Review Article

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Antibiotic Use, Its Resistance in Nepal and Recommendations for Action: A Situation Analysis

Basnyat B,[1,2] Pokharel P,[3] Dixit S,[4] Giri S[5]

[1]Global Abtibiotic Resistance Partnership (GARP)-Nepal, [2]Oxford University Clinical Health Research Unit, Patan Hospital, Kathmandu, [3]B.P. Koirala Institute of Health Sciences, Dharan, [4]Center for Molecular Dynamics, Kathmandu, [5]Nepal Public Health Foundation, Kathmandu, Nepal.

ABSTRACT

Antibiotics are crucial, life-saving medicines in the fight against infectious disease, but resistance to these drugs is growing all over. This article presents key findings from a detailed situation analysis produced by the Global Antibiotic Resistance Partnership (GARP)-Nepal working group.

In the absence of nationally-representative surveillance, it is not possible to fully describe antibiotic resistance in the country, but many important bacterial pathogens are highly resistant to most first-line and some second-line antibiotics, according to available reports. In credible studies, more than half of Escherichia coli, Klebsiella pneumoniae and Streptococcus pneumoniae isolates tested, and over 30 percent of some Shigella spp. and Vibrio cholerae isolates were resistant to first-line antibiotics. The findings for Neisseria gonorrheae and hospital-acquired Staphylococcus aureus are similar.

Antibiotic use in animal food is poorly documented in Nepal, but it is commonly acknowledged to be widespread, contributing to the overall antibiotic resistance burden. The volume of veterinary antibiotic sales in Nepal rose over 50 percent from 2008 to 2012, most through retailers without veterinarian prescription. Antibiotics are necessary to treat infections in animals, but they are also used extensively for preventing disease, a use that can be restricted without jeopardizing animal or human health. They may also be used for promoting animal growth, which can be eliminated with no health consequences.

Nepal has made important advances in reducing mortality and morbidity and increasing health coverage, but has not yet taken steps to address antibiotic resistance. The GARP-Nepal working group outlines the components of a national strategy on antibiotic resistance, consistent with the recent call by the World Health Organization for national action plans, to be developed collaboratively with stakeholders and partners from government and all relevant sectors.

Keywords: Antibiotics; antibiotic resistance; antibiotic use; bacterial disease; infectious disease; Nepal; resistance.

INTRODUCTION

Antibiotics are the 'miracle drugs' of the 20th century. When and where they are accessible, they have the potential to transform death in infancy and childhood from an ever-present danger into a rare event. Remarkably, Alexander Fleming, the discoverer of penicillin in 1928, made what may have been the first appeal for antibiotic stewardship: use penicillin only when necessary and do not 'under-dose'.[1]

The world has used penicillin and the rest of the available antibiotics at an ever-increasing rate. 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.

Yet 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.[2] While resistance is the primary concern, the desire to preserve antibiotics must be balanced with the aim of treating as much disease and saving as many lives as possible.

Correspondence: Dr Buddha Basnyat, Nepal Public Health Foundation, 101/2 Dhara marga, Maharajgunj, Kathmandu, Nepal. Email: buddhabasnyat@gmail.com, Phone: +9779851034187.

Antibiotics are also used to treat infections in animals, just as in humans. Animal health is an important source of productivity, but each use also contributes to growing resistance. In many cases antibiotics are used as growth promoters or to prevent disease, usually put in low doses in animal feed. This sub-optimal use increases the chance of bacteria developing resistance – in the case of growth promotion, without benefiting animal health, and in the case of disease prevention, a practice that can be avoided or reduced.[3]

Antibiotic resistance is no longer a concern for the distant future but is a pressing issue today, both globally and in Nepal. A comprehensive situation analysis was conducted by the Global Antibiotic Resistance Partnership (GARP)-Nepal with the objectives of documenting the current state of antibiotic access, use and resistance in the country; creating a baseline for what is known and identifying important information gaps; and identifying policies and actions that could set a course for antibiotic sustainability. This article summarizes the findings of that analysis.

Information included in the situation analysis was gathered through review of published and grey literature and interviews with key stakeholders from all sectors. No adequate surveillance system for tracking antibiotic resistance or documenting antibiotic use currently exists in Nepal, making it impossible to accurately report trends in either case. The published studies that have been carried out are included in this review, grouped by the major bacteria contributing to the infectious disease burden in Nepal.

