services to all; reducing mortality rate; and raising average life expectancy. The main policies of the LTHP included providing basic health services at village level and checking population growth to promote national development. Other priorities included development of basic health services, promotion of family planning and maternal and child welfare services, and production of a trained health workforce (WHO, 2007).

Second Long Term Health Plan–1997 to 2017

The 20-year second long-term health plan (1997-2017) aims for the overall improvement of health of the population, particularly for those whose health needs are often not met. The plan addresses disparities in health care with a special focus on equity. It also encompasses the principles of sustainability, community participation, decentralization, gender sensitivity, effective and efficient management and public-private partnerships, and aims to ensure the accessibility of health services and essential drugs for all communities and individuals (DoHS, 2009-10).

Three-Year Interim Plan–2007 to 2010

This plan established free basic health care services as a basic right for all people. To ensure the availability of primary health care services to each and every individual, different programs

focusing on marginalized and deprived communities were conducted. To improve the quality of health care services, government, private sector and NGO partnerships were strengthened. In addition, Community Drug Program and Community Cooperative Clinic services were encouraged. This plan aimed to strengthen the relationship between health science and medical and public health in order to make health services effective, efficient and pro-people (DoHS, 2009-10).

National Health Sector Program Implementation Plan I (2004 to 2009) and Plan II (2010 to 2015)

Nepal formulated "health sector strategy-agenda for reform" (HSRS) in 2003 with an aim of improving health status of Nepalese population through the development of health-sector. The main impetus for the development of this strategy was the prevailing disparities in health across social groups, geographic regions and genders, and the need to increase utilization of quality health care services. The strategy aims to improve health status through the provision of equal opportunities for quality health care services delivered through an effective health system, and thus to develop healthy and capable citizens and to support poverty alleviation. To achieve these goals, Government of Nepal introduced its first Nepal Health Sector Program (NHSP) from 2004-2009. The program provided operational guidelines to achieve the HSRS aims. The main focus of NHSP was to increase coverage and improve the quality of essential health care services (MoHP, 2004).

NHSP covers the entire sector, rather than isolated projects. NHSP has eight targets, three of which are designed to strengthen health service delivery. Those three targets are: a) delivery of essential health care services, b) decentralized management of services, and c) public private partnerships. The remaining five targets are designed to improve institutional capacity and management in the areas of: a) sector management, b) health financing and financial management including alternative financing, c) physical asset management and procurement, d) human resource management, and e) health management information systems and quality assurance (DoHS, 2009-10).

Second five-year health sector program (NHSP-IP II) run from 2010-2015 and was based on first NHSP, health sector reform strategies, and three-year interim plan. Some new components, including mental health, oral health, environmental health, community-based

newborn care, and community-based nutrition care and support were added into essential health care services under this program. The program also incorporated a non-communicable disease (NCD) control component in EHCS; programs for public-private partnerships (PPPs); governance and accountability; inter-sectoral coordination and collaboration; and sustainability were also added. The three objectives set out in the framework are:

- To increase access to and utilization of quality essential health care services;
- To reduce cultural and economic barriers to access health care services and harmful cultural practices in partnership with non-state actors; and
- To improve the health system to achieve universal coverage of essential health services (MoHP, 2010).

Organizations working on antibiotic resistance

Several organizations in Nepal are currently working to promote rational use of antibiotics. The most prominent are discussed below:

Alliance for the Prudent Use of Antibiotics (APUA), Nepal

Alliance for the Prudent Use of Antibiotics (APUA) has been promoting appropriate antibiotic use and curbing antibiotic resistance since 1981. APUA has a network of affiliated chapters in 66 countries, including Nepal. It conducts large-scale national and international research and educational projects to control and monitor antibiotic resistance. It facilitates the exchange of updated information by developing national and international partnerships among scientists, healthcare providers, consumers, and policymakers. On a basic level, APUA Nepal's initiatives aim to increase awareness and knowledge among the public. On a broader level, they aim to develop stronger infectious disease prevention capability and treatment; improve institutional and governmental antimicrobial policy; and establish local microbiology surveillance and diagnostics systems in the country (APUA, 2013).

International Network for Rational Use of Drugs (INRUD)

International Network for Rational Use of Drugs (INRUD)

was established in 1989 to design, test and disseminate effective strategies to improve the way drugs are prescribed, dispensed and used, particularly in resource poor countries. These goals are served by INRUD Nepal's brief and direct mission statement: "better health through research". The network now comprises 22 groups, seven from Africa (Ghana, Ethiopia, Kenya, Nigeria, Tanzania, Uganda and Zimbabwe), nine from Asia (Bangladesh, Cambodia, China, India/Delhi, India/Tamil Nadu, Indonesia, Nepal, Philippines and Thailand), and one from Latin America (Peru). Institutionally, the network includes groups from World Health Organization/Department of Essential Drugs and Medicines Policy, Harvard Medical School Department of Ambulatory Care, Karolinska Institute in Sweden, University of Newcastle in Australia, and a secretariat based in Management Sciences for Health in the United States. INRUD Nepal has been registered with the government since 1995, and has been involved in various activities that promote rational drug use in Nepal.

INRUD Nepal carries out different types of indicator and intervention-based studies, including studies on drug use indicators, district drug management, health seeking behaviors, treatment practices of healthcare providers, drug pricing methods and prescribing practices (INRUD, 2013).

Pharmaceutical Horizon of Nepal (PHON)

Pharmaceutical Horizon of Nepal (PHON) is a non-governmental organization (NGO) established in 1993 with the objective of improving the use of medicines through strategies of information, education and research for consumers. Its activities have been supported by national and international organizations, including Ministry of Health and Population, Department of Drug Administration, World Health Organization, USAID, GTZ, APUA-Boston, and United States Pharmacopeia (PHON, 2013).

National Regulatory Agencies

Department of Drug Administration (DDA)

Established in 1978 by the National Drug Act, Department of Drug Administration aims to prohibit inappropriate use of drugs or pharmaceuticals and inaccurate information related to the efficacy and use of drugs. DDA is responsible for ensuring safety, efficacy and quality of drugs made available for use, and controls drug production, marketing, and distribution. DDA has three

divisions: Registration and Licensing Division, Inspection Division, and Management Division (DDA, 2013).

Drug Consultative Council (DCC) and the Drug Advisory Committee (DAC)

Directed by the Minister of Health and Population, the Drug Consultative Council advises government on administrative matters related to drugs. The Drug Advisory Committee advises DDA on technical aspects of drug regulation, including research and development (DDA, 2013).

National Medicine Laboratory

Formerly called as the Royal Drug Research Laboratory, National Medicine Laboratory was established by the National Drug Act, 1978 to test and analyze the quality of drugs and monitor the standard of drug testing laboratories across the country. The laboratory has multiple components including microbiology, pharmacology and instrumental analysis (DDA, 2013).

Nepal Chemist and Druggist Association (NCDA)

Nepal Chemist and Druggist Association is a collaboration of businesses in pharmaceutical industry that deal with retailing and wholesaling. NCDA was formed in 1974 in order to enforce the price uniformity of drugs within the country (DDA, 2013).

2.6 Disease control programs

National Immunization Program

National Immunization Program (NIP) is a high priority program of Government of Nepal. Immunization is considered one of the most cost saving health interventions, and NIP has helped to reduce the burden of vaccine-preventable diseases (VPDs) and child mortality in Nepal. NIP was introduced in 1979, and by 2009 it supported routine immunizations for children and pregnant women for 10 diseases including TB, polio, diphtheria, pertussis, tetanus, hepatitis B, haemophilus influenzae type b, measles, tetanus and japanese encephalitis (DoHS, 2010-11). Government has added childhood pneumococcal vaccine to the national immunization schedule in 2015.

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Community based integrated management of childhood illnesses and newborn care

Community Based Integrated Management of Childhood Illness (CB-IMCI) Program is an integrated package of child survival interventions that address major childhood killer diseases such as pneumonia, diarrhea, malaria, measles and malnutrition in children aged 2 months to 5 years.

The major components of CB-IMCI are:

- Management of sick children less than 2 months of age for possible severe bacterial infection (PSBI), local bacterial infection, jaundice, hypothermia and low weight or feeding problems
- Management of sick children 2 months to 5 years of age for acute respiratory infection (ARI), diarrheal diseases and zinc supplementation (DoHS, 2010-11).

Malaria Control Program

National Malaria Control Program began in Nepal in 1954 with support from USAID. The objective of the program was to control malaria mainly in southern terai belt of central Nepal. The strategies for the malaria control program are:

- Vector control and personal protection;
- Early diagnosis and appropriate treatment;
- Malaria surveillance and epidemic preparedness; and
- Behavior change communication (BCC).

Major activities of the program include:

- Case detection and treatment;
- Prevention and control measures - two rounds of selective indoor residual spraying (IRS) in malaria prone areas;

- Epidemic prevention and control;
- Training and orientation; and
- Operational research

The program reported a decrease in proportion of *Plasmodium falciparum* infection from 2008-09 to 2010-11 but the proportion increases significantly to 46 percent in 2011-12. Annual parasite incidence, blood slide examination rate and clinical malaria cases were in decreasing order from 2008 to 2012 (DoHS, 2010-11) (DoHS, 2011-12) as indicated in table 2-8.

Tuberculosis Control Program

Tuberculosis (TB) is a major public health problem in Nepal. About 45 percent of the total population is infected with TB. Every year, 40,000 people develop active TB, of whom 20,580 have infectious pulmonary disease. Treatment by directly observed treatment short- course (DOTS) has reduced the number of deaths, but 5,000-7,000 people still die every year from TB. Expansion of the DOTS treatment strategy has proven effective in reducing TB-related mortality and morbidity in Nepal. TB case finding rate has increased from 70 percent in 2005-06 to 78 percent in 2012-13. Cure success rate in 2012-13 for TB was 90 percent, and for MDR-TB, it was 73 percent (DoHS, 2012-13).

Leprosy control program

Out of 3,253 new leprosy cases detected in Nepal, 2,228 cases received treatment by the end of 2013. Nationally, the prevalence rate has decreased from 0.77 in 2009-10 (DoHS, 2010-11) to 0.82 in 2012-13 (DoHS, 2012-13). The new case detection rate has declined from 1.99 per 10,000 population in 2008-09 to 11.9 in 2012-13 (DoHS, 2010-11) (DoHS, 2012-13).

Table 2-8: Malaria blood slide examination rate, parasite incidence, PF percent and CM

	2008-2009	2009-2010	2010-2011	2011-2012
Annual blood slide examination rate	0.75	0.68	0.66	0.65
Annual parasite incidence per 1,000	0.18	0.15	0.16	0.11
Proportion *P. falciparum* (PF percent)	22.18	20.48	15.71	46.00
Clinical malaria (CM)	113,872	10,8179	83,527	68,054

Source: (DoHS, 2010-11, 2012-13)

HIV control program

As of 2012, national estimates indicate that approximately 48,600 adults and children were infected with the HIV virus in Nepal (0.28 percent). About 84 percent of the infection was among adults (15-49) in 2012-13 which was reported to be 86 percent in 2010-11, 8 percent among children under the age of 15 in 2010-11 and 2012-13 and 7 percent among adults above 50 years of age in 2012-13 which was 6 percent in FY 2010-11 (DoHS, 2010-11) (DoHS, 2012-13).

The National Policy on HIV and AIDS (2010) envisions an AIDS free society and aims to reduce the impact of HIV by reducing new HIV infections. The major activities for the HIV control program are:

- HIV counseling and testing;
- The national antiretroviral treatment program; and
- Prevention of mother-to-child transmission

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2.7   Livestock Farming

In 2009-2010, approximately 7.2 million cattle, 4.8 million buffalo, 8.8 million goats, 0.8 million sheep, 1.1 million pigs, 25.8 million chickens and 0.4 million ducks were farmed in Nepal (APSD, 2012). About half of all livestock and poultry are raised in the hill region (47 percent), with 39 percent raised in the terai region and 14 percent in the mountain region (DoLS, 2010). Most livestock farming in Nepal is subsistence based, but commercialized farming is increasing.

2.8 Food and Animal Contributions to the Economy

Agricultural sector employs 66 percent of the population and contributes about 39 percent to the gross domestic product (GDP). Livestock sector is responsible for 27 percent of the agricultural contribution, or about 11 percent of the total GDP (MoAD, 2014).
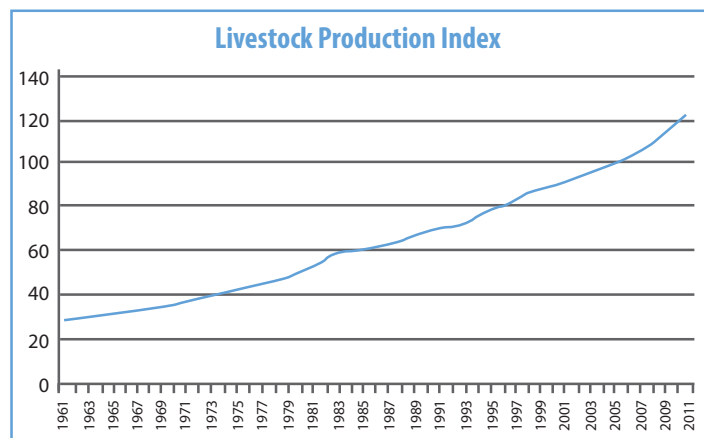
Production and Consumption

Milk, meat and egg production has increased by 3.2, 2.9 and 2.4 percent, respectively from 2001 to 2004 (DoLS, 2010).

Total milk production of cows and buffaloes was estimated to be 1,622,751 metric tonnes (mt) in 2011-12, while total meat production from buffaloes, sheep, goats, pigs, chickens and ducks was estimated to be 287,930 mt. Net production of meat was 172 thousand mt from buffaloes, 2.7 thousand mt from sheep, 53 thousand mt from goats, 18 thousand mt from pigs, 40 thousand mt from chickens and 0.2 thousand mt from ducks. Total number of eggs produced in 2011-12 was 801 million, of which 98 percent were produced by hens and 2 percent by ducks (APSD, 2012).

Livestock production index, which includes meat, dairy products, and other animal products such as eggs, honey, raw silk, wool, hides and skin was approximately 122 in 2011. Nepal's livestock production index has increased steadily from 1961 to 2011 (figure 2-3).

Figure 2-3: Livestock Production Index

Source: (Factfish, 2013)

Production increased for every product from 1980 to 2002, and is projected to continue increasing until 2015 (table 2-9). The annual growth rate of these products decreased between 1980-1990 and 1990-2000, except for goat meat and milk products (FAO, 2005). Meat, milk and eggs are also exported. Veterinarians strongly believe that antibiotics are used as growth promoters, especially for poultry, but there is no evidence of the use of antibiotics as growth promoters in feed.

Fish

Aquaculture remains a small-scale industry in Nepal. FAO estimates that fish production takes place on 395,000 hectares (ha) of rivers, 5,000 ha of small and medium-sized lakes, 1,500 ha of reservoirs and 11,100 ha of

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Table 2-9: Trends in annual consumption of meat, milk and eggs (1,000 metric tonnes)

Products	Years					Annual growth rate (%)	
	1980	1990	2000	2002	2015 (estimated)	1980-1990	1990-2000
Meat	127.4	186.6	237.3	246.2	370.7	3.9	2.4
Beef and buffalo	90.5	135.6	169.8	174.7	240.4	4.1	2.3
Mutton and goat	25.9	31.9	39.8	41.4	61	2.1	2.3
Pig	5.8	9.9	14.7	15.6	21	5.5	4.0
Poultry	5.3	9.1	13.0	14.5	48.2	5.6	3.6
Milk	484.2	536.1	699.0	744.4	1510.5	1.0	2.7
Eggs	13.6	17.3	21.4	23.9	42.6	2.4	2.2

Source: (FAO, 2005)

marginal swamps. Aquaculture production contributes about 2.5 percent to the agricultural GDP (FAO, 2011).

Animal Feed

While trade estimates for animal feed are not available, Department of Livestock Services requires a license to import and export animal feed under the Animal Health and Livestock Services Act, 2055 (1999), sections 10, 11, 17 and 19.

National Feed Industry Association (NFIA) reports 149 registered feed mills in Nepal. A total of 272,560 metric tonnes of feed were produced in 2001, with an annual growth rate of nearly 13 percent. Of the total feed production, 95 percent was for poultry, 4 percent for cattle, and the remaining 1 percent for pig, rabbit, horse and fish feed (Sharma, 2010). In 2007, 269 metric tonnes of poultry feed were produced, while in 2008, 463 metric tonnes were produced, with a yearly growth rate of 19 percent (Bhattrai, 2008).

2.9 Livestock Services in Nepal

Government of Nepal started livestock services since 1940 with the establishment of a veterinary dispensary in Tripureshwor, Kathmandu in response to the first outbreak of rinderpest. The dispensary was upgraded to a veterinary hospital with a single veterinarian in 1962, and veterinary services were expanded to 75 districts in 1983.

GoN provides veterinary services through various departments within the Ministry of Agricultural Development.

Veterinary Laboratories

Government of Nepal has established one central veterinary laboratory, 5 regional laboratories, 15 basic laboratories and 60 primary laboratories. Central Veterinary Laboratory (CVL) is a national veterinary reference laboratory and was formed in 1995 under the Department of Livestock Services. CVL is responsible for epidemic investigations and disease surveillance. It works through five regional veterinary laboratories (RVLs) located in each of the development regions (Biratnagar, Janakpur, Pokhara, Surkhet and Dhangadi), as well as through the National Avian Laboratory in Chitwan.

CVL also provides diagnostic facilities at district level through fifteen basic laboratories in 15 district livestock service offices (DLSOs) and 60 primary laboratories. Basic laboratories are capable of performing parasitological examinations, microbial cultures and sensitivity tests. They provide diagnostic services, such as parasitology, virology and serology, as well as surveillance and epidemic investigation services. Other, more specific services include rinderpest sero-surveillance, japanese encephalitis examination and post mortem examination of animals. Government also established National Foot and Mouth Diseases (FMD) Laborotary, Transboundary Animal Diseases (TADs) Laborotary, and National Avian Disease Investigation Laboratories in response to these national priority animal diseases.

Vaccination

Government of Nepal does not have any program for preventative animal vaccination. Vaccinations are administered when disease outbreaks occur in order to prevent the spread of disease. The vaccination campaign against peste de petit ruminants (PPR) disease in 2001 is an example of this kind of prevention.

Central Biological Production Laboratory, a government laboratory under the Directorate of Animal Health, is currently producing vaccines for rinderpest (GTV), haemorrhagic septicaemia, newcastle disease, fowlpox, rabies, black quarter disease, anthrax, swine fever, infectious bursal disease (Gumboro) and peste de petit ruminants (PPR), as well as combination vaccines (DoLS, 2011).

2.10 Government Policies

Government of Nepal has formulated important policies to regulate livestock production and ensure improved animal health. Nepal does not yet have an official veterinary drug act to regulate veterinary drug use. However, a draft was created in 2011 and is currently pending approval.

Feed Act -1976 and Feed Regulation Act-1984

The Feed Act set standards for animal feed ingredients, preventing adulteration of feed and prohibiting the reduction or elimination of natural properties of feed ingredients sale (Feed Act , 1976).

The Feed Regulation was created to enforce the standards set out in the Feed Act. It established feed inspectors and a feed standard fixation committee, as well as a licensing mechanism for feed production (Feed Regulation, 1984).

Animal Health and Livestock Services Act –1999

The purpose of this act was to support the systematization and development of national animal husbandry industry by regulating healthy production, sale, distribution, export and import of animal products. The act contains provisions for the establishment of animal quarantine check posts across the country (Animal Health and Livestock Services Act, 1999).

Slaughterhouse and Meat Inspection Act -1999

This act established slaughter houses and aimed to prevent the sale of unsafe meat and contamination of meat during and after the slaughtering process. The act requires inspection of animals by a qualified meat inspector before and after slaughtering, and that products for sale are approved with a stamp. Enforcement of this law has been difficult, as the infrastructure and inspectors are inadequate to enforce it (Animal Slaughterhouse and Meat Inspection Act, 1999).

Nepal Veterinary Council Act –1999

This act established Nepal Veterinary Council, an independent governmental organization responsible for improving animal health services and ensuring the quality of human resources needed for nationwide veterinary services (Nepal Veterinary Council Act, 1999).

Veterinary Drug Act (draft) – 2011

Nepal Veterinary Council drafted this act, which is currently awaiting approval from the cabinet. The act proposes the formation of a Veterinary Medicine Counseling Committee under the chairmanship of the Secretary of the Ministry of Agricultural Development. The committee will draft rules and regulation for veterinary drugs and will have authority to determine drug quality. If any drug is found to be substandard, the committee will be able to ban the use of that drug. The act also proposes the establishment of a veterinary drug quality and management office (Veterinary Drug Act (Draft), 2011).

2.11 Government Agencies and Offices with Missions Related to Animal Health and Production

Ministry of Agricultural Development

Ministry of Agricultural Development (MoAD) aims to reduce poverty by increasing production and productivity of the agricultural sector. The ministry also aims to develop competitive agricultural systems in global and regional markets, and to utilize sustainable agricultural practices. The ministry's main focus is to improve the national standard of living by transforming the existing subsistence farming system into a commercialized and globally competitive market (MoAD, 2014). The relevant departments and offices within the Ministry of Agricultural Development are described below:

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Department of Livestock Services

First established in 1939 as a veterinary dispensary, Department of Livestock Services serves several purposes: to increase livestock production and productivity, to improve the economic and social conditions of the poor through livestock farming, to expand disease control services for livestock, to expand exportable livestock products, to expand quality control services and to conserve endangered livestock breeds. The department advocates for vaccines, disease control and disease diagnostic services, quality control in veterinary medicines and vaccines, control of zoonotic diseases, improved animal health services and increased meat inspection (DoLS, 2014).

Directorate of Livestock Production

This directorate was established in 1995. It provides technical services to other divisions within the Department of Livestock Services such as National Livestock Breeding Center and National Cattle and Buffalo Promotion Center (DoLP, 2014).

Directorate of Animal Health

Directorate of Animal Health works with the Department of Livestock Services to prevent diagnose and control animal diseases. The directorate monitors disease outbreaks and coordinates emergency veterinary services when they occur, in addition to collecting and disseminating livestock data (DoAH, 2014).

Directorate of Livestock Training and Extension

The directorate was established in 1980 under the Department of Livestock Services. Its major purpose is to provide capacity building for its staff and farmers at grassroots level through training and education for the commercialization and diversification of the livestock sector (DoLTE, 2014).

Veterinary Standards and Drugs Administration Office

This office was established in 2004 to ensure the quality of veterinary drugs and to strengthen the capabilities of veterinary laboratories in biology and diagnostics (DoLS, 2011).

Central Biological Production Laboratory

The Central Biological Production Laboratory was established in 1971 to produce vaccines (DoLS, 2011).

Veterinary Public Health Office

This office was established in 2004 under the Ministry of Agriculture and Cooperatives, Department of Livestock Services, and Directorate of Animal Health at Tripureswor, Kathmandu with the objectives of controlling zoonotic diseases and protecting human health (DoLS, 2011).

Veterinary Epidemiology Centre

Veterinary Epidemiology Centre was established in 2004 to strengthen the epidemiological surveillance system in Nepal. It adopts new technologies and coordinates with other partners to strengthen existing surveillance mechanisms (DoLS, 2011).

Nepal Agriculture Research Council (NARC)

NARC was established in 1991. NARC is an autonomous research body that assists government in the formulation of agricultural policies and strategies and researches specific agricultural problems (NARC, 2014).

Nepal Veterinary Association (NVA)

A scientific and professional organization established in 1967, NVA has 655 veterinarian members with expertise in public health, natural resource management and animal health and production. The association aims to maintain up-to-date disease control methods, support and advocate for national livestock plans and animal welfare issues, and help to prevent, control and eradicate animal diseases to safeguard public health (NVA, 2014).

Nepal Veterinary Council (NVC)

Nepal Veterinary Council was established through the Nepal Veterinary Council Act, 2055, and is an independent governmental organization responsible for ensuring high quality veterinary services in Nepal and improving veterinary services nationwide. The council has 698 veterinarian members (NVC, 2014).

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Chapter **3** :
National Burden of Disease

I nfectious diseases continue to contribute significantly to the disease burden in Nepal, even as non-communicable diseases increase in prevalence. Acute respiratory infections (ARIs) and diarrheal diseases are the leading contributors to the burden of preventable diseases. ARIs and diarrhea are also the leading causes of death in children (WHO, 2013a). The most recent Global Burden of Disease figures estimate that the five leading causes of premature mortality in Nepal, based on the number of years of life lost (YLL), are lower respiratory infections, diarrheal diseases, neonatal encephalopathy (birth asphyxia and birth trauma), preterm birth complications and tuberculosis. While these causes have remained same since 1990, considerable gains have been made in reducing the years of life lost to these diseases (GBD, 2010). These gains are attributable to positive changes in overall health system and improved surveillance systems. Proper surveillance allows for rapid communication of disease occurrence and development of strategies to reduce disease burden. However, national surveillance systems remain limited and function primarily in urban areas.

Vector borne diseases like malaria, visceral leishmaniasis, lymphatic filariasis, japanese encephalitis and dengue are major public health problems, in addition to tuberculosis (TB) and some cases of HIV/AIDS (WHO, 2013a). Viral and parasitic diseases also contribute significantly to the overall disease burden. A recent systematic review of parasitic zoonoses showed that the highest annual burden of parasitic zoonoses was due to neurocysticercosis and congenital toxoplasmosis (Devleesschauwer et al., 2014).

In terms of bacterial infections, the incidence of diarrheal diseases, acute respiratory tract infections and bloodstream infections remain high. These diseases contribute directly to the burden of disease and often lead to the prescription of antibiotics, contributing to the rapidly emerging burden of antibiotic resistance. Urinary tract infections, tuberculosis, sexually transmitted infections and hospital-acquired infections, while less common as causes of mortality in Nepal, also contribute to the antimicrobial resistance burden. The prevalence of the most common bacterial diseases in Nepal are presented below:

Humans

3.1 Bacterial Disease Burden

The high disease burden caused by respiratory, diarrheal and bloodstream infections in all age groups makes them critical disease priorities and underscores the importance of ensuring universal access to antibiotics and their appropriate use. Information on the bacterial disease burden in Nepal is very limited. Literature published since 2005 is reviewed below. Each disease category is discussed separately, but the reader should be aware that more than one condition is often present, especially acute respiratory, diarrheal and bloodstream infections. These overlaps are addressed in many of the studies included.

3.1.1 Acute Respiratory Infections

Acute respiratory infections (ARIs) are a major cause of death in Nepal, and are the most common cause of morbidity and mortality in children under five years of age. ARIs are classified as upper respiratory tract infections (URIs) or the more serious lower respiratory tract infections (LRIs) (Jamison et al., 2006). The most common URIs are caused by viral pathogens. LRIs can be caused by a number of pathogens, each with a different epidemiology, pathogenesis, clinical presentation and outcome. The most common LRIs are pneumonia and bronchitis in children. Bacteria most frequently recovered from LRIs are Gram-positive bacteria such as *Staphylococcus aureus* and *Streptococcus pneumoniae* and Gram-negative bacteria such as *Haemophilus influenzae*, *Pseudomonas* species (spp.), *Acinetobacter* spp., and *Klebsiella* spp.

Khan and colleagues recently examined 304 bacterial isolates of which 246 were Gram-negative bacterial isolates and 58 were Gram-positive, sampled from 426 inpatients and outpatients with lower respiratory tract infections at Nepalgunj Medical College in Western Nepal. They found that among all isolates, *Pseudomonas aeruginosa* was the most commonly identified organism (38 percent), followed by *H. influenzae*, *Klebsiella pneumoniae*, *S. pneumoniae*, *S. aureus* and *Escherichia coli* (Khan, Singh, Ansari, & Gurung, 2013).

Though the incidence of ARIs has increased in recent years, the fatality rate has declined. Reported cases of ARI per 1,000 under-five population increased between 2010-11 and 2011-12. Reported ARI deaths per 1,000 under-five population and case fatality rates increased

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between 2009-10 and 2010-11, but decreased in 2011-12. The main reasons for the recent reductions in ARI death and case fatality rates are the early detection and proper management of ARI cases by health workers (DoHS, 2011-12).

Pneumonia

Pneumonia is an inflammatory condition of lungs that can be caused by bacteria or viruses. Bacterial pathogens are the most common cause of community-acquired pneumonia, and *S. pneumoniae* is the leading bacterial cause of pneumonia in the developing world (Wardlaw, Johansson, & Hodge, 2006). Other commonly isolated bacteria include *H. influenzae, Chlamydophila pneumoniae, Mycoplasma pneumoniae, S. aureus* and other Gram-negative bacilli. Common drug resistant bacterial causes of pneumonia are drug resistant *S. pneumoniae* (DRSP) and methicillin-resistant *S. aureus* (MRSA). Common symptoms of pneumonia are cough and fever accompanied by chills, shortness of breath, and chest pain during breathing and increased respiratory rates. Azithromycin, doxycycline and clarithromycin are the drugs of choice for treating community-acquired pneumonia in the adult outpatient population. Azithromycin with ceftriaxone or azithromycin with etrapenem are the preferred combination therapy treatment for hospitalized patients, while levofloxacin or moxifloxacin are used in monotherapy (Globalrph, 2014).

In Nepal, pneumonia remains a major cause of morbidity and mortality in children. Incidence in children under five declined slightly between 2009-10 and 2011-12 from 255 to 239 per 1,000 under five population (DoHS, 2011-12).

In Nepal Medical College Teaching Hospital, 84 percent of children (total n=73) had pneumonia and 16 percent had acute bronchiolitis in 2011 (Rijal, Sharma, Shrestha, & Upadhyay, 2011).

Numerous studies confirm *S. pneumoniae* as the most commonly identified pathogen in childhood pneumonia cases. In Patan Hospital, 16 percent of 142 blood culture from 2,039 children under-twelve years of age showed *S. pneumoniae* making *S. pneumoniae* the most common cause of bacteremia in children under one year of age in 2011 (Kelly et al., 2011). Likewise, in the same hospital, out of 44 culture-positive pathogens from 885 children 2-59 months of age, 36 percent were positive for *S. pneumoniae.* Additionally, of 199 cerebral spinal fluid (CSF) samples cultured, seven of the nine positive pathogenic-confirmed cultures (78 percent) were positive for *S. pneumoniae* in

2005-2006 (Williams et al., 2009a).

In Kanti Children's Hospital, pneumonia was diagnosed in 82 percent of 2,528 children aged two months to five years, and meningitis was diagnosed in 10 percent. Other severe bacterial diseases were diagnosed in 2 percent of the children and bacteremia was seen in 0.4 percent. Of 2,461 blood cultures, 22 were positive for *S. pneumoniae* (Shah et al., 2009a).

3.1.2 Diarrheal Infections

Diarrhea is defined as the discharge of three or more loose or liquid stools per day, or more frequent passage than is usual for an individual. It is usually symptomatic of an infection in the intestinal tract, which may be caused by a variety of bacterial, viral and parasitic organisms. Worldwide, rotavirus is the most common cause of diarrhea in children (NDDIC, 2014). The most common bacterial causes of diarrheal infections are *Salmonella* spp., *E. coli, Campylobacter, Shigella* spp. and *Vibrio* spp. These pathogens are spread through contaminated food or drinking water, or from person-to-person as a result of poor hygiene. The key measures recommended for the treatment of diarrhea are treatment with oral rehydration salts (ORS) solution and zinc supplements, intake of nutrient rich foods, and treatment with intravenous fluids in the case of severe dehydration.

Many studies have shown that contaminated water is the main source of diarrheal disease outbreaks in Nepal (Yadav et al., 2012). Bacterial pathogens are the most common cause of acute diarrheal infections in Nepal, which occur primarily during the rainy season (June to August) (Shakya, 2011).

Dysentery

Dysentery is an infection of the intestines that causes the passage of loose or watery stools that contain visible red blood (also referred to as bloody diarrhea). Other symptoms include abdominal bloating and pain, flatulence and nausea. Severe forms of the infection can also cause symptoms related to dehydration, such as decreased urine output, fevers and chills, excessive thirst, weight loss, muscle cramps, weakness, dry skin and mucous membranes. Dysentery is generally linked to poor sanitation conditions and is spread through contaminated food and water. Causative agents of dysentery can be viral, bacterial or protozoan. Bacterial dysentery is usually caused

by *Shigella*. *Shigella* spp. and *S. dysenteriae* type 1 causes the most severe form of dysentery and the largest outbreaks. Other *Shigella* spp. includes *S. flexneri*, *S. sonnei* and *S. boydii*. A variety of antibiotics can be used to treat the infection, but ciprofloxacin is the most commonly used. Hydration and treatment with ORS are generally sufficient to treat dysentery, and in general antibiotics are only prescribed when the infection is severe. Several studies have confirmed the presence of common pathogens such as *S. dysenteriae* and *S. flexneri* in cases of dysentery in Nepal (Bhattacharya, Khanal, Bhattarai, & Das, 2011; Kansakar, Malla, & Ghimire, 2007).

From 2003-2005, data from nine hospital laboratories throughout Nepal showed that among 118 *Shigella* isolates, the most prevalent strains were *S. dysenteriae* (42 percent) and *S. flexneri* (43 percent). A total of 26 *S. dysenteriae* isolates were type 1 strains (Kansakar et al., 2007). In another study on the prevalence of dysentery, 53 *Shigella* isolates were obtained from 1,396 clinical stool samples at the B.P. Koirala Institute of Health Sciences from August 2000 to July 2004. The findings showed that 79 percent of the *Shigella* spp. were isolated from children less than five years of age. The most prevalent species were *S. dysenteriae* type 1 (74 percent), followed by *S. flexneri* (23 percent) and *S. boydii* (4 percent) (Bhattacharya et al., 2011).

Cholera

Cholera is an acute and frequently epidemic disease caused by the *Vibrio cholerae* bacterium. Isolation of *V. cholerae* O1 or O139 from stools is the standard for defining a cholera case (WHO, 2013b). Cholera can be asymptomatic or symptomatic, and cases vary from mild to severe. Symptoms include huge volumes of watery diarrhea (sometimes referred to as "rice water stools"), vomiting and leg cramps. Similar to dysentery, cholera can be treated with oral rehydration therapy or other rehydration techniques. If left untreated, death can occur quickly due to dehydration. Physicians usually prescribe antibiotics for severe infections, and commonly prescribed antibiotics include tetracycline, doxycycline, furazolidone, erythromycin or ciprofloxacin in conjunction with IV hydration.

The most recent cholera outbreak in Nepal occurred during the rainy season of 2012 and has since been investigated in several studies. Pun and colleagues examined isolates from 21 out of 503 patients who were culture positive for *V. cholerae* at Sukraraj Tropical and Infectious Disease Hospital between July and August 2012 and found that all of the culture positive cases were O1 Ogawa serotype (Pun et al., 2013). The study linked the etiological agent and source of the outbreak to the poor condition of the water supply and sanitation system. Similarly, 6 of the 150 stool samples from Shantinagar VDC in Ilam district showed *V. cholerae* isolates, and eight water samples collected from households and common tanks contained coliforms indicating cross contamination (Rayamajhi et al., 2013). Lab analysis of 268 samples in National Public Health Laboratory collected from different hospitals between April 2010 and January 2011 showed a positive growth culture for bacteria, including *V. cholerae* (58 percent) followed by *Salmonella* spp. (26 percent) and *S. flexneri B* (16 percent). The highest numbers of *V. cholerae* were isolated from Nepalgunj, which had reported an outbreak in 2010 (77 percent) (Shah, Sharma, Shakya, & Upadhyay, 2013).

Yadav and colleagues focused on a cholera outbreak in the Saptari district of eastern Nepal in 2011 and found that 5 out of 111 samples showed positive growth, but because of the small sample size of positive isolates (n=5), it could not definitively confirm *V. cholerae* 01 El T or, Ogawa serotype as the causative agent of the outbreak (Yadav et al., 2012).

A cholera outbreak in the far-western region in 2009 identified *V. cholerae* O1 (53 percent of the total 50 samples) as the predominant causes followed by *E. coli* (47 percent) (Bhandari & Bhusal, 2013). Similarly, *V. cholerae* O1 biotype EI Tor serotype Ogawa was the major causative agent for the outbreak in Jajarkot district in 2009, as it was isolated from 5 out of 13 samples tested. The attack rate in this outbreak was 8 percent and the case fatality ratio was one percent (Bhandari, Maskey, Dixit, & Ghimire, 2010).

3.1.3 Bloodstream Infections and Meningitis

Bloodstream infections (BSIs) are generally classified as one of two major types–septicemia or bacteremia. In the most basic terms, bacteremia refers to the infection of the bloodstream through the invasion of bacteria, causing illnesses such as typhoid and paratyphoid. Septicemia is often used interchangeably with sepsis, and is the occurrence of bacteria in blood because of another severe infection in the body. It is a serious, life-threatening infection. Because BSI's are typically an outcome of meningococcal infections, meningitis has also been included in this section. Many studies have shown the high prevalence of BSIs in Nepal. Several of these studies are described below:

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Pandey and colleagues carried out a study from May to October 2010 with patients visiting Kathmandu Medical College with symptoms of blood stream infections. Out of a total of 1,089 blood samples, 13 percent were bacteriologically positive. Of the isolated pathogens, 84 percent were Gram-negative bacilli belonging to the *Enterobacteriaceae* family and 16 percent were Gram-positive cocci (Pandey, Raza, & Bhatta, 2013).

Neonatal sepsis

Globally, neonatal sepsis is one of the most common causes of neonatal mortality and morbidity (Jain, Jain, & Maheshwari, 2003). According to WHO, severe infections are responsible for more than one-third of global neonatal deaths each year, and neonatal sepsis and pneumonia are responsible for one million deaths each year (WHO, 2009).

Neonatal sepsis can be classified as early- or late-onset. Early-onset neonatal sepsis occurs in the first week of life and is usually maternally acquired. Late-onset neonatal sepsis may occur after the first week of life through the end of the neonatal period. The main bacterial agents for early-onset sepsis are *E. coli* and Group B *Streptococcus*. For late-onset infections the main agents are Coagulase-Negative *Staphylococci*, *S. aureus*, *E. coli*, *Klebsiella* spp. and *Pseudomonas* spp. WHO recommends the use of benzyl penicillin or ampicillin plus an aminoglycoside such as gentamicin for infants up to the age of 2 months. When the infection occurs 48 to 72 hours after admission to a health facility, it is considered to be a healthcare-associated infection. Below several studies are described that have investigated neonatal sepsis infections in Nepal.

Lab samples (blood, cerebrospinal fluid and urine) and environmental samples (cultures from various tools and areas in the NICU) analysis in the neonatal intensive care unit (NICU) of Manipal Teaching Hospital showed similar growth. Of the 27 lab samples *E. coli* was the primary causative organism (37 percent), followed by *K. pneumoniae* (19 percent) and *S. aureus* (19 percent) and from the 53 environmental samples *K. pneumoniae* was the main causative organism (23 percent), followed by *S. aureus* (19 percent) and *Enterococcus faecalis* (16 percent) in 2011 (Malla, Malla, & Rao, 2013).

In Chitwan Medical College Teaching Hospital (CMCTH), 80 of 377 neonatal blood samples showed bacterial growth with high risk factors for sepsis infections. Of these 80 isolates, 70 were early onset infections and 10 were late onset infections.

S. aureus was the most common isolate found in early onset sepsis (29 percent) followed by *Acinetobacter* spp. (23 percent) and *Klebsiella* spp. For late onset sepsis, *Acinetobacter* spp. (40 percent) was the most in 2010-2011 (Nepal, Acharya, Gautam, Shrestha, & Paudel, 2013). Similarly, between 2009 and 2010 in CMCTH, *S. aureus* was the main bacterial isolate (40 percent of 1,572 samples), followed by *Klebsiella* spp. (14 percent) (Gyawali & Sanjana, 2012). And between 2007-2009, case records of 215 out of 411 newborns positive for sepsis, early onset sepsis accounted for 61 percent of the cases, while late onset sepsis accounted for 39 percent. Of the 215 cases, 81 percent were neonates born outside the hospital and 19 percent were hospital deliveries (Khinchi, Kumar, & Yadav, 2010).

In BP Koirala Institute of Health Sciences, a retrospective study from January 2006 to February 2007 found that 103 of 513 suspected sepsis cases were positive for neonatal sepsis. The most common causative pathogens were *S. aureus* (39 percent) and Coagulase Negative *Staphylococcus* (CoNS) (21 percent). Among Gram-negative organisms, *Klebsiella* spp. (12 percent), *Enterobacter* spp. (10 percent) and *E. coli* (7 percent) were identified (Shrestha et al., 2007).

In a retrospective analysis conducted between 2000 and 2005 in NICU of Manipal Teaching Hospital, 183 out of 265 suspected sepsis cases were culture positive. Nosocomial sepsis accounted for 34 percent of the positive cases. A total of 119 isolates were cultured from blood (45 percent) and the remaining was cultured from urine (6 percent) and CSF (5 percent). Researchers concluded that Staphylococcal sepsis is common in both community acquired infections as well as nosocomial infections (Shaw, Shaw, & Thapalial, 2007).

Enteric fever (Typhoid and Paratyphoid)

Typhoid, also known as enteric fever, is generally caused by *Salmonella* Typhi or *Salmonella* Paratyphi. The majority of cases are attributed to the bacterium *Salmonella enterica* serovar Typhi (*S.* Typhi). However, *S. enterica* serovar Paratyphi A (*S.* Paratyphi A) is now recognized as an emerging agent of enteric fever in endemic regions, as confirmed in the studies below:

Typhoid is transmitted through the fecal-oral route, and ingestion of contaminated food or drink is a major risk factor. Symptoms usually develop one to three weeks after exposure, and range from mild or severe. These include high fever, malaise, headache, constipation or diarrhea, rose-colored spots on the chest and enlarged spleen and liver.

Typhoid tends to occur more during the rainy and summer seasons, much like the diarrheal diseases mentioned earlier. Typhoid fever is among the highest contributors to burden of disease in South Asia, with Nepal contributing to a large portion of this regional burden. Most studies have found higher infection rates among males and in younger age groups.

In a study carried out by Nasstrom and colleagues in 2014 at Patan Hospital showed for the first time that reproducible and serovar specific systemic biomarkers can be detected during enteric fevers. The challenge will be how to refine these tests so that they can be produced inexpensively to ensure the prompt diagnosis of enteric fever and appropriate treatment with specific antibiotics (Nasstrom et al., 2014).

A year-long study conducted at the Nepal Public Health Laboratory (NPHL) in 2008 found that of 59 blood isolates of enteric fever patients, 49 percent were *S*. Typhi and 51 percent were *S*. Paratyphi A. Additionally, *S*. Typhi isolates were more common from July to October, while *S*. Paratyphi A isolates were found throughout the year (Acharya et al., 2011).
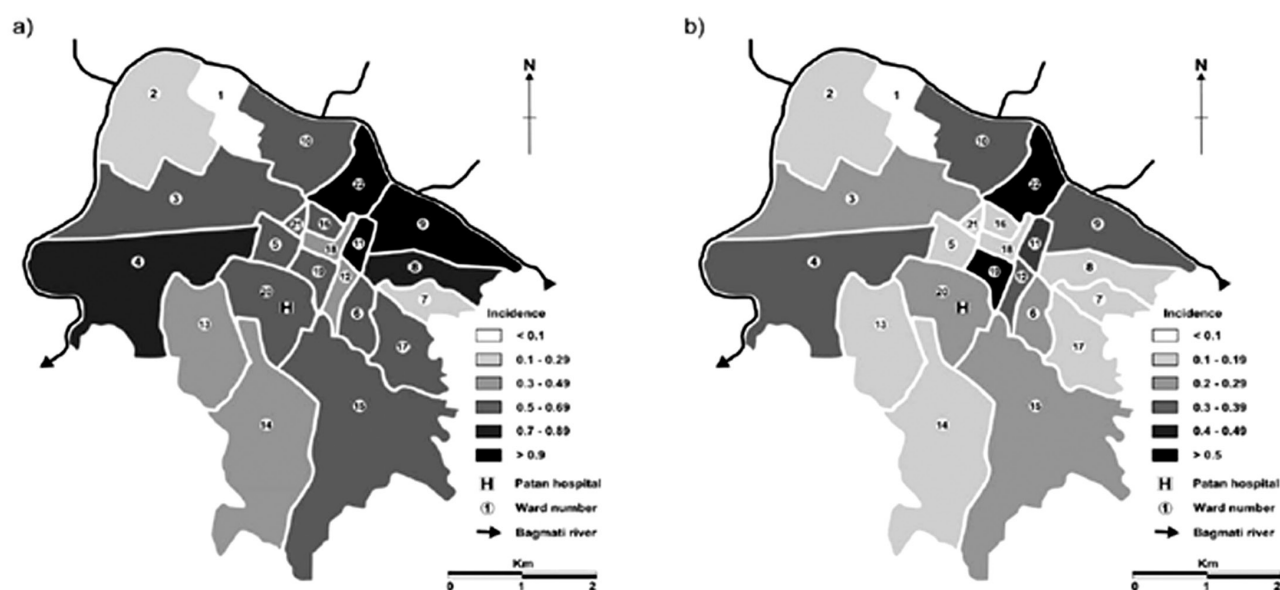
In Kanti Children's Hospital, 3 percent of 9,856 children with high fevers were positive for *S*. Typhi and *S*. Paratyphi A from April 2007 to March 2008. (Prajapati et al., 2008).

S. Typhi and *S*. Paratyphi were found to be the primary causative agents for enteric fever in several additional studies (Pokharel et al., 2009; Shah & Poudel, 2013).

In a study carried out at Patan Hospital from 2005-2009, 54,536 blood cultures were performed, of which 3,898 (7 percent) were positive for an invasive *Salmonella* infection. Of those, 68 percent were *S*. Typhi and 32 percent were *S*. Paratyphi A. The study showed that the prevalence of both *S*. Typhi and *S*. Paratyphi A was highest in July, and that population density was not related to incidence. A concentration of infections was identified to the east of Lalitpur Submetropolitan City (LSMC) (figure 3-1). The overall average incidence of enteric fever in LSMC was estimated to be 3.78 cases per 1,000 households during 2005–2009, while the average annual incidence was 0.82 per 1,000 population (Karkey et al., 2010).

A year-long study (2009-2010) conducted at Nepalgunj Medical College Teaching Hospital (NGMCTH) and Bheri Zonal Hospital compared the prevalence and distribution of typhoid fever between the two institutions. At NGMCTH, 1,092 of 4,657 enrolled patients (23 percent) were positive for typhoid infections caused by *S*. Typhi, while at Bheri Zonal Hospital, 1,814 of 5,496 enrolled patients (32 percent) were positive for typhoid infections caused by *S*. Typhi (Shah & Poudel, 2013). In a similar study that took place from June 2009 to June 2010 at Chitwan Medical College Teaching

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Figure 3-1: The geographical distribution of enteric fever cases in LSMC

Source: (Karkey et al, 2010)

Hospital, 191 out of 4,355 blood cultures were positive, of which *S*. Paratyphi A accounted for 57 percent and *S*. Typhi for 43 percent. No *S*. Paratyphi B was found (Acharya, 2012). In Nepal Medical College Teaching Hospital, a total of 26 organisms were isolated from 479 blood samples from feverish patients attending the outpatient department (OPD) between August 2008 and January 2009. Of those organisms, *S*. Typhi accounted for 35 percent and *S*. Paratyphi A for 65 percent. *S*. Paratyphi B was not isolated (Pokharel et al., 2009).