DISEASE BURDEN AND ANTIBIOTIC RESISTANCE IN HUMANS

Burden of bacterial infections

The leading causes of premature mortality from infectious diseases, many of bacterial origin, in Nepal in 2010 were lower respiratory infections (846 thousand years of life lost (YLLs)), diarrheal diseases (677 thousand YLLs), and tuberculosis (295 thousand YLLs).[2]

The burden 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 20 years.[4]

In 2013 there were 1,766,903 new diarrheal cases among children under 5 years of age, a slight increase from 2010. Diarrheal deaths decreased from 44 per 1,000 children <5 in 2010 to 36 in 2013.[5,6]

Streptococcus pneumoniae and Klebsiella pneumoniae

Streptococcus spp., *Staphylococcus aureus*, *K. pneumoniae*, *Haemophilus influenzae* type b, and *Pseudomonas aeruginosa* are common bacterial causes of pneumonia in Nepal. Several studies confirm *S. pneumoniae* as the most common pathogen in childhood pneumonia cases.[7-9]

Eight studies were identified, all conducted between 2004 and 2011,[7,10-16] reporting antibiotic resistance of *S. pneumoniae* and *K. pneumoniae* isolates from respiratory infections in Nepal. In many studies, more than half of all isolates were resistant to the commonly-used antibiotics cotrimoxazole and ciprofloxacin, with resistance to both drugs appearing to increase from 2000 through 2008 [10] (Table 1).

Enteric pathogens

Important bacterial causes of diarrhea include *Shigella*, *Campylobacter,* and *Salmonella* (including *S.* Typhi), *Escherichia coli*, and *Vibrio cholerae*. Most cases of viral and bacterial diarrhea do not require antibiotics for full recovery, with the exception of complicated, bloody diarrhea (dysentery). However, antibiotics are often inappropriately used to treat uncomplicated diarrhea, regardless of severity or cause.

Three studies were identified documenting antibiotic resistance among *Shigella* spp. [17-19] and three among *V. cholerae* [20-22] 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.[18] In the largest study, out of 118 isolates, one-third were resistant to all four antibiotics.[17]

Almost all *V. cholerae* isolates were resistant to nalidixic acid, cotrimoxazole and furazolidone, the three drugs for which resistance levels were tested. In a very recent study on 22 clinical isolates and two environmental samples, all isolates were found to be resistant to ampicillin, nalidixic acid and cotrimoxazole. [23]

Bloodstream infections

Major bloodstream infections (often referred to as bacteremia) include neonatal sepsis, typhoid and meningitis. These infections are often very serious and require prompt antibiotic treatment.

Table 1. Antibiotic resistance in S. pneumoniae and K. pneumonia.

Microorganism	Hospital/Study Area (sample size)	Antibiotic	Resistance Percentage	Citation
K. pneumoniae	Koshi Zonal Hospital (n=55)	Nalidixic Acid	87	APUA, 2012
		Cotrimoxazole	85	
		Ciprofloxacin	33	
		Nitrofurantoin	5	
	Pokhara (n=6)	Nalidixic Acid	83	APUA, 2012
		Azithromycin	66.7	
		Cefixime	75	
		Ampicillin and Ceftriaxone	0	
	Tertiary Care Hospital, Central Nepal (n=102)	Multidrug resistance	23	Mishra et al., 2014
S. pneumoniae	BPKIHS (n=26)	Cotrimoxazole	23	Khanal et al. 2010
		Ciprofloxazone	4	
		Cepfloxime, Chloramphenicol, Erythromycin, Penicillin, & Vancomycin	0	
	Kanti Children's Hospital (n=60)	Cotrimoxazole	52	Rijal et al., 2010
		Penicillin	6.5	
		Erythromycin	2.17	
		Chloramphenicol	2.17	
	Manipal Teaching Hospital (n=312)	Cotrimoxazole	34.3	Easow et al., 2011
		Erythromycin	7.4	
	Manipal Teaching Hospital (n=252)	Tetracycline	11.1	
		Chloramphenicol	0.4	
	Eleven laboratories around Nepal (n=934)	Cotrimoxazole,	56.6	Shakya & Adhikari, 2012
		Penicillin	4.7	
		Ampicillin	5	
		Erythromycin	5.3	
		Chloramphenicol	2.4	

Table 2. Antibiotic resistance in Salmonella spp.