Meningitis

Meningitis refers to an inflammation of a membrane known as the meninges, which envelopes the brain and spinal cord. In cases of bacterial meningitis, bacteria reach the meninges from the bloodstream after crossing the blood brain barrier. Three types of bacteria usually cause meningitis: *H. influenza* type b, *Neisseria meningitides*, and *S. pneumoniae*. However, *S. pneumoniae* and *H. influenzae* account for 80 percent of all cases of bacterial meningitis.

The first reported outbreak of a large meningococcal serotype group occurred in the Kathmandu Valley in 1983, with an attack rate of 103/100,000 (Cochi et al., 1987). The highest incidence was in infants (26 percent of the total) (Vyse, Wolter, Chen, Ng, & Soriano-Gabarro, 2011). While immunization was conducted to help curb the epidemic and to prevent future outbreaks, meningitis is still a concern in Nepal, especially among children.

In Patan Hospital, 4 percent of 7,751 children admitted to the children's ward from 2005 to 2008 were treated for meningitis, and of them bacterial growth was observed in 4 percent. *S. pneumoniae* was the most common bacteria isolated (46 percent) followed by *H. influenzae* type b (23 percent). β-hemolytic *Streptococcus*, α-hemolytic *Streptococcus*, *Pseudomonas* and *N. meningitides* were also isolated (Ansari & Pokhrel, 2011). Similarly, another study in the same hospital from April 2005 to December 2006 included a total of 885 children between 2 months and 5 years of age with fever and/or suspected pneumonia, meningitis or bacteremia. Among these children, 9 percent had meningitis. It was observed that 60 percent of children aged under 5 in urban Nepal who were admitted with fever and/or suspected invasive bacterial disease have clinical syndromes of meningitis (9 percent) and/or pneumonia (56 percent) (Williams et al., 2009b).

In Kanti Children's Hospital, 243 of 2,528 children (aged between 2 months and 5 years) with suspected invasive bacterial disease had meningitis from November 2004 through March 2007. Among the 243 cases, 62 cases were

definite meningitis. Out of the 1,485 children of 0–11 months of age, 2 percent had *S. pneumoniae* meningitis. Of the 547 children of 12–23 months of age, 0.7 percent had *S. pneumoniae* meningitis, and of the 496 children 24–59 months of age, 0.8 percent had *S. pneumoniae* meningitis (Shah et al., 2009b).

3.1.4 Tuberculosis

Tuberculosis (TB) is caused by various strains of *Mycobacterium,* particularly *M. tuberculosis*. Other TB causing mycobacteria are *M. bovis*, *M. africanum*, *M. canetti*, *M. microti*, *M. avium and M. kansasii*. *M. avium* and *M. kansasii* are less common and occur primarily in the immune suppressed. Tuberculosis primarily affects the lungs, but can also affect other parts of the body. Most infections are asymptomatic, but some progress into active disease, which can be fatal if not treated properly. TB is an airborne infection, spread when the infected person coughs sneezes or passes respiratory droplets into the environment. General symptoms are fever, chills, night sweats, loss of appetite, weight loss and fatigue.

From 2011 to 2012, 35,735 TB cases were registered through the National Tuberculosis Program (NTP). World Health Organization estimated that the prevalence of all types of tuberculosis cases for Nepal was 74,000 (243 per 100,000) while the incidence of all forms of TB incidence cases was around 50,000 (163 per 100,000). National Tuberculosis Center was formed in 1989, and deaths from tuberculosis have decreased overall with the introduction of National Tuberculosis Program in Nepal, from 9,712 (51 per 100,000) in 1990 to 6,200 in 2010 (21 per 100,000). In the past, TB predominantly affected young age groups (15-54 years), but recent figures show a shift towards older age groups (NTC/DoHS/MoHP, 2013; WHO, 2012).

Emergence of multi drug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) has made treatment difficult and expensive. MDR-TB is resistant to isoniazid (H) and rifampin (F). XDR-TB is resistant to injectable drugs and any form of quinolone. In 2010, about 700 patients were registered for MDR-TB, while eight were registered for XDR-TB (Banstola A, 2010). To date, teams from the National TB Program have conducted five national surveys in Nepal as part of the WHO IUATLD Global Project on Anti -Tuberculosis Drug Resistance Surveillance (NTC/DoHS/MoHP, 2013).

A cross-sectional prospective study was carried out in three districts of Eastern Nepal (Sunsari, Morang and Jhapa) in 2011 to investigate the prevalence of pulmonary tuberculosis in HIV infected people. Among the 242

HIV-infected participants, pulmonary tuberculosis was diagnosed in 27 percent (Yadav et al., 2011). In a similar study carried out in Pokhara among 184 HIV infected people from December 2006 to December 2007, the prevalence of pulmonary tuberculosis was 6 percent (Verma, Dhungana, Joshi, Kunwar, & Pokhrel, 2012).

3.1.5 Urinary Tract Infections

A urinary tract infection (UTI) is the infection of any part of the urinary system. UTIs are generally classified into following types:

- Urethritis: infection of the urethra
- Cystitis: infection of the bladder
- Pyelonephritis: infection of the kidneys

Women are at greater risk of developing a UTI than men. Common symptoms include frequent urination, discolored urine, pain when urinating and pelvic or rectal pain. Antibiotics are the typical treatment for a UTI, and the drugs most commonly recommended are sulfamethoxazole-trimethoprim, amoxicillin, nitrofurantoin, ampicillin, ciprofloxacin and levofloxacin. As confirmed by many studies, the most common pathogens responsible for UTIs include *E. coli*, *E. faecalis*, *Citrobacter freundii*, *Enterobacter aerogenes* and Coagulase Negative *Staphylococci* (CoNS). In numerous hospital-based studies, *E. coli* was found to be the predominant causative agent, with isolation rates between 55-90 percent.

In Kathmandu Medical College, *E. coli* (76 percent) was the most common pathogen isolated from 680 urine samples followed by *K. pneumoniae* (11 percent), *Acinetobacter* spp. (6 percent) and *Proteus* spp. from June 2009 to February 2010 (Raza, Pandey, & Bhatt, 2011). Similarly, in Chitwan Medical College Teaching Hospital, analysis of 400 urine samples of menopausal women with suspected UTIs showed growth of 9 species of UTI causing organisms in 43 percent of the samples. Of those*, E. coli* was the most common (65 percent). Other common pathogens included *Staphylococcus* spp. (12 percent), *Proteus* spp. (7 percent), *Klebsiella* spp. (6 percent) and *Enterococcus* spp. (6 percent) from December 2012 to April 2013 (Neupane et al., 2013).

In Kathmandu Model Hospital, following pathogens were found to be the most common cause of UTI among 250 samples: *E. coli* (82 percent), *E. faecalis* (6 percent), *C. freundii* (4 percent) and Coagulase Negative *Staphylococci* (2 percent) in 2009 (Khatri, Basnyat, Karki, Poudel, & Shrestha, 2012). Similar results were obtained in 2007 in Kathmandu Model Hospital. A total of 219 bacterial pathogens were isolated from 710 suspected cases of UTIs and the most common pathogen identified was *E. coli* (81 percent). Other pathogens included *Citrobacter* spp. (5 percent) and Coagulase-Negative *Staphylococci* (3 percent) (Baral et al., 2012).

In Kanti Children Hospital, 58 pathogens were isolated from 205 children aged 0 to 14 years. The most common organisms causing UTIs were *E. coli* (57 percent), *K. pneumoniae* (24 percent), *Proteus mirabilis* (7 percent) and *P. vulgaris* (3 percent) (Gautam & Pokherel, 2012).

3.1.6 Sexually Transmitted Infections

Gonorrhea, chlamydia and syphilis are some of the most common bacterial sexually transmitted infections (STIs). Gonorrhea is caused by *Neisseria gonorrhoeae*. Common symptoms in men are burning during urination and penile discharge. In women, the infection can be asymptomatic or symptoms may include vaginal discharge and pelvic pain. The infection is commonly treated with ceftriaxone in combination with either azithromycin or doxycycline.

Very few studies have investigated the prevalence of gonorrhea in Nepal. A study conducted in Manipal Teaching Hospital, from 2004 to 2010, found that 48 out of 119 patients attending the Venereology and Gynecology department had confirmed gonococcal infections. While the study was primarily focused on the resistance of *N. gonorrhoeae* to first line antibiotics, it also looked at gonorrhea co-infection with HIV and syphilis. Among the male gonorrhea cases (88 percent of the infected population), co-infection with HIV and syphilis was reported in 6 percent and 4 percent of patients, respectively (Bhatta et al., 2012).

Syphilis is a sexually transmitted disease caused by the bacterium *Treponema pallidum*. The major symptoms of syphilis include open sores, rashes, fever, swollen lymph glands, sore throat, patchy hair loss, headaches, weight loss, muscle aches and fatigue. Syphilis can be treated with antibiotics such as penicillin G benzathine, doxycycline or tetracycline (for patients who are allergic to penicillin).

Similar to gonorrhea, only a small number of syphilis studies have been conducted. Research conducted among 24,000 blood donors in Kathmandu Valley from December to August 2006 revealed that the seroprevalence of antibodies against *T. pallidum* was 0.42 percent. The sex-specific seroprevalence was 0.45 percent among male donors and 0.24 percent among female donors (Karki, Tiwari, Ghimire, Maharjan, & Rajkarnikar, 2008). A second study analyzed 504 suspected syphilis

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cases in Kathmandu Valley identified from June 2007 to May 2009. Overall, 180 (36 percent) were active cases, 44 (9 percent) were old/treated cases, 66 (13 percent) were false positives and 42 percent were not syphilis cases. The mean age of the positive syphilis cases was 31.8 years (Dumre, Shakya, Acharya, Malla, & Adhikari, 2011).

Chlamydia is a sexually transmitted infection caused by the bacteria *Chlamydia trachomatis*, which infects both men and women. It can cause potentially fatal ectopic pregnancies serious as well as permanent damage to a woman's reproductive system. Chlamydia is curable with antibiotic treatment. Azithromycin is safe to administer during pregnancy, while doxycycline may harm the development of the fetus (Marrazzo, 2014).

A cross-sectional study was carried out on 117 urine samples collected from HIV positive patients visiting HIV clinics in Sparsha, Nepal from January to March 2011. The results showed that only 4 percent were positive for *C. trachomatis* (Shrestha et al., 2013).

3.1.7 Healthcare-Associated Infections

The U.S. Centers for Disease Control and Prevention (CDC) defines healthcare-associated infections (HAI) as infections not present at admission that occur within 48 to 72 hours of admission to a healthcare facility, within three days of discharge, or up to 30 days following a surgical procedure. HAIs are often associated with devices common in hospitals, such as catheters or ventilators, as well as with a lack of good hygiene and hand-washing practices by facility staff. HAIs include central line-associated bloodstream infections, catheter-associated urinary tract infections and ventilator-associated pneumonia. Infections may also occur at surgery sites (CDC, 2013b).

Common organisms found in patients at hospitals and other healthcare settings include methicillin resistant *S. aureus* (MRSA)*, Streptococcus pyogenes, Acinetobacter*, *Clostridium difficile*, Carbapenem-resistant *Enterobacteriaceae*, *Mycobacterium abscessus*, *S. aureus*, vancomycin-intermediate *S. aureus,* vancomycin-resistant *S. aureus* and vancomycin-resistant *Enterococci* (VRE).

The majority of the HAI studies that have been carried out in Nepal have observed MRSA prevalence. Carbapenem-resistant *Enterobacteriaceae* (CRE) are a family of bacteria that are difficult to treat because they have high levels of resistance to antibiotics. Patients whose care requires devices such as ventilators and urinary or intravenous catheters, and patients who are taking long courses of certain antibiotics

are most prone to CRE infections. Another common HAI is *M. abscessus*, which has been known to contaminate medications and medical devices. Healthcare-associated *M. abscessus* can cause a variety of infections, usually in the skin and the soft tissues under the skin. It can also cause lung infections in people with chronic lung diseases. Vancomycin-intermediate and vancomycin-resistant *S. aureus* (VRSA) are staphylococcus bacteria that have developed resistance to vancomycin. Diabetic and renal disease patients are more likely to develop this infection. Invasive devices are also a potential nosocomial source of VRSA infections. Enterococci are bacteria that are normally present in the intestines and the female genital tract, as well as in the environment. Vancomycin-resistant Enterococci (VRE) are resistant to vancomycin, and most VRE infections occur in hospitals (CDC, 2013a).

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Methicillin-resistant *S. aureus* (MRSA) is a bacterium that causes infection in different parts of the body. MRSA is a major cause of nosocomial as well as community infections. The extent of MRSA carriage in communities is largely unknown and differs between geographical regions (Rijal et al., 2008). The symptoms of MRSA depend on the area of body that is infected. It often causes mild infections on the skin, such as sores or boils, but can also cause more serious skin infections and infect surgical wounds, the bloodstream, the lungs or the urinary tract. MRSA is any strain of *S. aureus* that has developed resistance to beta-lactam antibiotics, including methicillin, oxacillin, penicillin and amoxicillin.

A study conducted during June 2005 to July 2007 from patients visiting to Universal College of Medical Sciences Teaching Hospital, Bhairahawa reported that among 112 MRSA, 37 (33.1 percent) were from community acquired infections (Tiwari, Das, Sapkota, Sivrajan, & Pahwa, 2009).

In Manipal Teaching Hospital, among the samples collected from 58 stethoscopes during April-October 2010, *Micrococcus* spp. were the most commonly isolated pathogens. The study also revealed that only seven percent of healthcare professionals disinfect stethoscopes after every patient (Bhatta et al., 2011). Disinfection is important to prevent the transmission of infectious and drug resistant microorganisms from one patient to another. A study carried out by Longtin and colleagues in 2014 found that, after the examination of a patient, stethoscope diaphragms were second only to physicians' fingertips in terms of microorganism contamination levels (Longtin et al., 2014).

In National Medical College and Teaching Hospital, out of 112 nasal swabs taken from patients, attendants and health care workers (HCWs), 13 percent were *S. aureus* positive and 7 percent were MRSA positive. Among the MRSA positive samples, 75 percent were taken from surgical wards and the remaining 25 percent from the post-operative ward in 2008 (Shakya, Shrestha, & Mitra, 2010).

In Tribhuwan University Teaching Hospital, from November 2007 to June 2008, of a total of 149 nosocomial isolates, 45 percent were MRSA positive. The highest prevalence of MRSA was seen in lower respiratory tract infections (82 percent of infections) followed by skin infections (43 percent) and urinary tract infections (31 percent) (Shrestha, Pokhrel, & Mohapatra, 2009). Similarly, hospitals of Kathmandu and Lalitpur districts from November 2007 to June 2009 showed that 52 percent of the samples from Kathmandu (n=304) and 38 percent of the samples from Lalitpur (n=100) were positive for MRSA (Shrestha, 2013). Findings from another study conducted at BPKIHS from June 2003-June 2004 showed that, out of a total of 750 strains of *S. aureus*, 26 percent were MRSA positive. Most MRSA cases were found in the OPD (30 percent) and the surgery department (24 percent) (Kumari, Mohapatra, & Singh, 2008).

Other HAIs in hospital and community settings

The following section reviews studies of bacterial organisms in hospitals, other healthcare facilities and community settings.

Bhatta and colleagues tested the level of contamination of 58 stethoscopes, including diaphragms, bells and earpieces, from April to October 2010. Ninety-four organisms were isolated from 52 contaminated stethoscopes, and the majority of the contaminated stethoscopes had more than one organism. *Micrococcus* spp. and coagulase negative *Staphylococci* were the two most common isolates identified. Sixty-six percent of bells were contaminated, and *Micrococcus* spp. were the most common type of bacteria. Of the 116 earpieces, 72 percent were contaminated and aerobic spore bearers and *Micrococcus* were the two most prevalent isolates detected (Bhatta et al., 2011).

NICU of a hospital in Kathmandu showed that the prevalence of neonatal nosocomial infection was 33 percent, and the prevalence of *Citrobacter* spp. was 38 percent out of 89 neonates. Other species isolated includes *E. coli*, *Acinetobacter* spp., *Proteus* spp., *Enterobacter* spp. and *S. aureus* in 2010 (Khadka, Thapa, & Mahat, 2011).

Along with contaminated equipment, the environmental spread of bacterial infections in hospitals is common. For example, analysis of 160 environmental samples (43 from the air and 117 from surfaces) as well as 150 human samples (48 nasal and throat swabs; and 54 hand samples) from the staff working in Nepal Medical College Teaching Hospital showed that Gram-positive cocci were predominant among the bacterial isolates from the environment. In the human samples, 32 out of 54 hand samples were positive for *S. aureus*. Other isolates identified included *Bacillus* spp., *Micrococci* and Coagulase-Negative *Staphylococci* (Pant et al., 2006).

Very few studies of HAIs in the community have been carried out, though one study looked at *S. pyogenes* infections in schools. *S. pyogenes* causes infections of the respiratory tract, blood and skin that can be mild to severe. A study analyzed throat swabs from 350 students between the ages of 5 and 15 years attending four schools in the Kathmandu Valley, and isolated *S. pyogenes* from 11 percent of the children (Dumre et al., 2009).

3.2 Human Disease Surveillance

Surveillance of vaccine preventable diseases began in 1996 with the establishment of the early warning and reporting system, which was changed to Polio Eradication Nepal (PEN) in 1998. Neonatal tetanus and Japanese encephalitis were added to the surveillance system in 2005, and PEN was changed to the Program for Immunization Preventable Diseases (IPD). Diseases currently under surveillance include acute flaccid paralysis (AFP), measles and rubella, acute encephalitis syndrome (AES), and neonatal tetanus. The system includes 89 active surveillance sites and more than 576 zero reporting sites. Zero reporting sites report every week even if zero cases occur (DoHS, 2010-11). Reporting sites include hospitals, primary health care centers, health posts, sub health posts, private clinics and community informers.

Acute flaccid paralysis surveillance

AFP surveillance is generally carried out in children under 15 years of age. AFP cases increased from 65 in 1998 to 575 in 2011. However, confirmed polio cases have drastically decreased over the same period from 31 to 1. In 2001, 2002, 2003, 2004 and 2009 there was no confirmed polio case (table 3-1). This reduction is due to high polio immunization coverage, which has increased from 81 percent in 2008-09 to 83 percent in 2009-10 and 95 percent in 2010-11. Nepal got polio free status in 2014 from WHO.

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Table 3-1: Status of AFP Surveillance

Year	AFP Cases	Confirmed polio cases	Polio Compatible	Non-polio AFP rate
1998	69	31	-	0.41
1999	234	42	-	2.00
2000	211	29	-	1.96
2001	186	0	0	1.95
2002	197	0	1	2.00
2003	192	0	1	1.90
2004	214	0	0	2.16
2005	230	4	2	2.25
2006	364	5	2	3.50
2007	343	5	0	3.24
2008	426	6	0	3.94
2009	451	0	0	4.14
2010	598	6	0	5.15
2011	575	1		

Source: (WHO, 2010) (DoHS, 2011-12)

Measles and rubella surveillance

Measles surveillance was added to the national surveillance system in 2003. The number of suspected measles outbreaks has decreased considerably from 67 in 2003 to 33 in 2010. The number of confirmed measles outbreaks also decreased from 41 cases in 2003 to 7 cases in 2010, while the number of confirmed rubella outbreaks has increased from 13 in 2004 to 19 in 2010 (table 3-2) (WHO, 2010).

Japanese encephalitis surveillance

Japanese encephalitis (JE) surveillance started in 2004. Currently, there are 126 hospitals reporting acute encephalitis syndrome (AES) cases on a weekly basis, of which 85 are conducting active surveillance. Surveillance shows that the number of JE cases decreased from 669 in 2005 to 179 in 2010. Similarly, the case fatality rate decreased from 7.9 in 2005 to 0.6 in 2010 (table 3-3). JE vaccination has significantly contributed to the reduction in JE cases and the fatality rate.

In 2011-12, 118 of 1,308 AES cases were lab confirmed JE cases, while in 2010-11 there were 88 confirmed JE cases and 1,367 cases of AES (DoHS, 2011-12).

Table 3-2: Suspected and confirmed measles and rubella outbreaks 2004-2010

Year	Total number of suspected measles cases	Number of suspected measles outbreaks	Number (%) of outbreaks confirmed as measles outbreaks	Number (%) of outbreaks confirmed as rubella outbreaks	Number (%) of outbreaks confirmed as mixed measles and rubella outbreaks
2003	13,344	67	41 (61%)	-	-
2004	12,047	197	138 (70%)	13 (7%)	11 (6%)
2005	5,023	46	1 (2%)	36 (78%)	2 (4%)
2006	2,838	31	2 (6.5%)	24 (77%)	1 (3%)
2007	1,415	21+	3 (14%)	11 (52%)	1 (5%)
2008	2,089	39	6 (15%)	27 (69%)	1 (2.5%)
2009	4,340	66	2 (3%)	57 (89%)	-
2010	2,550	33	7 (21%)	19 (58%)	2 (6%)

Source: (WHO, 2010)

Table 3-3: Japanese encephalitis surveillance figures

Indicators	2005	2006	2007	2008	2009	2010
No. of districts with JE cases	40	43	47	48	34	40
No. of JE cases	669	295	442	340	147	179
JE deaths	53	42	61	39	7	1
Case fatality rate	7.9	14.2	13.8	11.5	4.8	0.6
JE cases under 15 years	382	158	313	235	108	116
JE cases above 15 years	287	137	129	105	39	63

Source: (DoHS, 2011-12)

Animals

3.3 National Burden of Disease in Animals

According to the Department of Livestock Services, foot and mouth disease (FMD), peste des petits ruminants (PPR), highly pathogenic avian influenza (HPAI) and classical swine fever (CSF) are the major infectious and transboundary animal diseases. Other frequently occurring diseases include haemorrhagic septicaemia, blackquarter disease, newcastle disease and infectious bursal disease.

These diseases are considered important due to the socioeconomic consequences of livestock morbidity and mortality (Thakuri, 2012). Some of these diseases may also impact human health through zoonoses, the transmission of disease from animals to humans. Parasitic zoonoses (PZs) are often neglected threats to public health in developing countries such as Nepal, where trichinellosis, toxocarosis, diphyllobothriosis, foodborne trematodosis, taeniosis, zoonotic intestinal helminths and protozoal infections are endemic (Devleesschauwer et al., 2014). In terms of morbidity, mortality and production losses, fasciolosis, parasitic gastroenteritis and ascariosis in pigs are also important parasitic diseases.

3.3.1 Bovines and Ruminants

Common bacterial diseases of bovines and small ruminants in Nepal include mastitis, black quarter disease and haemorrhagic septicaemia.
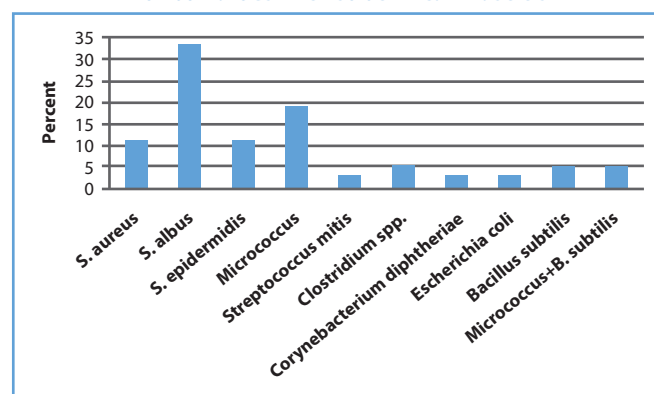
Bacterial mastitis

Mastitis is an inflammation of the mammary gland and udder tissue. It is usually caused by bacteria that invade the udder and produce toxins harmful to the mammary gland. Mastitis infections can be clinical or subclinical. Clinical mastitis visibly impacts the milk or the udder, producing clotted or watery milk and a swelling of the udder. Subclinical mastitis infection is not visibly apparent, though the quality and quantity of milk produced is often reduced in both clinical and subclinical cases. Mastitis is most commonly caused by the bacteria *S. aureus*, but *S. epidermidis* and *Streptococci* are also prevalent causes.

A 2012 study in Bhaktapur district estimated the prevalence of subclinical mastitis in 200 milk samples from 50 dairy cows. They found that 52 percent were positive for subclinical mastitis. Bacteria isolated in this study included *Staphylococcus*, *Streptococcus*, *E. coli*, *Corynebacterium*, *Salmonella* spp. and *Enterobacter* spp. Of these, *Staphylococci* were the most commonly isolated (50 percent) (Shrestha, 2012).

Dhakal and colleagues examined milk from 355 Murrah buffaloes with mastitis—23 with subclinical disease and 332 with clinical disease at the Veterinary Teaching Hospital, Chitwan from 2002 to 2005. The researchers identified organisms causing mastitis and the antibiotic susceptibility of mastitis pathogens. Coagulase-Negative *Staphylococci* (CoNS), such as *S. albus* and *S. epidermidis,* were the predominant organisms associated with the subclinical cases, while CoNS and coliforms were found in the clinical cases (figures 3-2 and 3-3). The most common pathogens found in milk from subclinical infections were CoNS, *S. albus* (33 percent) and *S. epidermidis* (11 percent), as well as micrococcus (19 percent). The most common pathogens isolated from clinical mastitis cases were CoNS (36 percent) and coliforms (11 percent) (Dhakal, Dhakal, Koshihara, & Nagahata, 2007).

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Figure 3-2: Frequency of organisms in the milk of buffaloes with subclinical mastitis

Source: (Dhakal, Dhakal, Koshihara, & Nagahata, 2007)

Figure 3-3: Frequency of organisms in the milk of buffaloes with clinical mastitis

Source: (Dhakal, Dhakal, Koshihara, & Nagahata, 2007)

Another cross-sectional study conducted in 2013 among 63 dairy livestock of the Archalbot and Chandreshwor village development committees (VDCs) in Lamjung district found a higher prevalence of subclinical mastitis in Chandeshwor (35 percent) than in Archalbot (24 percent). Isolated bacteria included *Streptococcus* (43 percent), *E. coli* (33 percent) and *Staphylococcus* (25 percent) (Khanal & Pandit, 2013).

Black quarter
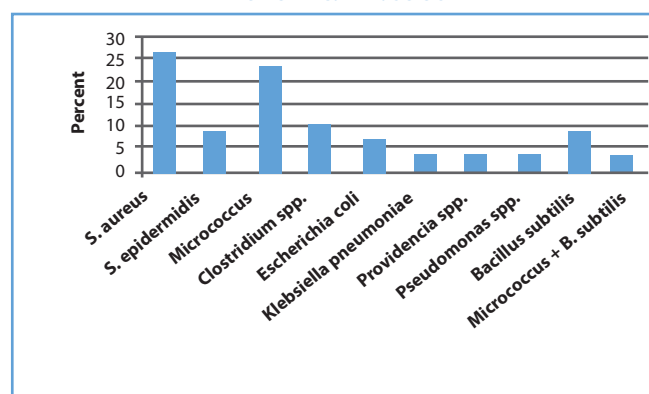
Black quarter is an infectious bacterial disease caused by the Gram-positive bacterium *Clostridium chauvoei*. Black quarter typically affects cattle, sheep and goats, and occasionally bison and deer. Young cattle from 6-24 months of age are the most affected group. The disease spreads through contaminated soil and grazing areas or through contact with wounds on the animals. Common symptoms include fever, loss of appetite, dullness, rapid pulse and heart rate, difficulty in breathing, lameness in the affected leg, swelling of the hip, back and shoulder and weakness followed by death within 12-48 hours of infection.

According to a report from Ministry of Agricultural Development, from 2011-12, black quarter disease occurred in cattle and buffalo in Nepal in 2011. The report recorded 114 outbreaks in 2011, of which 69 percent were in cattle. Of the 1,335 cattle and 587 buffalo affected, 109 cattle and 68 buffalo died. The report also noted that 125,494 cattle and 84,890 buffalo were vaccinated against black quarter disease in 2011 (MoAD, 2012).

Haemorrhagic septicaemia

Haemorrhagic septicaemia (HS), which occurs occasionally in Nepal, is a disease of cattle and buffaloes caused by the

Gram-negative bacterium *Pasteurella multocida* serotypes B:2 and E:2. HS is characterized by an acute septicaemia with high morbidity and mortality. In many Asian countries, outbreaks of this disease occur primarily during monsoon season due to the high humidity and temperatures. The disease is transmitted by ingestion or inhalation of the causative organism, which can be carried in the nasopharynx of infected animals. It is treated with a wide range of antibiotics and can be prevented by vaccination.

According to a report of the Ministry of Agricultural Development from 2011-12, there were 157 HS outbreaks in cattle and 102 outbreaks in buffalo in 2011. Out of 1,032 affected cattle and 765 affected buffaloes, 152 cattle and 132 buffaloes died of the disease. Vaccines were given to 185,058 cattle, 138,485 buffaloes and 6,502 goats (MoAD, 2012).

3.3.2 Poultry

Poultry industry is the most rapidly growing agricultural industry in Nepal. The major diseases affecting poultry are salmonellosis, fowl typhoid, colibacillosis and mycoplasmosis.

Salmonellosis

Salmonellosis is a common disease of poultry in Nepal. *Salmonella typhimurium* and *Salmonella enteritidis* are the most common species of bacteria causing the disease. Symptoms of salmonellosis include lethargy, ruffled feathers, diarrhea, loss of appetite and stunting in older birds. Sulphonamides, neomycin, tetracyclines, amoxicillin and fluoroquinolones are used to treat salmonellosis.

From 2010 to 2011 Central Veterinary Laboratory tested 181 serum samples for *Salmonella pullorum* and 180 for *Mycoplasma gallisepticum*. A total of 31 samples were positive for both antibodies, although of all the districts included (Chitwan, Parsa, Kathmandu and Bhaktapur) only Kathmandu reported positive samples (DoLS, 2010-11).

A total of 130 samples from 13 pellet feed mills and 50 samples from 5 mash feed companies were collected and examined for *Salmonella* spp. Nineteen (38 percent) of the mash feed samples and none of the pellet feed samples were positive. Most of the positive feed samples had high bacterial counts (Singh, Upadhaya, Lampang, Chaisowwong, & Hafez, 2013).

Ninety raw chicken samples from retail meat shops in Kathmandu, Lalitpur and Bhaktapur were collected from November 2008 to October 2009 and tested for *Salmonella*. *Salmonella* was isolated from 67 (75 percent) of the samples, showing a higher prevalence than was found in similar studies conducted in India (12 percent) and Thailand (57 percent) (Anjala Shrestha, Regmi, & Dutta, 2010).

A cross-sectional study was conducted from July to December 2011 in retail broiler meat shops in Chitwan district. Out of 26 processed retail broiler meat samples, S*almonella* was identified in 12: five from Bharatpur Municipality, three from Ratnanagar Municipality and four from VDCs around the Institute of Agriculture and Animal Science (Bhandari, Nepali, & Paudyal, 2013). In another study of meat from retail shops in Chitwan district, 8 out of 50 fresh chicken meat samples (16 percent) were found to be positive for *Salmonella* (Aryal & Karki, undated).

Fowl typhoid

Fowl typhoid, a common bacterial disease in Nepal, is caused by *Salmonella gallinarum*. The disease spreads rapidly, causing high morbidity and mortality. In mature chickens, common symptoms include lethargy, wing droop, difficulty breathing, poor feathering and decreased egg production. Fowl typhoid can also affect young chickens, and common symptoms are weakness, lethargy, decreased appetite and poor growth, and the case fatality rate can be up to 90 percent.

According to the Ministry of Agricultural Development, there were 53 outbreaks of fowl typhoid in 2011, affecting 27,048 chickens and killing 137 (MoAD, 2012).

Colibacillosis

Colibacillosis is caused by *E. coli*. *E. coli* infections in chickens can be severe acute infections or milder chronic infections. The symptoms of colibacillosis are ruffled feathers, labored breathing and coughing. Severely infected birds may exhibit diarrhea, swelling and congestion of the liver and spleen. Colibacillosis is treated with tetracyclines and sulfa drugs. Colibacillosis is a significant disease in poultry in Nepal.

According to the Ministry of Agricultural Development, there were 277 outbreaks of colibacillosis in 2011. During these outbreaks 3,206 chickens died and a total of 139,158 were infected (MoAD, 2012). Post mortem examinations of poultry by the Regional Veterinary Laboratory, Dhangadi in 2011-12 found 18 cases of colibacillosis. Similarly, pathological examinations in the Regional Veterinary Laboratory, Pokhara, reported 891 cases (CVL, 2012).

Another study found that 67 percent of 30 fecal waste samples taken from poultry farms were positive for *E. coli*. Other organisms isolated included *Shigella* spp. (17 percent), *Salmonella* spp. (10 percent) and *Proteu*s spp. (7 percent) (Shrestha, 2012).

3.3.3 Zoonoses

Zoonotic diseases are the diseases that can be transmitted from animals to humans and vice-versa. They are caused by many bacteria, viruses and parasites. Anthrax, brucellosis, verotoxigenic *E. coli*, leptospirosis, plague, Q fever, shigellosis and tularaemia are some examples of bacterial zoonotic diseases. Important bacterial zoonotic diseases prevalent in Nepal are described below:

Brucellosis

Brucellosis is a highly infectious disease, caused by *Brucella melitensis*. In humans, it causes septicaemia and severe fevers. Brucellosis can be transmitted to humans through drinking unpasteurized milk, eating undercooked meat or dairy from an infected animal, or through close contact with infected animals. In rare cases, brucellosis can be transmitted from person to person. The incidence of brucellosis can be decreased through improved food handling, preparation and animal husbandry.

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The seroprevalence of Brucella antibodies was investigated from September 2012 to January 2013. Blood samples were taken from 233 animals in the Kailali district, and the seroprevalence was 32 percent (16/50) in cattle, 13 percent (9/67) in buffalo and 3 percent (3/113) in goats. The overall seroprevalence for Brucella was 12 percent (28/233) (Pandeya et al., 2013).

Brucella abortus is a cause of abortion and retained placenta in yaks, but may not be the most important cause of this problem in Nepal. A study examining the seroprevalence of *B. abortus* antibodies in 67 serum samples from yaks in the Mustang and Myagdi districts found that all serum samples were negative for *B. abortus* antibodies (Aryal & Poudel, 2007). In a study conducted in Dang district from September to November 2009, among 100 serum samples of goats, 2 percent were positive for antibodies against *Brucella*. Brucellosis was found only in female Khari goats (4 percent) (Adhikari, 2012).
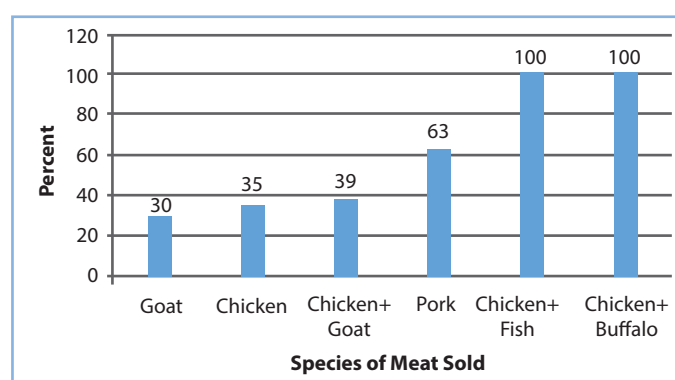
Salmonellosis

Salmonella can be transferred between humans and animals, primarily though the ingestion of contaminated food. Poultry is a major source of *Salmonella* infection. The bacterium is present in the digestive tracts of a wide range of mammals (including humans), birds and reptiles. Additionally, animal products such as eggs and milk can be contaminated with salmonella. Symptoms in humans include diarrhea, abortions, fever and decreased appetite, and infection can lead to pneumonia and blood poisoning. Researchers from the serology unit of the National Avian Disease Investigation Laboratory screened for *Salmonella* and *Mycoplasma* in commercial poultry serum samples from 2011 to 2012. The samples were collected from leghorn hybrid chickens, typically used for egg production for human consumption, and parent flocks. Of the 358 samples screened for *Salmonella*, 33 percent were positive. Of the 182 samples screened for *Mycoplasma*, 25 percent were positive (CVL, 2012).

A cross-sectional study was carried out in 82 retail shops in Kathmandu from November 2008 to May 2009, in which a total of 492 environmental swab samples were taken from knives, chopping boards and tables. The overall prevalence of salmonella was 40 percent. Out of 489 samples from the retail meat shops, 154 samples were positive for *S. typhimurium* (55 percent). The retail meat shops sold meat from varying numbers of species and used a varying number of knives. The prevalence

of *Salmonella* in the shops that sold two species of meat using two knives (one for each species) was lower than in the shops that only sold a single species of meat using two or more knives. *Salmonella* spp. were most commonly found in shops selling chicken and fish or chicken and buffalo (figure 3-4). The study revealed that of the total samples, 30 percent of the samples collected from knives used for chopping goat meat showed *Salmonella* growth and 100 percent of the samples from the shop that sell chicken+fish and chicken+buffalo showed the *Salmonella* growth. (Upadhyaya, Poosaran, & Fries, 2012).

Figure 3-4: Percentage of samples showing *Salmonella* growth

Source: (Upadhyaya, Poosaran, & Fries, 2012)

Bovine Tuberculosis

Mycobacterium bovis, a Gram-positive bacterium, is a causative agent of bovine tuberculosis (bTB) in cattle. *M. bovis* can occasionally cause tuberculosis in humans and other mammals through the inhalation of aerosols, direct contact with open wounds, or the consumption of unpasteurized milk. In its early stages, bTB is often asymptomatic. Progressive emaciation, a low–grade fluctuating fever, weakness and lack of appetite are common symptoms in later stages. In the terminal stages, animals may become extremely emaciated and develop acute respiratory distress. In some animals, the retropharyngeal or other lymph nodes enlarge and may rupture and drain. Enlarged lymph nodes can obstruct blood vessels, airways or the digestive tract. If the digestive tract is involved, intermittent diarrhea and constipation occur.

A cross-sectional study investigated the frequency and risk factors responsible for bovine tuberculosis around the buffer zone of the Koshi Tappu Wildlife Reserve. The

study analyzed 128 domestic buffalo from 94 households and 33 herds. Altogether, 12 percent of the buffalo and 36 percent of the herds had positive tuberculin tests. The association between buffalo with a positive test and human tuberculosis cases in households was not statistically significant (Lamichhaney & Thapaliya, 2008).

Another cross-sectional study tested for bovine tuberculosis in 100 animals (22 cattle and 78 buffalo) in six areas of Western Chitwan between August 2010 and January 2011. This study also interviewed animal owners from 60 households in order to assess the animal-human connection for tuberculosis. Out of all the animals, 15 percent were positive for bTB, with 15 percent of the buffalo and 34 percent of the cattle. Of all the households, 25 percent contained bTB positive animals (Pandey et al., 2013).

A study on the prevalence of bovine tuberculosis was carried out among cattle and buffalo in Kathmandu valley. A total of 35 samples from dairy cattle and 50 pooled serum samples from buffalo were collected and examined for tuberculosis. Out of all the samples from dairy cattle, 48 percent were found to be positive. Of the samples from buffalo, 28 percent were positive (Aryal, Bhattarai, Shah, & Karki, undated).

Another study was conducted on bovine tuberculosis among animals cared for by tuberculosis patients under treatment. Out of 50 animals reared by 25 tuberculosis

patients in Kavre district during the period of August to December 2009, 5 animals (10 percent) were found to be positive for tuberculin (Gaire & Joshi, 2012).

Leptospirosis

Leptospirosis is caused by bacteria of the genus *Leptospira*. Leptospirosis may cause high fevers, severe headaches, muscle pain, chills, redness of the eyes, abdominal pain, jaundice, hemorrhages in the skin and mucous membranes, vomiting, diarrhea and rash.

A descriptive cross-sectional study was conducted from October 2010 to September 2012 at Chitwan Medical College Teaching Hospital, Chitwan district. Out of 1,266 blood samples, 5 percent were positive for *Leptospira* (Nepal, 2013).

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Chapter **4**: Antibiotic Resistance

A ntibiotic resistance is a challenging public health issue worldwide. Widespread antibiotic use has led to increased resistance, making it more difficult and expensive to treat common bacterial diseases. This chapter reviews the current treatment options and state of antibiotic resistance for infections that contribute significantly to the disease burden in Nepal. These include acute respiratory infections, diarrheal diseases, bloodstream infections, urinary tract infections, sexually transmitted infections, tuberculosis and healthcare acquired infections.

Box 4-1: Definitions of antibiotic resistance

Resistant: Resistant bacteria are able to grow in spite of exposure to antibiotics that were once capable of blocking growth and killing the organisms. Scientifically defined, a strain is "resistant to a given antibiotic when it is inhibited in vitro by a concentration of this drug that is associated with a high likelihood of therapeutic failure."

Intermediate: Intermediate resistance indicates partial, but incomplete resistance, where bacterial growth is somewhat inhibited by exposure to antibiotics. Scientifically, the sensitivity of a strain "is said to be intermediate when it is inhibited in vitro by a concentration of this drug that is associated with an uncertain therapeutic effect."

Susceptible: When a strain of bacteria is susceptible to an antibiotic, the antibiotic prevents the growth of the bacteria and eliminates the bacterial infection from the body. "A bacterial strain is said to be susceptible to a given antibiotic when it is inhibited in vitro by a concentration of this drug that is associated with a high likelihood of therapeutic success."

Source: (Rodloff et.al., 2008)

HUMANS

A recent study using national antibiotic surveillance program data to analyze antibiotic resistance in Nepal found that *Streptococcus pneumoniae* and *Haemophilus influenza* demonstrated higher resistance to cotrimoxazole, at 58-74 percent and up to 60 percent, respectively. *Neisseria gonorrhoeae* had 14 to 30 percent resistance to ciprofloxacin, indicating a need to change the first line therapy for the management of gonococcal infection from ciprofloxacin to cefixime. The study also found increasing resistance of *S.*Typhi and *S.* Paratyphi A to nalidixic acid. All *Escherichia coli* isolates were resistant to quinolones such as norfloxacin and ofloxacin, and 99 percent were resistant to ciprofloxacin (Malla et al., 2014).

4.1 Acute Respiratory Infections (ARI)

Eight studies reviewed to understand the resistance pattern of ARI causing pathogens in different hospitals demonstrated that the resistance has increased for major antibiotics used.

Mishra and colleagues carried out a six-month study on 1,120 sputum, endotracheal aspirate and bronchial washing samples collected from patients at a tertiary care hospital, from which 533 bacteria were isolated. The most commonly isolated bacteria were *H. influenzae* (21 percent) and *Klebsiella pneumoniae* (19 percent). About 30 percent of the *H. influenzae* isolates were resistant to amoxicillin, while 36 percent of *Staphylococcus aureus* were susceptible to erythromycin. A total of 54 percent of the bacterial isolates were multidrug resistant (MDR). Multidrug resistance was more common in *K. pneumoniae* (23 percent) followed by *Pseudomonas* (21 percent), *Acinetobacter calcoaceticus-baumannii* complex (21 percent), *E. coli* (12 percent) and *S. aureus* (9 percent) (Mishra et al., 2014).

According to Alliance for the Prudent Use of Antibiotics (APUA)-Nepal's study, only 8 percent and 5 percent of the urinary isolates (n=132) were susceptible to cephalexin and amoxicillin, respectively at Tribhuwan University Teaching Hospital, Kathmandu from 2006 to 2007. No isolate from pus was susceptible to amoxicillin, and only 5 percent of the pus isolates (n=37) were susceptible to cephalexin, 25 percent (n=37) to cotrimoxazole, and 63 percent (n=37) to gentamicin. None of the isolates from
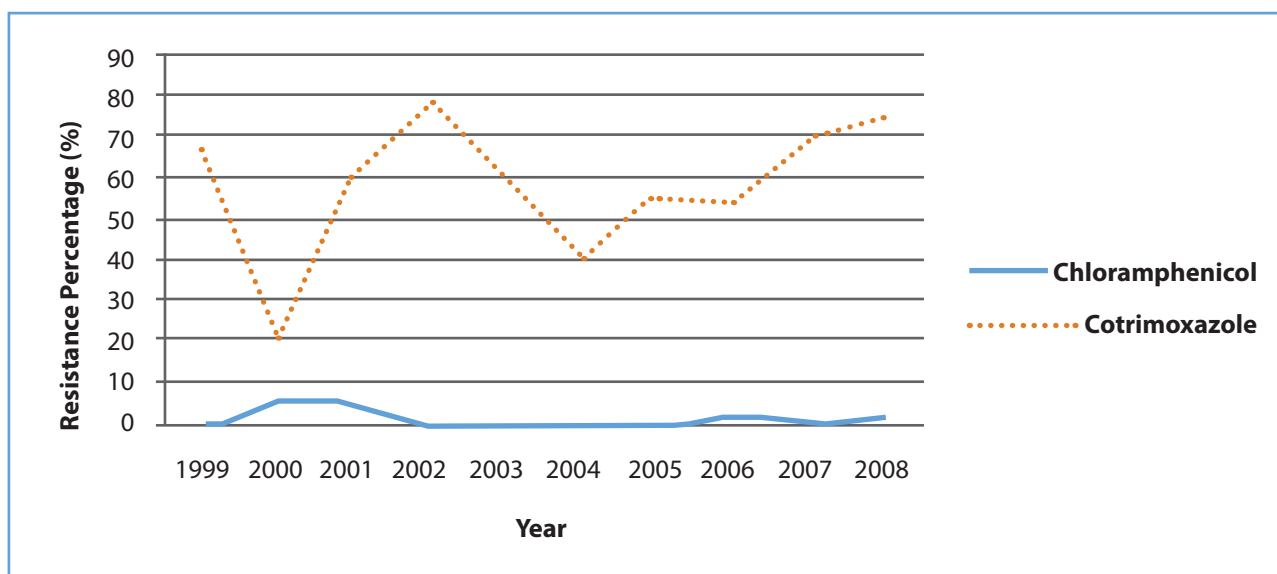
sputum were susceptible to amoxicillin and only 5 percent of the sputum isolates were susceptible to cephalexin. Likewise, in Koshi Zonal Hospital, of the 55 *K. pneumoniae* urine isolates, 67 percent of the isolates were sensitive to ciprofloxacin, 15 percent to cotrimoxazole, 13 percent to nalidixic acid and 95 percent to nitrofurantoin in 2011. In Western Regional Hospital, Pokhara all the *K. pneumoniae* isolates (n=6) were sensitive to ampicillin and ceftriaxone. Sensitivity to azithromycin, cefixime and nalidixic acid was reported as 25 percent, 33.3 percent and 17 percent respectively in 2007-2008 (APUA, 2012).