Microorganism (sample size)	Hospital/Study Area	Antibiotic	Resistance Percentage	Citation
S. Typhi (n=43)	Kanti Children Hospital	Chloramphenicol	2.4	Rai GK, Karki S, & Prajapati B, 2012
S. Paratyphi A (n=17)		Chloramphenicol	0	
S. Typhi (n=29)	Nepal Public Health Laboratory	Ampicillin	7	D Acharya, DR Bhatta, S Malla,SP Dumre, N Adhikari and BP Kande, 2011
		Chloramphenicol	3	
		Ciprofloxacin	3	
		Cotrimoxazole	7	
S. Paratyphi A (n=30)		Ampicillin	10	
		Chloramphenicol	3	
		Ciprofloxacin	10	
		Cotrimoxazole	3	

Table 3. Antibiotic resistance in E. coli.

Microorganism (sample size)	Hospital/Study Area	Antibiotic	Resistance Percentage	Citation
E. coli (n=327)	Kathmandu Medical College (KMC)	Amoxicillin	83	Bhatt et al, 2013
		Norfloxacin	60	
		Cefixime	51	
		Ciprofloxacin	49	
		Ofloxacin	60	
E. coli (n=136)	Kathmandu Medical College (KMC)	Ciprofloxacin	59	Raza, Pandey & Bhatt, 2011
		Norfloxacin	57	
		Cotrimoxazole	39	

Four small hospital-based studies of sepsis infections [24-27] reported resistance to antibiotics. Resistance 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 were ampicillin, cefotaxime, ceftriaxone, imipenem, ceftazidime, and piperacillin.

Salmonella spp.

A comprehensive meta-analysis analyzed 32 antibiotic resistance studies conducted over 18 years (1993-2011) in Nepal of *Salmonella* Typhi and *Salmonella* Paratyphi A., the main bacteria responsible for typhoid and paratyphoid.[28] 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.[28] In fact, nalidixic acid resistance better reflects ciprofloxacin resistance, implying high levels of resistance to ciprofloxacin and calling into question treatment of enteric fever with ciprofloxacin. Recent studies have demonstrated increasing susceptibility of *Salmonella* spp. towards first-line antibiotics chloramphenicol, ampicillin and cotrimoxazole (Table 2).

E. coli

E.coli is the most common bacterial cause of urinary tract infections, which are appropriately treated with antibiotics. Nepal's National Public Health Laboratory reported on resistance rates of *E. coli* from 2006 to 2010. Resistance rates were well above 50 percent for all the drugs tested, which included, from greatest to least resistance: amoxicillin, cefixime, amoxicillin-clavulanic acid, nalidixic acid, ceftazidime and cefotaxime. Resistance to all drugs increased from 2006 to 2010 [29] (Table 3).

Neisseria gonorrhoeae

Antibiotic resistance studies on sexually transmitted infections remain limited in Nepal. The two identified studies reported high rates of resistance of *Neisseria gonorrhoeae* to penicillin, tetracycline and ciprofloxacin.[30,31]

MRSA

Most of the healthcare-acquired infection (HAI) studies in Nepal have reported a high prevalence of MRSA and other resistant bacteria in patient isolates and on equipment.[32-34] MRSA was frequently seen to be 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.[35] The lack of studies and ongoing surveillance point to potential underreporting of HAIs.

Mycobacterium tuberculosis

Reports of resistance of *M. tuberculosis* to first-line drugs are discrepant, with some reporting relatively low resistance rates (3 and 18 percent, respectively, for new and retreated cases) [36] and others reporting quite high rates (35 percent and higher for each drug individually and up to 23 percent to all first-line drugs).[37] Drug prevalence status among new TB cases for at least Refampicin and isoniazid from 1996 to 2012 is shown in table 4. 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, but the uncertainty of resistance levels calls for added attention.

Table 4. Drug Resistance Surveillance among new TB cases.

Year	1996-97	1998-99	2001-02	2006-07	2010-11
Drug Resistant TB cases (Percent)	1.2	3.6	1.3	2.9	2.2

Source: (*NTC annual report, 2012-13).*

WORLD HEALTH ORGANIZATION (WHO) REPORTED ANTIBIOTIC RESISTANCE IN NEPAL

A recent WHO report includes data from Nepal on antibiotic resistance rates for six combinations of bacterial pathogens and antibiotics.[38] The bacteria were *E. coli*, *S. aureus*, non-typhoidal *Salmonella*, *Shigella* spp., *K. pneumoniae*, and *N. gonorrhoeae*.