Some of the studies reported that most of the isolates were resistant to the commonly-used antibiotics cotrimoxazole. Among 26 samples from children who grew pneumococci in their blood, cerebrospinal fluid or body fluids at Patan Hospital during 2007 to 2009, relatively high resistance was observed to cotrimoxazole (77 percent), and no resistance to penicillin, ampicillin, cefotaxime, erythromycin or ofloxacin (Chhetri et al., 2012). In Kanti Children's Hospital, 52 percent of isolates recovered from 3,774 children (2 months to 5 years of age) with suspected pneumonia showed high resistance towards cotrimoxazole (52 percent), while 7 percent of the isolates were intermediately resistant to penicillin. Only 2 percent of the isolates were resistant to erythromycin, choloramphenicol and cefotaxime each from 2004 to 2008 (Rijal et al., 2010). Similarly from 2004 to 2007, of 2,528 children (2 months to 5 years of age) admitted to Kanti Children's Hospital for pneumonia, meningitis or bacteremia, 68 percent were resistant to cotrimoxazole, 7 percent to erythromycin, 4 percent to cefotaxime and 4 percent to penicillin (Shah et al., 2009). In BP Koirala Institute of Health Sciences, Dharan, 26 isolates of *S. pneumonia* from various clinical specimens obtained from 30 patients, 77 percent were suceptible to cotrimoxazole and 96 percent to ciprofloxacin. All of the isolates were susceptible to cefotaxime, chloramphenicol, erythromycin, penicillin and vancomycin from 2005 to 2006. However, the minimum inhibitory concentration (MIC) – the lowest antibiotic concentration capable of inhibiting visible bacterial growth overnight–of penicillin was found to be higher against certain isolates (Khanal et al., 2010).

In Manipal Teaching Hospital, from 2000 to 2007, out of 312 *S. pneumoniae* isolates, 35 percent were resistant to one antibiotic, nine percent to two antibiotics and one percent to three antibiotics. Of the total isolates identified over seven years, 5 percent were resistant to penicillin, and resistance to penicillin increased over time, from 0 percent in 2000 to 21 percent in 2007. Of the 15 penicillin-resistant isolates, 33 percent were also resistant to cotrimoxazole, and 27 percent were also resistant to erythromycin. Of the 297 penicillin-susceptible strains, 34 percent were resistant to cotrimoxazole. 55 percent of isolates were sensitive to all antibiotics tested in the study. The most common co-resistant isolates were to cotrimoxazole and tetracycline (4 percent) and to cotrimoxazole and erythromycin (3 percent) (Easow et al., 2011).
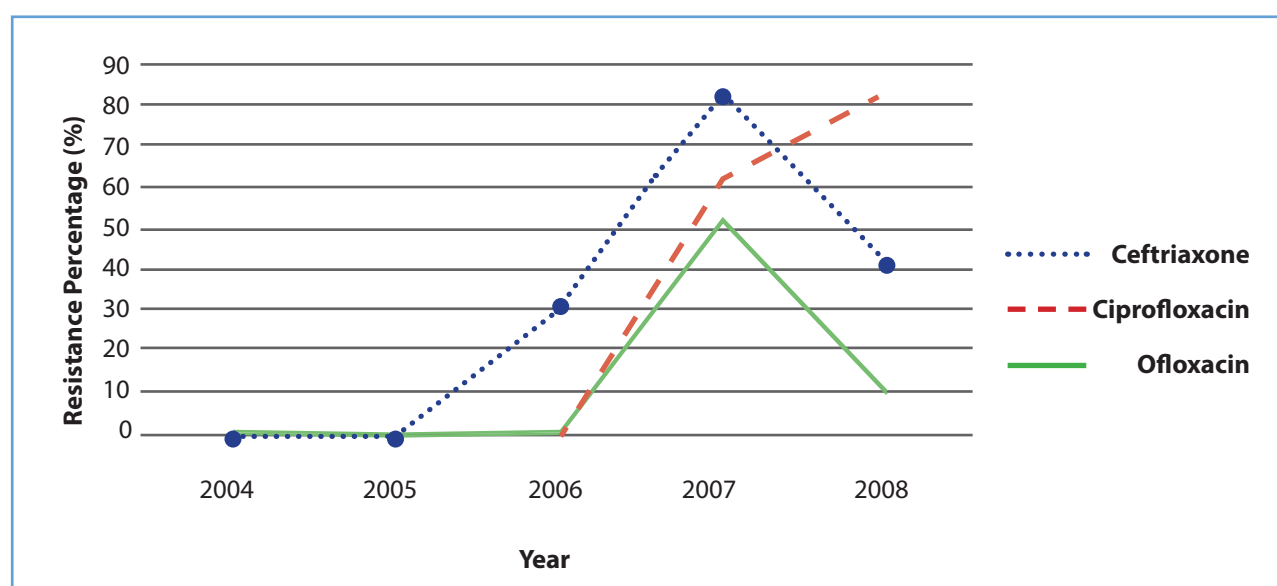
A 9-year study (1999 to 2008) among 934 isolates of *S. pneumonia* collected from eleven laboratories around Nepal showed the antibiotic resistance level of cotrimoxazole and ciprofloxacin in increasing order from 2000 to 2008. The study reported that in 2008, resistance to cephalexin was the highest (88 percent), followed by gentamicin (44 percent) and azithromycin (25 percent). With the exception of erythromycin, which showed decreasing resistance patterns (from 11 to 2 percent), resistance increased for all antibiotics over the course of the 9-year study period. From year 1999 to 2008, penicillin resistance increased from 4 to 8 percent, ampicillin resistance increased from 2 to 11 percent and cotrimoxazole resistance increased from 65 to 74 percent. Ceftriaxone resistance increased from 0 in 2004 to 8 percent in 2007 and ciprofloxacin resistance increased from 0 in 2004 to 8 percent in 2008 , and ofloxacin resistance increased from 0 in 2004 to 5 percent 2007 (figures 4-1 and 4-2). In addition, more isolates were multi drug resistant in 2008 compared to 2004. In 2004, 4 percent of isolates were resistant to two antibiotics, where as in 2008, 13 percent of isolates were resistant to two or more antibiotics (Shakya & Adhikari, 2012).

Figure 4-1: Resistance patterns of chloramphenicol and cotrimoxazole 1999-2008

Source: (Shakya & Adhikari, 2012)

Figure 4-2: Resistance patterns of ceftriaxone, ciprofloxacin and ofloxacin 2004-2008

Source: (Shakya & Adhikari, 2012)

4.2 Diarrheal Diseases

The antibiotic resistance pattern of *Shigella* and *V. cholorae,* two major diarrheal disease causing pathogens in Nepal also showed increased resistance to major antibiotics. Some studies demonstrating the AMR pattern of these pathogens are described below:

Antimicrobial resistance patterns of *Shigella* spp. to fifteen antibiotics was studied from September 2011 to March 2013 at Nepalgunj Medical College and Teaching Hospital, Banke. From a total of 458 stool samples, *Shigella* strains were isolated in 65, including *S. flexneri* (43 percent), *S. dysenteriae* (28 percent), *S. boydii* (22 percent) and *S. sonnei* (8 percent). The highest number of isolates showed resistance to nalidixic acid (95 percent) followed by ampicillin (85 percent), cotrimoxazole (82 percent) and ciprofloxacin (46 percent) (Khan, Singh, Ansari, & Asthana, 2014).

A study assessing 118 *Shigella* isolates collected at 9 hospital laboratories in Nepal from 2003 to 2005 found that 33 percent of *Shigella* isolates were resistant to 3 or more antibiotics (including ampicillin, cotrimoxazole, nalidixic acid and ciprofloxacin). All of the *Shigella* isolates were susceptible to ceftriaxone and azithromycin (Kansakar, Malla, & Ghimire, 2007).

A cross sectional study conducted in 2011 at Kanti Children's hospital analyzed 525 stool samples of children with acute diarrhea, from which 12 *E. coli*, 24 *Shigella* spp. and 10 *Salmonella* spp. were isolated. Of the *E. coli* isolates, five were resistant to ampicillin and four were resistant to cotrimoxazole, amikacin and nalidixic acid, respectively. None of the *E. coli* isolates were resistant to chloramphenicol. Overall, 58 percent of the *E. coli* isolates were resistant to two or more antibiotics. The *Shigella* isolates were most commonly resistant to nalidixic acid (54 percent), followed by ampicillin (50 percent), cotrimoxazole (50 percent) and tetracycline (42 percent). The *Shigella* isolates also showed resistance of 8 percent to norfloxacin, gentamicin, ciprofloxacin and ofloxacin. In total, 58 percent of *Shigella* isolates were multi-drug resistant. Among the 10 *Salmonella* isolates in the study, 70 percent were resistant to ampicillin, 60 percent to nalidixic acid and 40 percent to gentamicin, ceftazidime and cefotaxime. *Salmonella* isolates were least resistant to chloramphenicol (10 percent), tetracycline (10 percent), cotrimoxazole (20 percent) and amikacin (20 percent). Seventy percent of the *Salmonella* isolates were MDR (Ansari et al., 2012).

A total of 51 stool samples were tested from Accham, Baitadi and Doti districts during the period of April to September 2009. *Vibrio cholerae* were isolated from 27 samples, all of which showed resistance to nalidixic acid and cotrimoxazole (Bhandari & Bhusal, 2013).

Of 57 *V. cholerae* isolates tested in Kathmandu valley from 2008 to 2009, researchers found that all isolates were resistant to furazolidone, nalidixic acid and cotrimoxazole. Twenty-six percent of isolates were also resistant to ampicillin and 32 percent were also resistant to erythromycin. None of the isolates were resistant to ciprofloxacin or tetracycline (Karki et al., 2011). Another study of antibiotic resistance in *V. cholerae* cases conducted at the National Public Health Laboratory (NPHL) in 2005 found that among 53 *V. cholerae* isolates, all were resistant to nalidixic acid and cotrimoxazole, and furazolidone resistance was 85 percent. No isolates were resistant to ampicillin, ciprofloxacin, erythromycin or tetracycline (Adhikari et al., 2010).

4.3 Blood Stream Infections

Antibiotic resistance was also observed in blood stream infections. Some studies reflecting resistance pattern of BSI causing agents to major antibiotics are described below:

Researchers at Kathmandu Medical College in 2010 assessed the antibiotic susceptibility patterns of 138 confirmed cases of bacterial blood stream infections. Gram-negative bacteria showed the highest resistance for ampicillin (22 to 83 percent), cefuroxime (7 to 67 percent) and ceftriaxone (4 to 67 percent). Resistance to ofloxacin and amikacin ranged from 0 to 67 percent. Of the 22 Gram-positive isolates, 100 percent were resistant to penicillin and 46 percent were resistant to cotrimoxazole. No Gram-positive bacteria were resistant to oxacillin or vancomycin (Pandey, Raza, & Bhatta, 2013).

Another study conducted at Manipal Teaching Hospital (MTH) from 2006 to 2007 analyzed isolates from 96 patients with confirmed bacterial blood stream infections. Among the 41 Enterobacteriaceae isolates, the highest resistance was found to amoxicillin (66 percent), followed by cefuroxime (37 percent), ampicillin (29 percent) and cefazolin (29 percent). Only 2 percent of the isolates were resistant to netilmicin and 8 percent to amikacin, while 2 percent of isolates were resistant to both netilmicin and amikacin. Among the 27 non-fermenter isolates, 30 percent were resistant to amikacin and 19 percent were resistant to gentamicin and ceftazidime. Non-fermenters showed no resistance to imipenem or bramycin. Of the 13 *S. aureus* isolates, 23 percent were identified as MRSA. Forty–six percent of *S. aureus* isolates were resistant to erythromycin, 38 percent to gentamicin and 15 percent to ciprofloxacin (Easow, Joseph, Dhungel, Chapagain, & Shivananda, 2010).

Neonatal Sepsis

In Chitwan Medical College Teaching Hospital, analysis of 238 isolates from cases of neonatal septicemia showed that resistance to antimicrobials was high among Gram-negative Enterobacteriaceae. Ninety-four percent of isolates were resistant to ampicillin, followed by ceftazidime (87 percent), ceftriaxone (83 percent) and cefotaxime (79 percent). Among *Pseudomonas* spp. isolates, 71 percent showed resistance for cefotaxime followed by piperacillin (69 percent), carbenicillin (69 percent) and ceftazidime (67 percent). Among *Acinetobacter* spp., 73 percent showed resistance for ceftazidime, followed by piperacillin (66

percent) and cefotaxime (65 percent). Among Gram-positive bacteria, 96 percent were resistant to penicillin, followed by cotrimoxazole (61 percent) and cefotaxime (51 percent) in 2009-2010 (Gyawali & Sanjana, 2013).

In Dhulikhel Hospial, of the 23 culture-positive neonates, *Klebsiella oxytoca* isolates (n=11) were resistant to ampicillin, aztreonam, cefotaxime and cloxacillin. Among *Pseudomonas* spp. (n= 4), resistance to amoxicillin, aztreonam, amikacin, gentamicin and ciprofloxacin was observed. Among Methicillin Resistant *Staphylococcus aureus* (MRSA) isolates (n=3), resistance was seen to ampicillin, aztreonam, cefotaxime and cloxacillin in 2009-2010 (Shrestha, Shrestha, & Gurung, 2012).

Of 161 positive blood, cerebrospinal fluid, urine, stool, and swab cultures from the neonatal unit of Patan Hospital during 2006-2007, resistance to penicillin ranged from 33-71 among the different types Gram-positive bacteria. Resistance was also reported to amoxicillin (46-71 percent), cefotaxime (18-55 percent) and chloramphenicol (18-25 percent). Among the Gram-negative bacteria, 50-100 percent of isolates were resistant to amoxicillin, 33-44 percent were resistant to chloramphenicol, 22-71 percent were resistant to gentamicin, 25-37 percent were resistant to cefotaxime, 21-63 percent were resistant to ciprofloxacin, 21-50 percent were resistant to amikacin and 22-47 percent were resistant to ofloxacin (Shrestha, Adhikari, Rai, & Shreepaili, 2010).

In Manipal Teaching Hospital's NICU, *S. aureus* (56 isolates) was the most common pathogen isolated from 131 isolates causing septicemia from 2000 to 2005. Isolates showed 100 percent resistance to penicillin and ampicillin, followed by 89 percent to methicillin, 71 percent to ofloxacin, 63 percent to piperacillin and 57 percent to erythromycin. *S. aureus* isolates were 100 percent susceptible to Imipenem/ Cilastatin (Imi-Cil) and vancomycin. Among 25 *K. pneumoniae* isolates, the second most commonly detected pathogen, 50 percent of the isolates were sensitive to ceftriaxone, while 58 percent were sensitive to ampicillin, amoxycillin-clavulanic acid, piperacillin, ceftazidime and gentamicin, respectively. All *K. pneumoniae* isolates were sensitive to Imi-Cil (Shaw, Shaw, & Thapalial, 2007).

Typhoid and Paratyphoid

Chloramphenicol was once the drug of choice for the treatment of *S*. Typhi, but resistance developed to this drug in the late 1980s and fluoroquinolones, such as ciprofloxacin, were used instead (Butler et al., 1999). However, widespread

resistance with many fluoroquinolones has developed in the Indian Subcontinent since the late 1990s, and the time needed to clear the infection is now usually prolonged even with higher doses of fluoroquinolones. Gatifloxacin, a newer generation fluoroquinolone, is inexpensive and should be the preferred drug for the treatment of enteric fever in developing countries. Unfortunately, it is not readily available commercially. In addition, gatifloxacin resistant strains have been recorded in a recent trial (August 2014) comparing the effectiveness of gatifloxacin against ceftriaxone. Azithromycin may be a better choice for the treatment of enteric fever in South Asia, given these resistance patterns. In addition, as illustrated by a large scale randomized controlled trial of enteric fever carried out at Patan Hospital in Nepal, chloramphenicol has now made a comeback as an effective drug against enteric fever (Arjyal et al., 2011). Older drugs, such as chloramphenicol and cotrimoxazole, may also need to be used more regularly to combat this increasing resistance.

National Public Health Laboratory analyzed the antimicrobial susceptibility of 24 *S*. Typhi and 17 *S*. Paratyphi A isolates obtained from patients with an enteric fever clinical diagnosis in 2008. Out of the 41 isolates, 78 percent were resistant to nalidixic acid. All of the isolates were found to be susceptible to ciprofloxacin and ofloxacin (Acharya, Malla, Bhatta, Adhikari, & Dumre, 2012).

Kathmandu Medical College and Teaching Hospital, Sinamangal, analyzed 32 *S*. Typhi and 1 *S*. Paratyphi A isolates from 33 pediatric patients. The study reported resistance to chloramphenicol and ciprofloxacin at the frequency of 24 percent and 21 percent, respectively. Resistance to cefixime and ceftriaxone was detected in 6 percent of isolates. No isolates were resistant to ofloxacin (Bajracharya et al., 2006).

In Dhulikhel Hospital among 114 *S*. Typhi isolates, all were sensitive to amoxicillin-clavulanic acid. More than 95 percent of the isolates were sensitive to chloramphenicol, ceftazidime, ceftriaxone and cotrimoxazole. In addition, 2 percent of the isolates showed MDR patterns. Of the total (114) *S*. Typhi isolates, 40 were randomly selected, of which 32 strains (80 percent) showed nalidixic acid resistance with decreased susceptibility to ciprofloxacin from 2009 to 2010 (Acharya, Trakulsomboon, Madhup, & Korbsrisate, 2012).

In Kathmandu Medical College, the antibiotic susceptibility patterns of 47 *S*. Typhi isolates and 31 *S*. Paratyphi A isolates showed that *S*. Typhi isolates were least suscepti-

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ble to ampicillin (70 percent), cotrimoxazole (92 percent), and chloramphenicol (94 percent). *S.* Typhi isolates were the most susceptible to ciprofloxacin (100 percent), gentamicin (98 percent), ofloxacin (96 percent) and ceftriaxone (96 percent). Six percent of the isolates were MDR. *S.* Paratyphi A isolates were least susceptible to ampicillin (26 percent) and gentamicin (97 percent). All of the *S.* Paratyphi A isolates were susceptible to chloramphenicol, cotrimoxazole, ciprofloxacin, ceftriaxone and ofloxacin. None of these isolates were MDR from 2010 to 2011(Raza, Tamrakar, Bhatt, & Joshi, 2012).

A research team from APUA Nepal conducted studies in three different hospitals from 2007 to 2010 in order to analyze the sensitivity patterns for *S.* Typhi and *S.* Paratyphi. In a 2007-2008 study at Western Regional Hospital, Pokhara of 25 *S.* Typhi isolates collected, 44 percent were sensitive to ampicillin and 61 percent were susceptible to cotrimoxazole. All isolates were sensitive to azithromycin, cefixime, chloramphenicol, ciprofloxacin and gentamicin. Likewise another study of 2007 at Tribhuwan University Teaching Hospital (TUTH), Kathmandu analyzed 69 *S.* Typhi and *S.* Paratyphi A serotypes and found that the isolates were least sensitive to ofloxacin (42 percent) and ciprofloxacin (42 percent). Isolates were most sensitive to chloramphenicol (93 percent) and ampicillin (91 percent). But in 2009, analysis of 92 *S.* Typhi isolates in TUTH, the isolates were least sensitive to nalidixic acid (48 percent). All isolates were sensitive to azithromycin, cefotaxime, ceftazidime, ceftriaxone, ciprofloxacin, imipenem and ofloxacin and of 110 *S.* Paratyphi A isolates, 35 percent were susceptible to nalidixic acid. All *S.* Paratyphi A isolates were sensitive to azithromycin, cefotaxime, ceftazidime, ceftriaxone, ciprofloxacin, imipenem and ofloxacin. In 2010 study at the Mechi Zonal Hospital, Jhapa, the susceptibility patterns of *S.* Typhi to different antibiotics showed that out of 4 isolates of *S.* Typhi detected in blood samples, all were sensitive to ceftriaxone, and sensitivity to cotrimoxazole, ampicillin and ofloxacin was observed in 75, 50 and 50 percent of isolates, respectively (APUA, 2012).

A study was conducted from 2009 to 2011 analyzing 400 isolated strains of *S.* Paratyphi A and *S.* Typhi collected from 4,820 blood cultures from patients aged 2 to 60 years at 5 different hospitals and laboratories across Nepal. Among the 400 isolates, 72 percent were multi-drug resistant (Gautam, Pokhrel, Bhatta, & Shrestha, 2012).

In Nepal Medical College Teaching Hospital, Kathmandu, drug susceptibility patterns of *S.* Typhi and *S.* Paratyphi A isolates was performed from 2008 to 2009 . Of the 9 *S.* Typhi isolates, resistance to bramycin was detected in 44 percent, to gentamicin in 33 percent, to ampicillin in 22 percent and to ofloxacin in 22 percent. Of the 17 *S.* Paratyphi A isolates, resistance to gentamicin was detected in 29 percent, to bramycin in 18 percent and to ampicillin in 12 percent. None of the isolates were resistant to amikacin or ofloxacin (Pokharel et al., 2009).

Of the total 235 isolates (195 *S.* Typhi and 40 *S.* Paratyphi A) collected from 2007 to 2008 at Kanti Children's Hospital, 19 percent were resistant to amoxicillin, 7 percent to ofloxacin and 7 percent to cotrimoxazole. No isolate was resistant to cefotaxime, while one percent were resistant to ceftriaxone and two percent were resistant to ciprofloxacin (Prajapati et al., 2008).

In Patan Hospital, among 409 *S.* Typhi and 200 *S.* Paratyphi A isolates, highest resistance was observed for nalidixic acid (51 percent of *S.* Typhi and 75 percent of *S.* Paratyphi A isolates). Less than 4 percent of isolates tested were resistant to amoxicillin, chloramphenicol, cotrimoxazole, ciprofloxacin, ofloxacin and ceftriaxone in 2004 (Maskey et al., 2006).

Of 541 *S.* enteric Typhi and Paratyphi A isolates from 4,105 blood culture samples collected from patients with febrile illness visiting TUTH in 2004, 5 percent were resistant to two or more antibiotics. Among the MDR isolates for both serotypes, most isolates were resistant to ofloxacin (71 percent, n=20), followed by ampicillin (29 percent, n=8), ciprofloxacin (29 percent, n=8) and cotrimoxazole (25 percent, n=7). All isolates were susceptible to cefotaxime, ceftriaxone and imipenem, while all isolates were resistant to ampicillin and ciprofloxacin (Pokharel et al., 2006).

4.4 Urinary Tract Infections

Studies have illustrated that resistance of UTI causing agents to major antibiotics used to treat UTI have also increased. Some of the studies are described below:

In Kathmandu Medical College (KMC), analysis of 416 isolates of patients with confirmed UTIs showed that of the 384 Gram Negative isolates, resistance was reported to cefixime (50 percent), cotrimoxazole (50 percent), amoxicillin (48 percent), cefotaxime (47 percent) and ciprofloxacin (46 percent). Of the 327 *E. coli* isolates, 83

percent were resistant to amoxicillin, 60 percent were resistant to norfloxacin, 51 percent were resistant to cefixime and 49 percent were resistant to ciprofloxacin. Of the 32 Gram-positive isolates, 56 percent were resistant to erythromycin, 53 percent were resistant to norfloxacin, 44 percent were resistant to ciprofloxacin and 41 percent were resistant to cefotaxime. Among the 13 isolates of *E. faecalis,* 62 percent were resistant to norfloxacin, amoxicillin, ciprofloxacin and erythromycin, respectively in 2011 (Bhatt et al., 2013). Similarly, *E. coli* (20 percent) was the most common isolate (20 percent) of the total 680 urine samples in KMC with lowest resistance to cephalexin (30 percent), followed by cotrimoxazole (39 percent), norfloxacin (57 percent), ciprofloxacin (59 percent) and ofloxacin (60 percent). *K. pneumoniae*, the second most common isolate, was 26 percent susceptible to cephalexin, 52 percent susceptible to cotrimoxazole, and 64 percent susceptible to norfloxacin from June 2009 to February 2010 (Raza, Pandey, & Bhatt, 2011).

A total of 11,022 urine samples from patients visiting B. P. Koirala Institute of Health Sciences (BPKIHS) from August 2009 to August 2010 yielded Gram-positive (4 percent) and Gram-negative (19 percent) bacterial isolates. Gram-positive isolates included *S. aureus* (47 percent), *Enterococcus* spp. (34 percent), *E. faecalis* (18 percent) and Coagulase-Negative *Staphylococci* (1 percent). Ninety-four percent of the Gram-positive bacteria isolates were resistant to penicillin and 91 percent were resistant to nalidixic acid (Baral et al., 2013).

National Public Health Laboratory tested 602 *E. coli* isolates from 2005 to 2010. Out of the total, 56 percent of isolates were multi-drug resistant. Eighty percent of the *E. coli* isolates were resistant to amoxicillin, followed by cefixime (73 percent), amoxicillin-clavulanic acid (70 percent), nalidixic acid (69 percent), ceftazidime (63 percent) and cefotaxime (63 percent). Almost all of the antibiotics showed increasing resistance over the course of the study period (table 4-1). MDR isolates also increased over time, from 41 percent in 2006 to 88 percent in 2010 (Shakya et al., 2012).

Table 4-1: Antibiotic resistance of *E. coli*

Antibiotics	Percent resistance observed in each year				
	2006	**2007**	**2008**	**2009**	**2010**
Amoxicillin	67.2	83.7	72.9	83.7	82.17
Nitrofurantoin	1.5	19.1	11.2	7.57	30.4
Cotrimoxazole	49.3	65.1	61.5	61.9	57.6
Norfloxacin	52.7	53.3	45.0	50	53.5
Ciprofloxacin	33.7	47.9	50.5	51.6	53.2
Gentamicin	15.3	39	36.7	37.2	44.4
Ofloxacin	36.3	47.8	56.7	50.4	54.1
Ceftriaxone	16.3	32.2	31.7	25.7	35.2
Amoxycillin-clavulanic acid	25	57.1	60	88.5	90
Nalidixic Acid	72.7	67.7	71.9	66.6	63.2
Azithromycin	33.3	29.2	36.6	54.1	50
Cefixime	50	63.6	60	91.3	92.8
Ceftazidime	-	43.7	75.8	64.8	60.8
Cefotaxime	-	50	78.1	68.4	53.8

Source: (Shakya et al., 2012)

Among 208 *E. coli* isolates isolated from 250 samples at Kathmandu Model Hospital, 33 percent were susceptible to amoxicillin, 52 percent were susceptible to cotrimoxazole, and 63 percent were susceptible to ofloxacin. Among 14 *Enterococcus faecalis* isolates, the most common Gram-positive bacteria isolated, only 15 percent were susceptible to cloxacillin, followed by cephalexin (22 percent), norfloxacin (36 percent), ciprofloxacin (43 percent) and cotrimoxazole (43 percent) (Khatri, Basnyat, Karki, Poudel, & Shrestha, 2012). Similarly, of 219 bacterial isolates recovered from 710 urine samples in Kathmandu Model Hospital, 97 percent of the Gram-negative bacteria were resistant to ceftazidime, 92 percent were resistant to ceftriaxone, 73 percent to gentamicin, and 58 percent to amoxicillin. Only 12 percent and 13 percent of the Gram-negative bacteria were resistant to amikacin and nitrofurantoin respectively. Out of the 178 *E. coli* isolates, 56 percent showed resistance to amoxicillin, followed by cotrimoxazole (54 percent), norfloxacin (37 percent), ciprofloxacin (36 percent) and cefixime (30 percent). Additionally, 38 percent of *E. coli* isolates were confirmed to be resistant to three or more antibiotics in 2007 (Baral et al., 2012).

APUA Nepal conducted a study on urine isolates from 4 different hospitals to analyze the sensitivity patterns of *E. coli*. Of the 572 isolates tested at Tribhuwan University Teaching Hospital in 2007, 5 percent were susceptible to cephalexin, followed by amoxicillin (21 percent) and nalidixic acid (32 percent). Another study conducted at the same hospital on 726 *E. coli* isolates identified in urine in 2009 showed that only 11 percent of the isolates were sensitive to cephalexin and only 13 percent were sensitive to ampicillin. At Western Regional Hospital in Pokhara between 2007 and 2008, 48 isolates were identified from urine samples, of which 8 percent were susceptible to cotrimoxazole and 22 percent were susceptible to nalidixic acid. All isolates were susceptible to ceftriaxone, cephalexin and chloramphenicol. Of the 48 isolates tested at Mechi Zonal Hospital, Jhapa in 2010, only 21 percent of the isolates were susceptible to ampicillin, while 83 percent were susceptible to amikacin. Of the 55 isolates from urine tested at Koshi Zonal Hospital, Biratnagar, only 18 percent were susceptible to cotrimoxazole and 20 percent were susceptible to ciprofloxacin. Ninty-five percent of the isolates were resistant to nitrofurantoin (APUA, 2012).

APUA Nepal conducted a similar study on the sensitivity patterns of *E. coli* from pus samples in Tribhuwan University Teaching Hospital, Kathmandu. Of the 135 samples analyzed in 2007, 9 percent of the isolates were susceptible to

cephalexin, while 70 percent were susceptible to gentamicin. In 2009, of the 138 samples tested, only 7 percent were susceptible to ampicillin and only 9 percent were susceptible to cephalexin. Eighty-six percent of the isolates were susceptible to amikacin (APUA, 2012).

In Kanti Children's Hospital, examination of 538 pathogenic isolates from 1,878 midstream urine samples from children showed that among *E. coli* isolates, resistance was highest for cephalexin (97 percent), followed by nalidixic acid (78 percent), cotrimoxazole (77 percent) and norfloxacin (64 percent). *E. coli* isolates were sensitive to amikacin (62 percent), chloramphenicol (50 percent) and nitrofurantoin (47 percent). All *Proteus* spp. isolates were resistant to cephalexin and nitrofurantoin. A total of 42 percent of the isolates were resistant to nalidixic acid and 38 percent were resistant to cotrimoxazole. *Proteus* spp. isolates were 80 percent susceptible to both cefotaxime and ceftriaxone, and 75 percent susceptible to both ciprofloxacin and ofloxacin. Similarly, 75 percent of *Klebsiella* spp. isolates were resistant to both cotrimoxazole and nitrofurantoin, followed by cefotaxime (67 percent) and ceftriaxone (60 percent). Eighty-eight percent of *Klebsiella* spp. isolates were susceptible to ofloxacin in 2007 (Rai, Upreti, Rai, Shah, & Shrestha, 2008).

4.5 Sexually Transmitted Infections

Gonorrhea

Antibiotic resistance is also observed in gonococcal infection. Two studies showing AMR status of *N. gonorrhoeae* are listed below:

In a retrospective study from Manipal Teaching Hospital in Pokhara conducted from 2004 to 2010, 40 specimens from urethral, cervical and conjunctival discharges were collected from suspected cases of gonococcal infections. Over the course of the study period, isolates were resistant to penicillin (68 percent), followed by tetracycline (45 percent) and ciprofloxacin (43 percent). None of the isolates were resistant to ceftriaxone over the course of the study. Resistance to penicillin increased over time, from 40 percent of isolates in 2004 to 100 percent of isolates in 2010 (Bhatta et al., 2012).

A 2009 study at the Nepal Medical College and Teaching Hospital examined 30 isolates of *N. gonorrhoeae* obtained from male patients with suspected acute gonococcal urethritis.

Resistance was found to be highest for penicillin (60 percent), followed by tetracycline (33 percent) and ciprofloxacin (20 percent). None of the isolates were resistant to ceftriaxone (Bhargava, Shakya, Mondal, & Rijal, 2010).

4.6 Tuberculosis

The National TB Control Program 2011-2012 Annual Report noted an increasing prevalence of drug resistance rates among new TB cases. Multi-drug resistance (MDR) surveillance showed a prevalence of 1 percent in 1996-1997 and 3 percent in 2010-2011 among newly diagnosed cases. For those previously treated, the prevalence of MDR TB in 2011 was 18 percent. Additionally, the prevalence of XDR-TB cases among those with MDR-TB was 8 percent (NTC, 2012).

A study from 2007-2008 conducted by the German-Nepal Tuberculosis Project (GENETUP) in Kalimati, Kathmandu, tested 141 *Mycobacterium tuberculosis* isolates. Twenty-two percent of isolates were resistant to at least one drug and 9 percent were MDR. Six percent of isolates were resistant to all 4 drugs (table 4-2) (Regmi, Shrestha, & Katuwal, 2013).

Table 4-2: Resistance of *M. tuberculosis* isolates

Characteristics	Drugs	Resistance	
		Number	Percent
Total (n=141)		**31**	**21.9**
Mono resistance	RMP	17	12.1
	INH	19	13.4
	EMB	11	7.8
	SM	24	17.1
Poly resistance	RMP+INH	12	8.5
	RMP+SM	13	9.2
	RMP+EMB	10	7.1
	INH+EMB	8	5.6
	INH+SM	12	8.5
	SM+EMB	10	7.1
	RMP + INH+SM	10	7.1
	RMP+SM+EMB	10	7.1
	INH+SM+EMB	8	5.6
	RMP+INH+EMB	8	5.6
	RMP+INH+SM+EMB	8	5.6
MDR		12	8.5
Abbreviations: RMP=rifampin, INH=isoniazid, EMB=ethambutol, SM=streptomycin			

Source: (Regmi et al., 2013)

Of the 110 isolates from 110 previously treated and new smear-positive pulmonary TB patients analyzed at National Tuberculosis Centre, Thimi, Bhaktapur from 2011 to 2012, 58 percent were sensitive to all drugs and 42 percent were resistant to one or more drugs. A total of 31 percent of isolates were MDR, and 23 percent of all isolates were resistant to all four drugs. Depending on the type of test used, resistance to isoniazid ranged from 33-35 percent and to rifampin from 31-32 percent. For streptomycin, resistance ranged from 31-33 percent, and to ethambutol ranged from 26-27 percent (Lamsal et al., 2013).

A total of 113 *M. tuberculosis* isolates collected from the National Tuberculosis Center and the Supranational Reference Laboratory, Germany during 2009 to 2010 found that resistance to isoniazid ranged from 45-46 percent, to rifampin from 35-36 percent, to streptomycin from 31-32 percent, and to ethambutol was about 12 percent (Sah, Bhatta, Ghimire, & Sherchand, 2012). Whereas of 121 *M. tuberculosis* isolates, resistance to isoniazid ranged from 23-30 percent, to streptomycin from 20-26 percent, and to ethambutol from 17-19 percent, while rifampin resistance was about 22 percent during 2008-2009 (Mandal, Basnyat, Khadka, & Bhatta, 2010).

A total of 109 MDR isolates and 49 non-MDR isolates were collected from 158 patients living in 9 different cities throughout Nepal as part of GENETUP from 2007 to 2010. Of the 109 MDR isolates, 94 percent were resistant to three or more first-line anti-TB drugs and 72 percent were resistant to all four. Of the 49 non-MDR isolates, 84 percent were susceptible to all first line drugs (Poudel et al., 2012). Similarly, GENETUP Kathmandu and Garhwal University analyzed 20 *M. tuberculosis* isolates and found that 85 percent of the isolates were resistant to streptomycin and 60 percent were resistant to ethambutol in 2008 (Bhatt, Bhatt, & Shrestha, 2011). In 2006, 4 percent of the isolates from 550 patients showed multi-drug resistance. Of the MDR strain, 85 percent were resistant to streptomycin and 60 percent were resistant to ethambutol (Bhatt, Bhatt, & Shrestha, 2010).

4.7 Healthcare acquired infections

Methicillin-resistant *Staphylococcus aureus*

Methicillin-resistant *S. aureus* (MRSA) is a common cause of hospital and community acquired infections. Various studies have shown the high prevalence of MRSA in hospitals in Nepal and its growing resistance to commonly used antibiotics. Studies on hospital and community acquired MRSA are summarized below:

In Kathmandu Medical College Teaching Hospital, 26 percent of 111 *S. aureus* isolates from pus, wound swabs and urine samples were identified as MRSA and 74 percent were identified as methicillin-sensitive *S. aureus* (MSSA). Of the 29 MRSA isolates, 76 percent were also resistant to cephalexin and 17 percent to ciprofloxacin. Of the 82 MSSA isolates, resistance was highest to penicillin (100 percent), cephalexin (31 percent) and cotrimoxazole (20 percent). Only 2 percent of MSSA isolates were resistant to amikacin in 2009-2010 (Pandey, Raza & Bhatta, 2013).

In Chitwan Medical College Teaching Hospital, a total of 600 *S. aureus* isolates from skin and soft tissue were analyzed of which 408 (68 percent) were confirmed as MRSA. Ninety-six percent of MRSA isolates were resistant to cotrimoxazole, followed by chloramphenicol (92 percent) and erythromycin (75 percent). However, susceptibility was observed to vancomycin in 78 percent of the isolates, followed by amoxycillin-clavulanic acid (47 percent), gentamicin (45 percent) and nitrofurantoin (45 percent) in 2008 to 2009 (Jha, 2010). Similarly, resistance of *S. aureus* isolates (n=348) was 40 percent to methicillin of which 82 percent of strains were resistant to cephalexin, 71 percent to ciprofloxacin, 38 percent to gentamicin, 32 percent to cefotaxime and 20 percent to cotrimoxazole from 2007 to 2009 (Sanjana, Shah, Chaudhary, & Singh, 2010).

Of 149 *S. aureus* isolates from blood, pus, swabs, plural fluid and urine samples at Tribhuvan University Teaching Hospital in Kathmandu, 45 percent were MRSA. Among the 149 isolates, 95 percent were resistant to chloramphenicol, 93 percent to rifampicin, 62 percent to fluoroquinolone and 53 percent to erythromycin. All the isolates were susceptible to vancomycin and teicoplanin. Among the MRSA isolates, all were resistant to fluoroquinolone, followed by erythromycin (95 percent), gentamicin (94 percent) and cotrimoxazole (85 percent). All of the MRSA isolates were susceptible to nitrofurantoin from 2007 to 2008 (Shrestha, Pokhrel, & Mohapatra, 2009).

In Universal College of Medical Sciences Teaching Hospital, Bhairahawa 162 *S. aureus* isolates from blood, pus, swabs, aspirate, fluids, and urine were tested from 2005 to 2007. Sixty-nine percent of these isolates were MRSA, of which 40 percent were multi drug resistant. Isolates were primarily resistant to cotrimoxazole

(73 percent) and erythromycin (69 percent). All were susceptible to vancomycin (Tiwari, Das, Sapkota, Sivrajan, & Pahwa, 2009).

MRSA carriage studies

Researchers from the National Medical College Teaching Hospital, Birgunj, conducted a study in 2008 on 14 *S. aureus* isolates from nasal samples from patients, visitors and health care personnel. Out of the 14 *S. aureus* isolates, 57 percent were methicillin resistant. The prevalence rate of MRSA was 7 percent in the study population. Of the MRSA isolates, 38 percent were resistant to ciprofloxacin, tetracycline and gentamicin. All MRSA isolates were sensitive to erythromycin and vancomycin (Shakya, Shrestha, & Mitra, 2010).

A 2007 study conducted at the Western Regional Hospital of Pokhara assessed MRSA prevalence in 57 nasal swabs from healthy school children and 45 clinical samples from patients admitted to the hospital positive for *S. aureus*. Researchers found that among the isolates from healthy children, 56 percent were MRSA, while among the isolates from hospitalized patients, 76 percent were MRSA. Of the *S. aureus* isolates from healthy children, 69 percent were resistant to cloxacillin and 41 percent were resistant to ofloxacin. Among *S. aureus* isolates from hospitalized patients, 85 percent were resistant to cloxacillin, followed by tetracycline (44 percent), ofloxacin (44 percent) and ciprofloxacin (24 percent) (Rijal et al., 2008)

Conjunctivitis

A prospective study was conducted from January 2009 to December 2010 on clinically diagnosed cases of acute infective conjunctivitis in Kathmandu University Hospital, Dhulikhel. Of the 11 cases with bacterial growth, only one isolate was susceptible to ceftazidime, two isolates to ofloxacin and three isolates to cefazolin and norfloxacin, respectively. All isolates were susceptible to gentamicin and chloramphenicol (Sthapit, Tuladhar, Marasini, Khoju, & Thapa, 2012).

Diabetic foot infections

In a study conducted from 2004 to 2005, researchers examined bacterial isolates of patients admitted to Bir Hospital, Kathmandu with diabetic foot infections. Among 18 Gram-negative isolates, 78 percent were resistant to cephalexin, 72 percent were resistant to amoxicillin-clavulanic acid, and 50 percent were resistant to ciprofloxacin. Among 24 Gram-positive isolates, 92 percent were resistant to ampicillin and 25 percent were resistant to erythromycin. Only one isolate showed resistance to gentamicin, and two isolates were resistant to ciprofloxacin and cloxacillin, respectively (Sharma, Khadka, Joshi, & Sharma, 2006).

Neonatal Citrobacter

While Citrobacter is not one of the most common organisms that cause nosocomial neonatal infections, a study analyzing resistance in these infections has been conducted. From January to March 2010, researchers at a NICU in a hospital in Kathmandu analyzed 12 *Citrobacter* spp. isolates from neonates admitted to the NICU. All of the isolates were multi-drug resistant, showing susceptibility only towards quinolones. None of the isolates were sensitive to ampicillin, piperacillin, cephalexin or cotrimoxazole. Isolates were susceptible to ofloxacin (92 percent), ciprofloxacin (83 percent) and norfloxacin (83 percent) (Khadka, Thapa, & Mahat, 2011).

ANIMALS
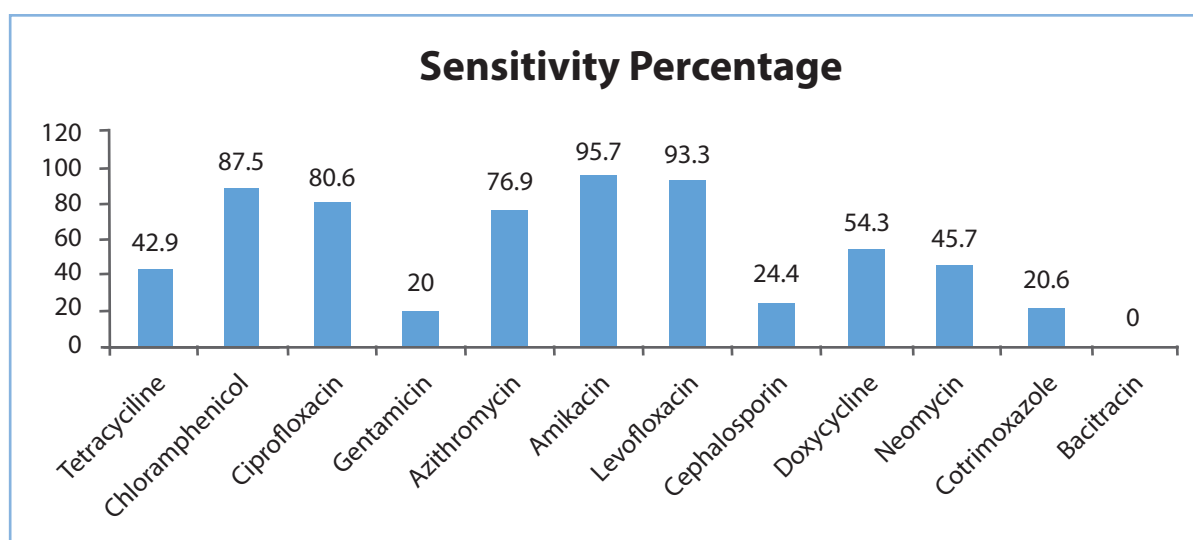
4.8 Antibiotic resistance in animals

Relatively few studies of bacterial infections in livestock and other food producing animals in Nepal have also reported on the resistance profiles of the bacterial contaminants. The following section summarizes studies that have included information on resistance.

4.8.1 Poultry

A total of 291 samples were collected from the postmortem unit of the National Avian Disease Investigation Laboratory, Bharatpur, Chitwan from 2011 to 2012 for bacterial culture. Bacterial isolates were identified in 168 of the samples, which were also processed for antibiotic sensitivity. All bacteria were resistant to bacitracin. Bacteria were highly sensitive to amikacin, levofloxacin, chloramphenicol, ciprofloxacin and azithromycin (figure 4-3) (CVL, 2012).

Figure 4-3: Sensitivity of bacterial isolates to common antibiotics

Source: (CVL, 2012)

A study of 200 poultry meat samples from retail shops in Kathmandu in 2007 investigated the prevalence of multi-drug resistant *Salmonella* spp. Overall prevalence of *Salmonella* spp. in Kathmandu valley was 13 percent. Among 26 isolates of *Salmonella*, 50 percent belonged to serogroups B, D and E. Isolates showed resistance to tetracycline and nalidixic acid. Multi-drug resistance was observed in only 4 percent of *Salmonella* isolates (Shrestha, Pokharel, & Manandhar, 2008).

A study was carried out among 181 birds in Pokhara to assess the prevalence of salmonellosis in poultry in 2009. The findings showed a salmonellosis prevalence of 34 percent among the sampled birds. A total of 64 samples from infected birds' livers, spleens, hearts, lungs, gallbladders and intestines were collected from postmortem cases. Antimicrobial sensitivity tests showed that all isolates were resistant to ampicillin and 71 percent of isolates were resistant to cefotaxime (Shrestha, Shrestha, & Devkota, 2010).

E.coli

A study conducted in seven hatcheries in Chitwan district from October to December 2012 reported that 10 percent of the total sample (n=140) was infected with *E. coli*. Antibiotic resistance testing showed that 93 percent of the isolates were resistant to amoxicillin. Resistance was also observed to erythromycin (86 percent), tetracycline (86 percent), enrofloxacin (50 percent), gentamicin (43 percent) and ciprofloxacin (36 percent) (Shah, 2013).

4.8.2 Cattle

Clinical Mastitis

A total of 377 cattle and buffalo samples were examined from 2011 to 2012 in the microbiology unit of the Regional Veterinary Laboratory, Pokhara, of which 241 samples were tested for clinical mastitis. Out of the total samples tested, 66 percent were positive for a pathogen. Isolated bacteria included *E. coli* (25 percent), *Klebsiella* spp. (11 percent), *Staphylococcus* spp. (10 percent), *Streptococcus* spp. (14 percent), *Bacillus* spp. (8 percent) and others (15 percent). Seventeen percent of the samples showed no growth. In antibiotic sensitivity testing, the isolates demonstrated resistance to oxytetracycline, cotrimoxazole and amoxicillin/ampicillin (CVL, 2012).

Samples of various animal species were subjected to microbiological examination by the Regional Veterinary laboratory, Dhangadhi, from 2011 to 2012. Bacteria identified among all animal groups included *Streptococcus* spp. and *Staphylococcus* spp. (table 4-3).

Antibiotic sensitivity tests of the milk samples showed that enrofloxacin was the most effective, followed by cloxacillin, gentamicin, ampicillin and penicillin (CVL, 2012).