Out of 140 isolates included, 64 percent of *E. coli* isolates were resistant to fluoroquinolones and 38 percent were resistant to third-generation cephalosporins. Smaller data sets showed MRSA 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.[38]

ANTIBIOTIC RESISTANCE BURDEN IN 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. [39]

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. The commonest bacteria 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*.[40]

In many countries, antibiotics are or were previously used as growth promoters in food animals. The main reason for phasing out this practice (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, although the use patterns are poorly documented.

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. A survey of distributors of veterinary medicine and feed supplements conducted in 2000 and 2001 found that in six Nepali districts, annual sales were NRs. 492 million (USD 6,739,726). Antibiotics represent 13 percent of the total expenditure on veterinary drugs.[41] The volume of veterinary antibiotic sales rose more than 50 percent between 2008 and 2012, according to a recent survey. In that survey, 71 percent of veterinary drug sales were based on retail sales without the prescription of veterinary professionals.[42]

CONFRONTING ANTIBIOTIC RESISTANCE

The GARP network of eight countries has identified six primary strategies to improve antibiotic use at the national level. The details vary from country to country, but the strategies are similar. They are:

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 the veterinary sector;
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

The current situation in Nepal related to these aims is presented below.

1. Reduce the need for antibiotics by improving public health

The National Immunization Program in Nepal has achieved coverage rates of over 80 percent for most included vaccines.[6] 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 added a childhood pneumococcal vaccine in 2015, but has not yet scheduled the addition of the *Rotavirus* vaccine. In 2014, 92 percent of the population had access to an improved water source while just 64 percent had access to improved sanitation, compared to 66 and 6 percent in 1990, respectively. Access to both is lower in rural areas, particularly for sanitation.[43]

2. Improve hospital infection control and antibiotic stewardship

National infection control and antibiotic stewardship guidelines have not been established in Nepal. Some hospitals have developed manuals on nosocomial infection control and appointed infection control committees and others have not yet taken these steps.[44]

Evidence of inappropriate prescribing of antibiotics in Nepal has been shown in several studies across different healthcare facilities, particularly for ampicillin, amoxicillin, ceftriaxone and gentamicin. In 11 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.[45-55] Antibiotics were prescribed inappropriately in 10 to 42 percent of patients, and for both therapeutic and prophylactic purposes.[47- 54]

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

Appropriate antibiotic treatment requires trained staff and well-equipped facilities to ensure correct diagnoses and 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 specialists and technicians to manage these labs remains limited.[56]

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.

3. Rationalize antibiotic use in the community

Antibiotics can be purchased routinely in the community, from pharmacies, drugs 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. However, neonatal mortality remains high. 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

Information on the patterns of antibiotic use in animals is almost all anecdotal. Antibiotics for animals are commonly bought from informal vendors with no training and are often stored in conditions conducive to spoilage.

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.

No veterinary AMR surveillance network exists. The Central Veterinary Laboratory conducts epidemic investigations 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

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

Existing laws guide drug purchasing, distribution and use, and a national formulary includes essential medicines and specifies which health providers may prescribe them. However, no national policies are in place to guide antibiotic use.

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. Creating policies to guide

antibiotic use is the most sustainable way to ensure that changes are maintained.

STAKEHOLDER PRIORITIES

GARP-Nepal convened more than 60 stakeholders and interested professionals at the launch of the situation analysis in December of 2014. Participants identified the following priorities:

- *Raise awareness about the public health crisis*
- *Collaborate with the government to improve guidelines and policies*
- *Focus on antibiotic use and resistance in animals*
- *Ensure access to antibiotics to all who need them*
- *Take an ecological approach*

CONCLUSIONS

Though limited information is available, these studies clearly indicate that antibiotic resistance is a serious concern for Nepal, as it is for all countries. Reducing inappropriate antibiotic use and ensuring access to effective medications when needed is key to reducing morbidity and mortality from bacterial diseases and maintaining antibiotic effectiveness. Considering the current situation 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, especially the government, and those involved with both human and animal health.

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