Table 4-3: Microbiological culture results from animal samples

Animal	Sample	Number of sample	Bacteria identified
Cow	Milk	97	*Streptococcus* spp., *Staphylococcus* spp., *Corynebacterium* spp.
Buffalo	Milk	73	*Streptococcus* spp., *Staphylococcus* spp., *Corynebacterium* spp., *Pseudomonas* spp.
Goat	Nasal and vaginal swab	23	*Streptococcus* spp., *Staphylococcus* spp., *Bacillus* spp.
Poultry	Liver	24	*E. coli, Streptococcus* spp., *Staphylococcus* spp., *Aspergillus* spp., *Penicillium* spp., *Candida* spp.
	Lungs	7	*E. coli, Streptococcus* spp., *Staphylococcus* spp., *Corynebacterium* spp.
	Intestinal swab	4	*Streptococcus* spp., *Staphylococcus* spp., *Corynebacterium* spp.,

Source: (CVL, 2012)

Table 4-4: Antibiotic sensitivity tests on antibiotics used to treat mastitis in cattle

S.N	Bacterial species isolated	No. of isolates tested	Antibiotic sensitivity percentage							
			G	T	En	Ampi	Am	Cp	Dx	Co
1	*E. coli*	150	94	97	96	77	70	96	90	95
2	*Staphylococcus* spp.	185	97	92	79	67	70	98	89	91
3	*Streptococcus* spp.	12	75	78	75	66	_	85	_	_
4	*Bacillus* spp.	12	80	80	80	66	_	75	_	_
5	*Klebsiella* spp.	5	80	81	83	66	_	82	_	_
6	*Pseudomonas* spp.	2	50	_	50	50	_	100	_	_

Abbreviations: G=gentamicin,   T=tetracycline,   En=   enrofloxacin,   Ampi=ampicillin, Am=amoxicillin, Cp=ciprofloxacin, Dx=doxycycline, Co=cotrimoxazole, - means not used

Source: (CVL, 2012)

The California mastitis test (CMT) and a bacteriological culture were conducted on a total of 404 milk samples by the Central Veterinary Laboratory, Tripureshwor, Kathmandu from 2011 to 2012. Of the total samples, 79 were found to be negative. Antibiotic sensitivity tests were conducted on all samples that were positive for bacteria. Of the antibiotics tested, gentamicin and tetracycline were found to be the most effective for the treatment of mastitis in cattle, followed by ciprofloxacin (table 4-4) (CVL, 2012).

From 2011 to 2012, the Regional Veterinary Laboratory, Biratnagar examined 784 milk samples, of which 375

had a positive CMT result. Isolated bacteria included *E. coli, Staphylococcus* spp., *Streptococcus* spp., *Klebsiella* spp., *Pseudomonas* spp. and *Enterobacter* spp. Among the isolates, 79 percent were resistant to cefotaxime, 67 percent were resistant to chloramphenicol, 54 percent were resistant to tetracycline, 44 percent were resistant to gentamicin, 35 percent were resistant to ciprofloxacin and 20 percent were resistant to enrofloxacin (CVL, 2012).

Incidence of subclinical mastitis (SCM) in Biratnagar sub-metropolitan city and the nearby villages of Morang and Sunsari districts were investigated from October 2006 to March 2007. Milk samples from 190 cattle were tested, of

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which 14 percent of animals were affected. *Staphylococci* were the most prevalent bacterial isolates found in the culture of positive samples (38 percent). Eighty-eight percent of the isolates were sensitive to enrofloxacin (Yadav & Deo, 2010).

The study conducted by Dhakal and colleagues on milk from 355 Murrah buffaloes with clinical and sub clinical mastitis found fifty-five isolates of *Staphylococcus* spp., 23 isolates of *Streptococcus* spp. and 149 isolates of coliforms with resistance to antibiotics. Mastitis pathogens have developed significant resistance to ampicillin and penicillin and showed increasing rates of resistance to gentamicin and enrofloxacin (table 4-5).

Table 4-5: Antibiotic sensitivity of clinical mastitis bacteria

Year (number of isolates)	Percent Sensitivity						
	G	Cl	Ex	P	Am	Str	T
Coliform **(149**)							
2002 (60)	90	79	96	ND	ND	50	89
2003 (36)	93.8	71	95	ND	ND	87	92
2004 (20)	87.2	84	93	ND	ND	79	85
2005 (33)	84.8	87	92	ND	ND	84	85
Staphylococcus spp. **(55)**							
2002 (18)	92.5	90	93	80.5	70.7	ND	79
2003 (19)	90.6	84	92	75	69.4	ND	83
2004 (12)	73.3	64	88	68.4	55.6	ND	69
2005 (6)	71.4	57	80	60	53.3	ND	57
Streptococcus spp. **(23)**							
2002 (4)	87.5	100	100	77.8	66.7	ND	100
2003 (7)	88.9	86	91	90.9	70	ND	91
2004 (6)	100	100	83	100	83.3	ND	100
2005 (6)	83.3	78	83	75	66.7	ND	67
Abbreviations: G=gentamicin, Cl=chloramphenicol, Ex=enrofloxacin, P=penicillin, Am=ampicillin, Str=streptomycin, T=tetracycline, ND=not determined							

Source: (Dhakal, Dhakal, Koshihara, & Nagahata, 2007)

E. coli

Researchers conducted a study on 63 samples collected from various restaurants in Bharatpur municipality from September to December 2012. It was found that the prevalence of *E. coli* in minced buffalo meat samples was 21 percent. All the *E. coli* isolates were resistant to ampicillin, followed by tetracycline (38 percent), cotrimoxazole (23 percent), chloramphenicol (8 percent), gentamicin (8 percent) and nitrofurantoin (8 percent) (Deubanjar, 2012).

MRSA

A cross-sectional study was carried out from October 2012 to January 2013 among 400 milk samples from 100 cattle in Pokhara Valley. Sixty-four percent of the samples showed the growth of Gram-positive bacteria, 33 percent showed Gram-negative bacteria and the remaining 3 percent showed no growth. The prevalence of *S. aureus* was 30 percent, and for MRSA it was 11 percent. Among the *S. aureus* isolates, 38 percent were resistant to cefoxitin (Joshi, 2012).

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Chapter **5**:
Antibiotic
Supply Chain

HUMANS

5.1 Antibiotic Use in Human Health

According to the World Health Organization (WHO), "more than half of all medicines are prescribed, dispensed or sold inappropriately worldwide" (WHO, 2010, 2013). In developing countries, less than 40 percent of patients in the public sector and 30 percent in the private sector are treated according to clinical guidelines (WHO, 2010). Irrational prescription and use of antibiotics has been identified as one of the many drivers of antibiotic resistance, and it has been observed among health professionals in Nepal (DDA, 2011). This section reviews current studies on antibiotic prescription practices in Nepal.

5.1.1 Antibiotic Prescription and Use

Many studies have shown that antibiotics are highly prescribed in Nepal. According to Pharmaceutical Horizon of Nepal (PHON), amoxicillin was the top selling drug in Nepal in 2004-05 (PHON, 2006). Studies listed below also showed that antibiotics are commonly prescribed in Nepal. Ampicillin, amoxicillin, ceftriaxone and gentamicin are the most commonly prescribed antibiotics in the studies listed below. Most of the studies reviewed were conducted at Manipal Teaching Hospital, a part of the Manipal College of Medical Science, located in Fulbari, Pokhara. Other studies were conducted at BP Koirala Institute of Health Sciences at Dharan and at Chitwan Medical College. All studies showed high rates of antibiotic prescription, and in some cases more than two antibiotics were prescribed to a single patient.

Gyawali and colleagues conducted a six-month study in 2006 analyzing the prescription of injectable and intravenous fluids to 938 patients from Manipal Teaching Hospital. A total of 8,203 drugs were prescribed to the patients, with a mean of 8.75 per patient. Of the 938

patients, 535 (57 percent) received a parenteral anti-microbial, 252 (27 percent) received a prescription for a single injectable anti-microbial, and 161 (17 percent) received two injectable antimicrobials. Among the patients who received intravenous antimicrobials, the most frequently prescribed were metronidazole (32 percent), gentamicin (30 percent), ampicillin (28 percent) and cefotaxime (28 percent). Of the total drugs prescribed, ciprofloxacin (32 percent) and a combination of beta lactams, gentamicin and metronidazole (44 percent) were more commonly prescribed in the department of obstetrics and gynecology, compared to the departments of medicine, pediatrics and surgery, while amoxicillin/clavulanic acid was most frequently prescribed in the department of medicine (Gyawali, Shankar, Saha, & Mohan, 2009).

In 2008, a prospective study analyzed drug prescribing and dispensing patterns for patients visiting outpatient pharmacy at Manipal Teaching Hospital. Overall there were 4,231 pharmacy visits and 10,591 prescribed drugs, for an average of 2.5 drugs per visit. Antimicrobials accounted for the highest percentage of drugs prescribed (20 percent) followed by anti-inflammatory and analgesic drugs (15 percent). Authors also found that the percentage of adequately labeled drugs was just 2 percent (Ghimire, 2009).

Box 5-1: Guidelines for labeling Drugs

According to the guidelines, the brand or generic name of every medicine should be written in English and Nepali. The batch number, date of manufacture and expiration, medicine group (Ka, Kha, Ga), and information regarding dosage, precautions, and the method of reconstitution should be written in Nepali. Price, batch number, and manufacture and expiration dates can be written in English (Guidelines for labeling Drugs, 2007).

The prescribing patterns of fluoroquinolones at Manipal Teaching Hospital were analyzed over a five-month period from 2003 to 2004. During this period, 263 patients were prescribed fluoroquinolones. The most commonly prescribed fluoroquinolones were ciprofloxacin (239 patients) and norfloxacin (20 patients). Fluoroquinolones were commonly co-prescribed with other antibiotics including metronidazole (35 percent of all patients),

gentamicin (13 percent of all patients) and ampicillin (6 percent of all patients). Fluoroquinolones were prescribed for surgical antibiotic prophylaxis in 110 patients (42 percent), for bacteriologically proven infections (BPI) in 47 patients (18 percent) and for non-BPI in 61 patients (23 percent). The authors found that fluoroquinolones were inappropriately prescribed in 110 patients (42 percent), and 45 of the inappropriate prescriptions were for patients that had viral infections. The authors also found that antibiotics contributed to 57 percent of total drug costs (Shankar et al., 2007).

A drug use study conducted from December 2003 to March 2004 at Manipal Teaching Hospital looked at antibiotic prescriptions given to 356 patients admitted to pediatric wards. Acute gastroenteritis was the most common reason for hospitalization (17 percent). The 356 patients were prescribed a total of 1,614 drugs, with a mean of 4.5 drugs per patient. Antibiotics were the most commonly prescribed drugs (23 percent), followed by antipyretic and anti-inflammatory medication (11 percent). Of the nine most commonly prescribed drugs, three were antibiotics: ampicillin (10 percent of the total drugs), cefotaxime (3 percent of the total drugs) and gentamicin (2 percent of the total drugs). The study found that antibiotics were not prescribed in only 30 percent of admissions. One antibiotic was prescribed in 147 admissions (41 percent), two were prescribed in 80 admissions (23 percent), and three were prescribed in 19 admissions (5 percent). In 44 patients, antibiotics were prescribed for viral infection, and in 41 patients they were prescribed without a definite diagnosis. In total, the authors reported that antibiotics were inappropriately prescribed to 93 patients (26 percent). The authors also reported that antibiotic prescriptions contributed to 53 percent of the total drug costs (Shankar, Upadhyay, Subish, Dubey, & Mishra, 2006).

Another study conducted by Lamichhane and colleagues assessed prescribing patterns among patients at outpatient departments in Manipal Teaching Hospital in 2004. Among a random selection of 1,600 patients, 1,261 patient files were analyzed, excluding patients whose medical records were not available. The most common reasons for hospital visits were for upper respiratory tract infections and acid peptic disease. Antibiotics were the most commonly prescribed group of drugs, accounting for 17 percent of prescriptions. The most commonly prescribed groups of antibiotics were the penicillin group (37 percent of the total antibiotics prescribed) followed by quinolones (20 percent), macrolides (12 percent), tetracyclines (9 percent) and aminoglycosides (5 percent).

Of the most commonly prescribed drugs, amoxicillin was the third most common (3 percent) and ampicillin with cloxacillin was the sixth most common (2 percent) (Lamichhane, Giri, Pathak, Panta, & Shankar, 2006).

Researchers conducted a six-month analysis of prescriptions for 200 pediatric dental patients at BP Koirala Institute of Health Sciences in Dharan. In total, 357 drugs were prescribed, with an average of 1.78 drugs per patient. Of the 357 prescriptions, 133 (37 percent) were antimicrobials. Penicillin was the most commonly prescribed antimicrobial (n=120), followed by amoxicillin (n=114), metronidazole (n=13) and ampicillin and cloxacillin (n=6) (Paudel, Sah, & Jaiswal, 2010).

Shankar and colleagues conducted an observational study from 2005 to 2006 at Manipal Teaching Hospital to assess drug administration patterns among older patients. Among 548 patients enrolled in the study, the total number of drugs prescribed was 4,236, averaging 7.73 drugs per patient. Antibiotics were prescribed to 287 of the enrolled patients (52 percent). Only 30 of those patients were prescribed antibiotics for bacteriologically-proven infections (BPI). The mean cost of antibiotics was 681.52 Nepalese rupees, accounting for about 40 percent of the total amount of money spent on drugs in this study (P. R. Shankar, Upadhyay, Subish, Bhandari, & Das, 2010).

Researchers conducted a retrospective study analyzing antimicrobial chemotherapy in hospitalized patient at BP Koirala Institute of Health Sciences in 2006. Among 428 hospitalized patients, 274 patients (64 percent) received a total of 584 antimicrobial prescriptions, averaging 2.13 per patient. Sixty-six percent of prescriptions were for therapeutic purposes, while 24 percent of prescriptions were for prophylactic purposes. The authors determined that 10 percent of patients were given antimicrobials inappropriately. The most commonly prescribed classes of antimicrobials were cephalosporin (34 percent), nitroimidazole (16 percent) and macrolides (14 percent). Ceftriaxone was the most commonly prescribed antimicrobial agent (30 percent), followed by metronidazole (16 percent) and azithromycin (13 percent). A total of 72 patients (26 percent) received one antimicrobial, 118 (43 percent) received two and 84 (31 percent) received three or more. Additionally, the authors found that only 26 patients (10 percent) received a culture and sensitivity test (Paudel, Sharma, & Das, 2008).

A study analyzed antimicrobial prescriptions among patients in a dental outpatient department of Chitwan Medical College Teaching Hospital, Bharatpur from 2011 to 2012. A total of 1,173 prescriptions were given

for 2,709 drugs, with an average of 2.3 drugs per patient. Of the 1,173 prescriptions, 837 (71 percent) included antimicrobials; the most commonly prescribed type of medication. The most commonly prescribed antibiotic was amoxicillin (31 percent of patients), followed by metronidazole (21 percent of patients) and ampicillin and cloxacillin (15 percent of patients) (Sah & Kumar, 2012).

Another study analyzed antibiotic prescription patterns among 339 outpatients at the Chitwan Medical College Teaching Hospital, Bharatpur in 2008. Researchers found that 955 drugs were prescribed, with an average of 2.81 drugs per patient. The most commonly prescribed drugs were antibiotics (17 percent), followed by drugs for peptic ulcer syndrome (15 percent). Azithromycin, ciprofloxacin and amoxicillin were the most frequently prescribed antibiotics. Of the 158 antibiotic prescriptions, the most common classes of antibiotics were macrolides (41 percent), fluoroquinolones (28 percent) and penicillin (20 percent). Of the 149 patients who were prescribed antibiotics, 9 were given a prescription for two antibiotics. Antibiotics were prescribed for therapeutic purposes for 103 patients (69 percent) and prophylactically for 46 patients (31 percent), but no patients had a bacterial confirmation (Kumar, Shaik, Kathi, Deka, & Gambhir, 2010).

In a five month long study conducted at the Armala sub health post, Kaski district, 20 percent of 1,375 patients visited the health facility for Acute Respiratory Infections (ARI). Other common causes for attending the facility included wounds, trauma and injuries (9 percent), acid peptic disease (6 percent), skin infections (5 percent), dysentery (5 percent), scabies (4 percent) and enteric fevers (3 percent). During 1,464 visits, 2,198 drugs were prescribed with a mean of 1.5 drugs per prescription. Among the total prescribed drugs, 46 percent were antibiotics. The highest number of antibiotics were prescribed to ARI patients (199 patients) followed by those with wounds and traumatic injuries (111 patients), skin infections (65 patients) and enteric fever (42 patients). Cotrimoxazole was the most commonly prescribed antibiotic (12 percent) (Shankar et al., 2005).

5.1.2 Antibiotic Sales

According to DDA, 45 Nepalese pharmaceutical companies produce allopathic medicines for human use and 8 Nepalese pharmaceutical companies produce veterinary medicines in Nepal (DDA, 2012).
Antibiotic use has been steadily increasing in Nepal over time. A study conducted by Pharmaceutical Horizon of Nepal (PHON) from 2005 to 2006 collected data from various public and private institutions. The

study showed that sales of allopathic drugs had a retail value of 63.9 million USD for private importers and of 40.85 million USD for domestic industries (table 5-1) (PHON, 2006).
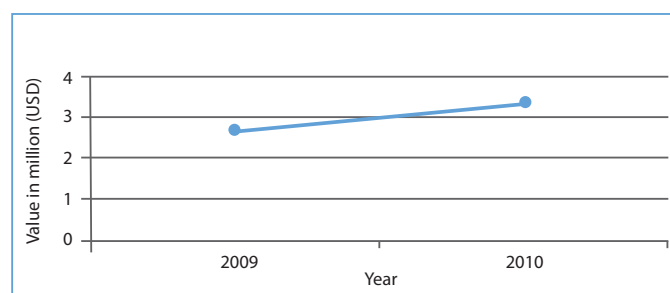
Table 5-1: Retail value of drugs sold in Nepal (2005-2006)

System	Retail sales value in millions, USD	
	Private importers	Domestic industries
Allopathic	63.9	40.85
Ayurvedic/ Unani	4.4	3.16
Veterinary	2.5	1.54
Homeopathic	0.056	-

Source: (PHON, 2006)

The quantity of antibiotics imported by Nepal has increased over time. Antibiotics and their derivatives worth 2.7 million USD were imported in 2009. In 2010, the import value increased to 3.3 million USD (Figure 5-1).

Figure 5-1: Value of imported antibiotics and their derivatives (USD)

Source: (http://www.indexmundi.com/trade imports/?country=np&commodity=294190)

5.1.3 Antibiotic Consumption

Amoxicillin was the top selling drug in 2005-06 among domestic industries (table 5-2). Sixty-five percent of drug consumption was attributed to public and private sector imports. The public sector provided 9 percent of the total drugs consumed in Nepal, while domestic industries produced 35 percent of the medicines consumed. The rest of the drugs are obtained through international imports (PHON, 2007).

Table 5-2: Top 15 selling drugs

1. Amoxicillin	6. Ciprofloxacin	11. Iron Preparations
2.Vitamin Preparations	7. Methyl ergometrine	12. Ampicillin + Cloxacillin
3.Topical Skin Preparations	8. Large Volume Parenteral	13. Ofloxacin
4. Cough Preparations	9. Cefadroxil	14. Ibuprofen + Paracetamol
5. Diclofenac	10.Metronidazole + Diloxanide	15. Vaccines, Sera and Toxoids

Source: (PHON, 2006)

Total consumption of antibiotics in 2005-06 was worth 33.83 million USD, of which 49 percent was produced by domestic industries. Amoxicillin was the top-selling antibiotic, followed by ciprofloxacin, cefadroxil and metronidazol with diloxanide (PHON, 2006).

5.2 Antibiotic Supply Chain

Government of Nepal distributes certain essential medicines through government health facilities for free. These essential medicines are procured by the logistics management division (LMD) upon the receipt of requisition orders from MoHP's divisions and health facilities. The LMD carries out procurement through an international competitive bidding process in accordance with World Bank guidelines or through a national competitive bidding process according to Nepal's public procurement act and regulations.

Box 5-2: Public Procurement Act - 2007 & Public Procurement Regulations - 2007

The Public Procurement Act - 2007
The Procurement Act was created in order to make the public procurement process more transparent. It determines the procedure to be followed in public procurement and promotes competition, transparency, honesty, accountability and reliability. The act provides equal opportunities to the producers, sellers, suppliers, entrepreneurs and service providers to participate in public procurement processes (The Public Procurement Act, 2007).

The Public Procurement Regulations - 2007
The Public Procurement Regulations outline the planning and cost estimation process for procurement. The regulation state that all procurement related

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plans and budgets must be prepared by a public entity. They also regulate the selection of procurement contracts, qualification criteria, technical capability and technical specifications and provisions related to bidding and consultancy services (The Public Procurement Regulations, 2007).

5.2.1 Channels for Drug Procurement and Distribution

Logistics management division (LMD) was established by the MoHP in 1997. LMD is responsible for all logistic activities, including purchase and supply of equipment, essential drugs, contraceptives and vaccines for health facilities across the country. LMD supplies the procured supplies to five regional medical stores (RMS); Biratnagar, Hetauda, Butwal, Nepalgunj and Dhading, which then distribute the supplies to their respective districts. An interrelated system of procurement exists between government entities, international non-governmental organizations (INGOs) and private firms.

Public sector employs several supply channels for procurement and distribution including:

- LMD-RMS-DPHO-Health facilities
- National Family Health Program (NFHP)-DPHO-Health facilities
- INGO-DPHO-Health facilities
- DPHO-NGOs-Health facilities
- CDP-Health facilities (Harper, Brhilikova, Subedi, & Bhattrai, 2007).

Abbreviations: DPHO- District Public Health Office; CDP- Community Drug Program

Public Sector Procurement

The mechanisms for public sector procurement of pharmaceuticals are the central "push and pull" system, district level procurement and community drug programs.

Push refers to drugs being supplied in predetermined amounts to districts, and pull refers to supply being matched to consumption, and drugs being supplied in amounts requested by districts (DRC, 2012).

In addition to the drug supply provided by the central government, government allocates funds to allow districts to purchase drugs directly. All of the drugs for health posts pass through district offices, which procure drugs through tender (Harper, Brhlikova, Subedi, & Bhattarai, 2007). District health offices regulate health facilities, including district hospitals, primary health care centers (PHCCs), health posts (HP) and sub health posts (SHP). Each health office also ensures an adequate stock of drugs according to the drug requirement. For example, district hospitals prioritize stocking medicines for advanced tertiary care, while SHP medication stocks are for out-patient primary care.

Since 1995, government of Nepal has been implementing community drug programs (CDPs) to help overcome deficiencies in the procurement system. CDPs were originally started by UNICEF as a component of their Child Health Program. In CDPs, wholesalers are identified in each district and Village Development Committees (VDCs) to procure drugs directly through them. This program has been introduced so that communities can get access to drugs directly, but in spite of this plan there continues to be limited availability of drugs at health posts.

International non-governmental organizations

INGOs, such as Medical Services for Management Trust-Nepal (MSMT); Social Action for Rural Health and Development (SARDHAN) and Britain Nepal Medical Trust (BNMT) are actively involved in drug procurement in Nepal. INGO procurement was established to ensure the availability of drugs at affordable prices.

MSMT was established in 2004 and provides essential high quality drugs, medical and surgical equipment at affordable prices. MSMT also consultants on pharmaceutical information, inventory control and store management for non-profit health care providers. Over 90 percent of

MSMT supplies go to mission hospitals and other health institutions outside Kathmandu Valley.

5.2.2 Procurement

The procurement act outlined procedure which must be followed in the drug procurement process. The steps in drug procurement process are:

1. Planning and tendering
2. Quality assurance and supply
3. Distribution
4. Monitoring and evaluation

Planning and tendering

According to the Procurement Act, first step of the drug procurement process is procurement planning. Logistic Management Division (LMD) takes a lead in planning the types and quantity of drugs to procure at central, regional and district levels. Tendering process is then initiated at the central and regional levels. Bidders are selected on the basis of their qualifications. After evaluation, a copy of the tender is sent to each regional store.

Quality assurance and supply

Quality assurance is a component of the central government's procurement process, but it is not a component of procurement process at regional and district levels. In centrally managed procurement, pre and post-shipment inspection is performed by an ISO certified laboratory on random samples collected from supplies (Stoermer, Sharma, Napierala, & Silwal, 2009). In 2013, LMD introduced a mechanism to ensure higher quality assurance for the drugs it procures. This mechanism requires WHO pre-qualification certification for most internationally procured drugs and vaccines when a sufficient number of bidders or manufacturers qualify for proper competition. When the number of bidders is small, bidders must have experience in successfully supplying drugs to the public sector within the past three years. LMD also performs laboratory tests to check the quality of drugs and vaccines.

Distribution

Once procured, drugs are stored in regional stores, from which they are distributed to district stores within the area of their jurisdiction. District stores distribute the drugs to each health facility.

Drugs ultimately reach consumers through different channels, including INGOs, retail drug outlets, government health facilities and private health facilities (figure 5-2). Public health facilities, including government hospitals, health posts, and sub health posts, can all provide drugs to patients. INGOs procure their own drugs and distribute them directly to beneficiaries. Private companies procure drugs and sell them to consumers at retail pharmacy outlets. Three of the main contributors to Nepal's drug distribution system are super-stockists, stockists and retailers. DDA provides certificates to retail and wholesale businesses.
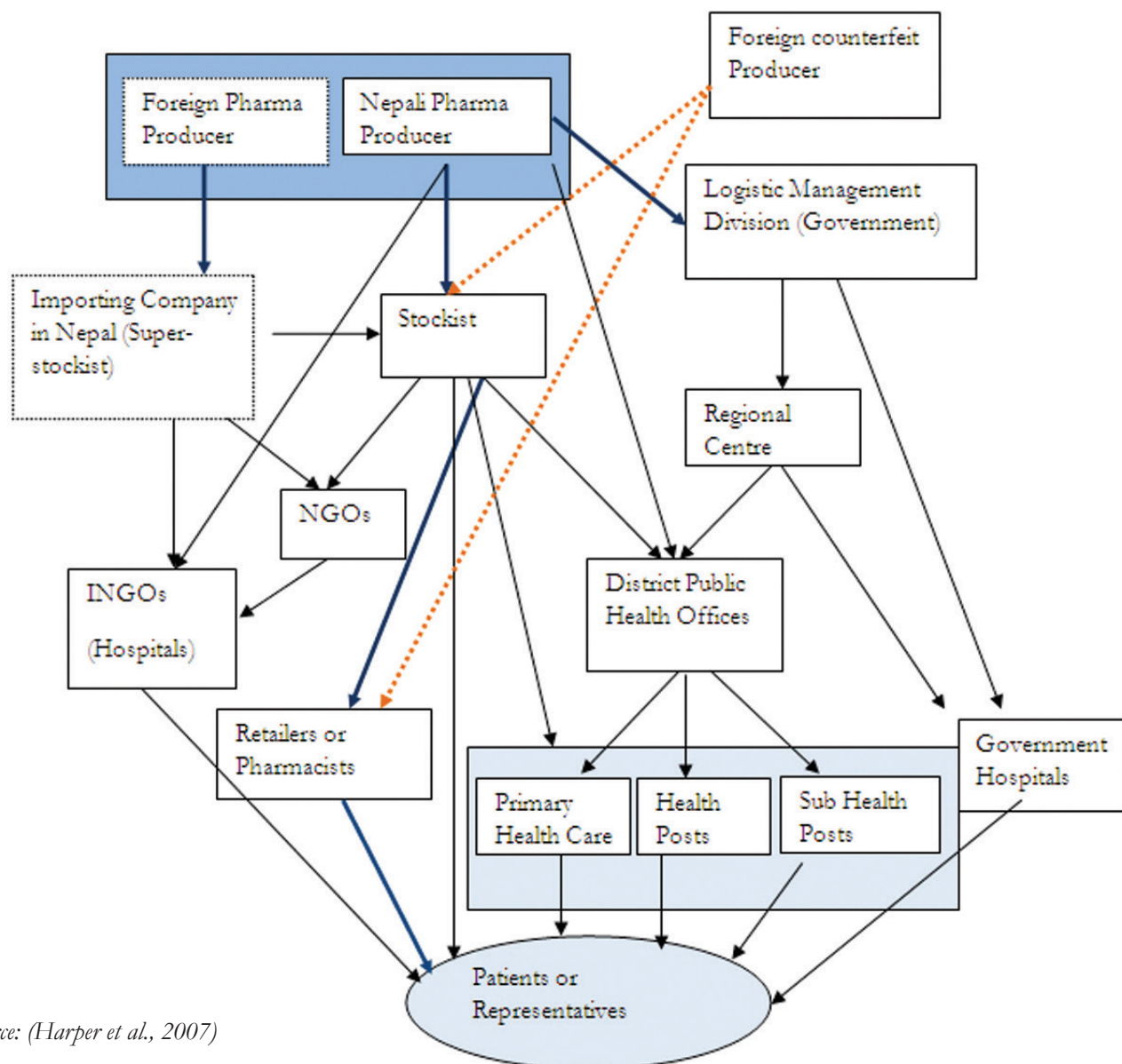
Super-stockists are importers that stock, market and distribute products of foreign pharmaceutical companies.

Wholesalers, which must be registered with DDA, sell products to retailers. Drugs are sold to consumers by retailers in various community outlets. Retailers have to be registered with DDA (Harper et al., 2007), which has developed guidelines for the establishment of community outlets. A diploma in pharmacy is required to open a pharmacy in Nepal.

Monitoring and evaluation

There is a set mechanism for monitoring and evaluating drugs at the national, regional, district and health facility levels (Manfreid, Sunder, Christoph, & Raj, 2009).

Figure 5-2: Distribution channels for pharmaceuticals in Nepal

Source: (Harper et al., 2007)

5.2.3 Drug Pricing

Nepal has a competitive market system in which domestic and foreign manufacturers can compete. DDA is responsible for developing and implementing drug pricing policies. Government of Nepal has made an effort to regulate the price of drugs. Two important government policies related to drug pricing are the National Drug Policy of 1995 (see section 2.5) and the Drug Act 2035.
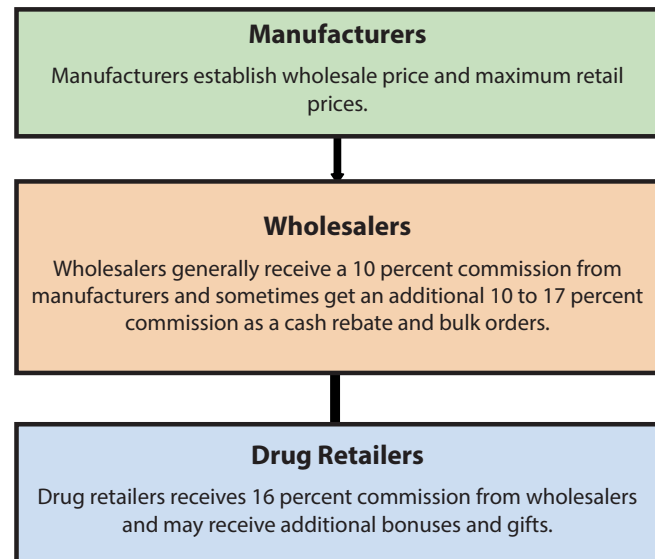
Box 5-3: Drug Act - 1978

The Drug Act - 1978 contains a provision for monitoring and fixing the price of drugs. This act also established Drug Price Monitoring Committee to advise Government of Nepal. The committee is interdisciplinary in nature and includes representatives from various ministries and departments. The Chief Drug Administrator of the committee is DDA President, along with a senior technical officer designated by the DDA Member Secretary and two drug experts nominated by committee members. Representatives come from the following ministries, departments and specialties: MoHP, Ministry of Supply, Ministry of Law, Nepal Chemist and Druggist Association, Nepal Consumer Association, Nepal Pharmaceuticals Association, Association of Pharmaceutical Products of Nepal, Department of Industry, Department of Customs and Department of Taxation.

The prime responsibility of the drug price monitoring committee is to advise GoN on how to protect national interests, to make drugs available to consumers at affordable prices, and to determine the prices of drugs that are imported or manufactured within the country. However, the committee is not very active, and studies have shown that variation exists in the prices of some drugs throughout the country.

A study carried out by the International Network for the Rational Use of Drugs revealed that the pricing mechanism used by drug manufacturers (figure 5-3) is influenced by various factors such as the price of raw materials, staff salaries, electricity costs, marketing costs and training costs. Prices are marked up as drugs pass through the supply chain, as each link in the distribution process receives a commission (INRUD, 2007).

Figure 5-3: Pricing structure for drugs

Source: (INRUD, 2007)

Few studies have been conducted on the price structure of drugs in Nepal. A study comparing Nepalese and Indian brands looked at 37 Nepalese and 397 Indian drugs and identified 40 single or fixed dose combinations for study. Of the total 40 drugs, 48 percent were found to have more than 100 percent price variation and 63 percent showed more than 75 percent price variation. Indian brands showed higher variation (109 percent) than Nepalese brands (63 percent). Generally, Nepalese brands were cheaper than Indian brands (Shankar, Subish Mishra, & Saha, 2006).

5.3 Drug availability and accessibility

Though Government of Nepal has made a tremendous effort to ensure that health services, including drugs, are available throughout the nation and accessible to each citizen regardless of their gender, ethnicity, or location, many studies have revealed disparities in service utilization. Availability and accessibilty of drugs and health services vary particularly with respect to geographical location. Some of these studies are summarized below:

An evaluation was conducted by Development Resource Center (DRC) in collaboration with National Planning Commission (NPC) and Japan International Cooperation Agency (JICA). The essential drug procurement and supply system of the GoN was evaluated in 4 district

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hospitals, 5 primary health care centers, 11 health posts and 32 sub health posts in 5 districts of Nepal, including Sankhuwasabha, Mahottari, Mustang, Dailekh and Kanchanpur. The study reported that just 17 percent of the health facilities in mountain region, 52 percent in terai region and 57 percent in hilly region have year round drug availability. Sixty-seven percent of respondents (n=100) were able to receive all the drugs that were prescribed, 27 percent received some of the drugs and 6 percent did not receive any drugs from their health facility. Seventy-eight percent received drugs free of cost, while others purchased drugs from private clinics and pharmacies. In 80 percent of the health facilities in mountain region, stock outs of free medicines were observed at least once in a year. Stock outs were observed at least once in 52 percent of the health facilities in terai region and in 43 percent in hilly region. The findings also showed that 34 percent of respondents of the terai region, 29 percent of the mountain region and 12 percent of the hill region took less than 30 minutes to reach health facility, while 12 percent of the respondents of mountain region required one hour to reach the nearest health facility (DRC, 2012).

A field survey measuring the prices of reproductive health commodities during April and May of 2005 in 83 public, private and INGO medical outlets showed that the availability of commodities was highest in private sector outlets in eastern region (45 percent) and lowest in public sector outlets in western region (17 percent). The mean availability of commodities in mountain region (27 percent) was comparatively lower than in terai region (37 percent) and hilly region (35 percent). The availability of condoms was highest in the terai region (88 percent). Products such as condoms, oral contraceptive pills, injectable contraceptives and uterine devices were primarily available in public sector outlets (USAID, 2006).

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5.4 Antibiotic Use in Animals

Many antibiotics are important to treat both human and animal diseases. The Food and Agriculture Organization listed clinically important antimicrobials for human and veterinary use in 2008 (table 5-3).

Table 5-3: Antimicrobials important to humans and animals

Clinically important antimicrobials	
Human	**Veterinary**
Aminoglycosides	Aminoglycosides
Cephalosporins (3rd and 4th generation)	Cephalosporins
Macrolides	Macrolides
Penicillins	Penicillins
Quinolones	Quinolones
Tetracyclines (only tigecycline)	Tetracyclines
Ansamycins	Phenicols
Carbapenems	Sulfonamides
Glycopeptides	
Oxazolidinones	
Streptogramins	
Drugs treating mycobacterial diseases	

Source: (FAO, 2007)

Veterinary drug consumption in Nepal

Nepal does not have veterinary drug use guidelines, and as a result antibiotics may be used without consultation with veterinarians and without laboratory confirmation of infectious agents. Sub-therapeutic use of antibiotics for growth promotion is a common practice (Thapaliya, 2014; personal communication), though there is no evidence to support this.

A quanification study carried out by Pharmaceutical Horizon of Nepal from 2004 to 2005 and from 2005 to 2006 showed that veterinary drug use increased by about 35 percent between the two periods. Veterinary drug sales was 3.01 million USD in 2004-05, and 4.04 million USD in 2005-2006 (Table 5-4).

Table 5-4: Consumption of veterinary drugs in Nepal

Year	Imported (Million USD)	Domestic (Million USD)	Total (Million USD)
2004/05	1.99	1.02	3.01
2005/06	2.5	1.54	4.04

Source: (PHON, 2006)
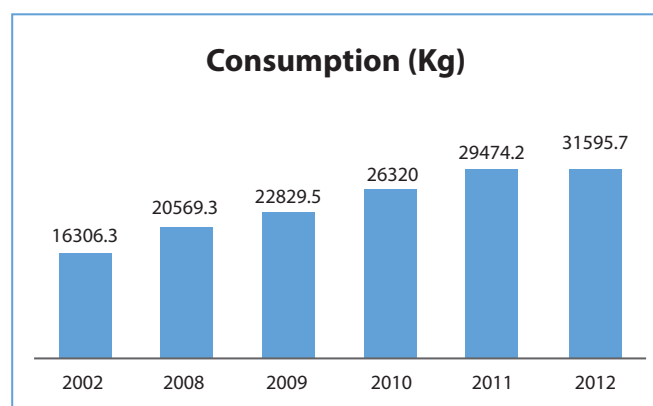
Bhandari and Singh conducted a survey of the major distributors of veterinary medicines and feed supplements in Bhairahawa, Nawalparasi, Narayanghat, Kathmandu, Bhaktapur, Birgunj and Biratnagar in 2000 and 2001. The survey showed that antibiotics accounted for 13 percent of total drug and feed supplement sales, equivalent to 671,429.80 USD. The same study revealed that there is high consumption of antibiotics in the veterinary sector. The total quantity of antibiotics consumed annually was 9,403 kg. Tetracyclines (7,899 kg), enrofloxacins (529 kg) and neomycin with doxycycline (229 kg) were the top three antibiotics consumed (table 5-5) (Bhandari & Singh, 2003).

Table 5-5: Quantity of antibiotics consumed annually

S.N	Antibiotics	Quantity (kg)
1	Tetracyclines	7,899
2	Enrofloxacins	529.1
3	Neomycin+doxycycline	229.47
4	Ampicillin	137
5	Tiamutin	109.46
6	Cephalexin	92
7	Ampicillin+cloxacillin	90.02
8	Doxycycline+colistinsulphate	88.38
9	Gentamicin	75.53
10	Tylosin	71
11	Penicillin+streptomycin	48.97
12	Flumequin	16.96
13	Chloramphenicol	16.5

Source: (Bhandari & Singh, 2003)

Another cross-sectional survey was conducted from 2008 to 2012 among veterinary drug importers, wholesalers, retailers and pharmaceutical manufacturers. Total antibiotic consumption grew by 54 percent from 2008 to 2011, with a per annum growth rate of 11 percent (figure 5-4).
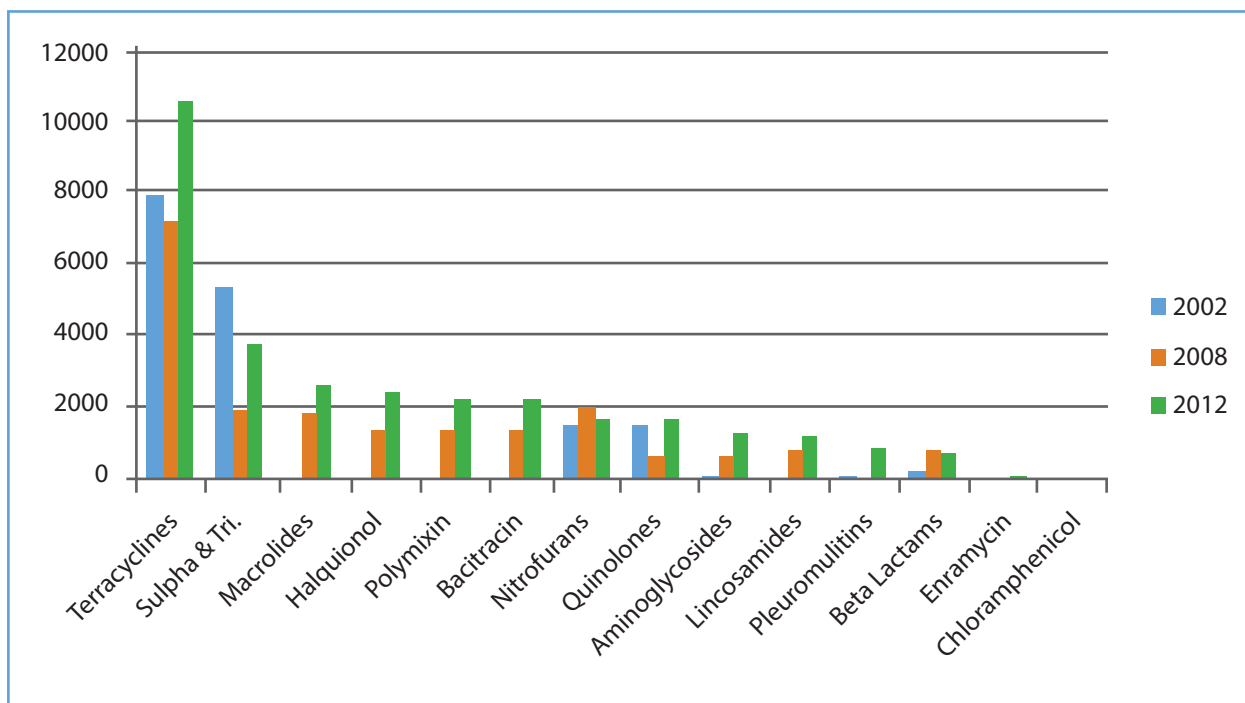
Figure 5-4: Antibiotic consumption of veterinary drugs, 2002-2012

Source: (Bhandari & Singh, 2003; Khatiwada, 2013)

The categories of antibiotics most frequently administered were penicillins, aminoglycosides, quinolones and macrolides. Tetracycline was the most commonly used antibiotic, followed by folate inhibitors, halquinol, nitrofurans and macrolides (figure 5-5).
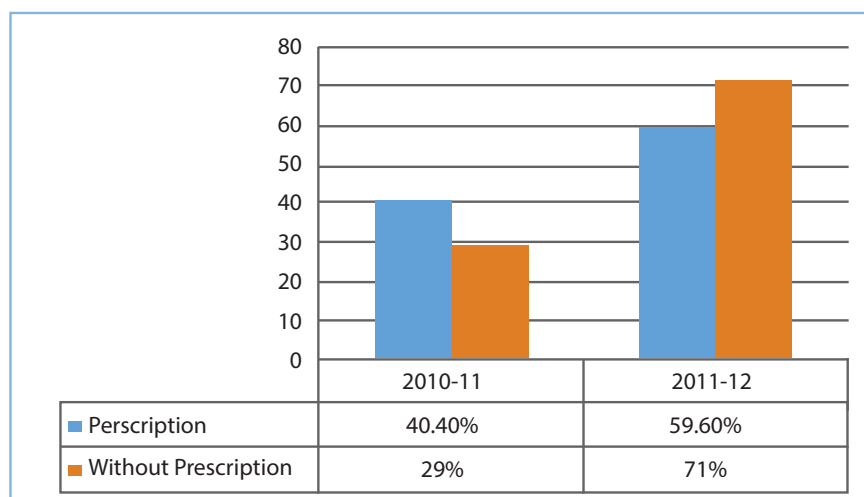
A study by Khatiwada in 2013 reported that 71 percent of veterinary drug sales were based on self-prescription by retailers from 2011 to 2012 (Khatiwada, 2013). Sales without prescriptions increased in Kathmandu valley between 2010-11 and 2011-12 (figure 5-6).

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Figure 5-5: Antimicrobial groups used in food-producing animals in Nepal

Source: (Bhandari & Singh, 2003; Khatiwada, 2013)

Figure 5-6: Prescription patterns for veterinary drug sales in Kathmandu Valley

	2010-11	2011-12
■ Perscription	40.40%	59.60%
■ Without Prescription	29%	71%

Source: (Khatiwada, 2013)

5.5 Livestock feed

Nepal is dependent on neighboring countries, particularly India and Bangladesh, for the raw materials required for the production of animal feed. Crop residue, grains and grain by-products, green forage and fodder and leaves are the main feed resources available in Nepal (table 5-6). Feed industries are categorized into 3 types in Nepal on the basis of their production (table 5-7).

Table 5-6: Feed resources available in Nepal

Feed categories	Feed resources
Crop residues	Rice straw, wheat straw, maize stover, pulses residues, oil crop residues, maize cobs and sugarcane tops.
Grains and grain by-products	Broken rice, rice bran, wheat, wheat bran, barley, barley bran, soy bean, soybean cake, mustard cake and molasses
Green forage	Fodder crops and pastures
Fodder tree leaves	From forest plants and planted fodder trees

Source: (Animal Nutrition Division, 2014)

Table 5-7: Categories of feed producers

S.N	Classification	Average quantity produced per day	Total no.
1	Small industries	Less than 5 mt per day	67
2	Medium industries	5-10 mt per day	52
3	Large industries	More than 10 mt per day	30

Source: (Sharma, 2010)

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GARP - Nepal Inaugural Meeting

Meeting with Veterinarians

GARP - Nepal Working Group Meeting with Dr. Ramanan Laxminarayan, Director, CDDEP

Dissemination Workshop, 15 December, 2014

About NPHF

Nepal Public Health Foundation (NPHF) was established in April 2010 with a mission to have concerted public health action, research, andpolicy dialogue for health development, particularly of the socio-economically marginalized population. NPHF has a vision to ensure health as the right and responsibility of the Nepali people with its focus on major public health issues such as Health Policy and Systems, Human Resource, Communicable Disease, Non-Communicable Disease, Malnutrition etc.

NPHF has been able to act as an umbrella organization to voice concernin public health thematic areas and at a same time developing as an academic organization by continuously supporting to individuals and organizations through training and workshops. NPHF board comprised of professionals from multiple disciplines.

Besides, NPHF acts as a watch dog to scrutinize Government policies and operations especially its adherence to national and internationalcommitments such as commitments made in Interim Constitution, 2007 of Nepal and Health related Millennium Development Goals (1, 4, 5 and 6), aid harmonization, alignment and partnership including national level governance and accountability responsiveness and public private partnership

About CDDEP

The Center for Disease Dynamics, Economics & Policy (CDDEP) was founded with the objective of using research to support better decision-making in health policy. The CDDEP team employs a range of expertise— including economics, epidemiology, disease modeling, risk analysis, and statistics—to produce actionable, policy-oriented studies on malaria, antibiotic resistance, disease control priorities, environmental health, alcohol and tobacco, and various other issues.

The strength of CDDEP derives from its researchers' experience in addressing national and regional health problems, as well as truly global challenges, while recognizing the circumstances in which the answers must fit. The outcomes of individual projects go beyond the usual models to inspire new strategies for analysis, and innovative approaches are shared through publications and presentations focusing specifically on methodology.

Founded in 2009 as a center of Resources for the Future, CDDEP is an independent non-profit organization. With offices in Washington D.C. and New Delhi, CDDEP works with distinguished academics and policy analysts around the world.

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