School of Public Health

Antibiotic use in the general population in Rupandehi district of Nepal and factors associated with prescribing practices

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Declaration

To the best of my knowledge and belief, this thesis contains no material previously published by any other person except where due acknowledgment has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007) - updated March 2014. The proposed research studies received human research ethics approval from the Curtin University Human Research Ethics Committee (HRE2017-0394) and the Nepal Health Research Council (Reg,no. 189/2017).

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Abstract

Background

Antibiotic resistance is a serious threat to global public health. The causes of resistance are complex and include the behaviour of both service providers and consumers. Consequences of resistance are severe not only for population health but also for health care delivery given the increase in costs associated with treating antimicrobial resistant infections. Appropriate use of antibiotics contributes to decreasing the resistance rate; however, in Nepal, little is known about the extent of antibiotic use and factors associated with inappropriate use. The aim of the study was to assess antibiotic use in the general population in the Rupandehi district of Nepal and factors associated with prescribing practices.

Methods

A mixed-methods sequential explanatory design was adopted incorporating quantitative and qualitative methods to address the research question from different perspectives:

- Data on antibiotic use collected through two cross-sectional studies using administrative patient data from public health facilities and exit interviews with consumers who had attended private pharmacies.
- A household survey using a structured questionnaire examined the knowledge, attitudes and practices (KAP) of community members related to antibiotic use.
- Interviews conducted with service providers and policy makers, in which their views were sought on issues relating to practices of antibiotic prescribing, dispensing and use.

The data were collected from six public health facilities, 33 private pharmacies, 220 households and 17 key informants. The World Health Organization (WHO)

guidelines were used to select the public health facilities, private pharmacies and households. Key informants were recruited based on a mixed sampling approach, which included selecting a purposive sample of participants on the guidance of the chief of the district public health office followed by a snowball technique.

Descriptive statistics and multiple regression modelling were used to analyse data relating to the patterns of antibiotic use and the knowledge, attitudes and perceptions of community members about antibiotic use. Data from the informant interviews were analysed with a hybrid process of inductive and deductive thematic analysis.

Results

The literature review indicated that inappropriate antibiotics use occurred in many low- and middle-income countries (LMICs), with inappropriate use arising from the behaviour of both patients and providers. Key results from the studies were:

<u>Antibiotics prescribing and use</u>

The proportion of patients receiving at least one antibiotic was above the WHO recommended value (20.0 to 26.8%) in both public health facilities (44.7%) and private pharmacies (38.4%). The most commonly prescribed class of antibiotics was Cephalosporins in both public (29.9%) and private (38.0%) facilities, while Ceftriaxone accounted for the highest rate of antibiotic use in public (22.9%) and Cefixime in private (16.9%) facilities. Guidelines do not recommend cephalosporins as a first-line treatment for some indications. High prescribing rates of antibiotics for selected conditions (e.g. diarrhoeal cases, respiratory tract infections) in both public (83.2% and 72.4%, respectively) and private (91.3% and 93.3%, respectively) facilities appeared contrary to international recommendations. Being younger and older age increased the likelihood of an antibiotic prescription in both the public and private sectors ($p=<0.001$).

Knowledge, attitudes and practices

Community members had relatively good knowledge about aspects of antibiotic use other than identifying antibiotics. In regards to the concept of antibiotic resistance, this issue was well known but imperfectly understood. Half of the community members (50.9%) were unsure whether skipping doses would contribute to the development of antibiotic resistance, 88.2% indicated they would go to another doctor if not prescribed an antibiotic when they thought one was needed and nearly half (47.7%) believed antibiotics helped them get better more quickly if they had a fever. Most respondents reported correct practices in accessing and using antibiotics, however, 84.6% at least sometimes preferred an antibiotic when they have a cough and sore throat. Respondents with higher levels of education tended to have better knowledge, more appropriate attitudes and better practices about antibiotic use. Moreover, people living in rural areas were less likely to have better knowledge about antibiotic use, while females were more likely to report better practices.

Factors influencing antibiotic prescribing, dispensing and use

The personal behaviour of patients and providers is explicitly interrelated. Patients appear to be unaware of the negative implications of self-medication, which is reflected in their practices. Also, the use of over-the-counter medicines is common, with a lack of money to pay consultation fees to doctors a contributing factor. Providers have a strong desire to please patients so as to retain them, thus prescribe or dispense antibiotics to maintain good provider-patient relationships rather than based on clinical needs. Since the public health facilities do not always have a sufficient choice of antibiotics, prescribers often select available ones rather than following clinical guidelines.

Antibiotics were found to be prescribed based on clinical judgement as a result of unavailable diagnostic services in many facilities. Although, some providers sought to update their knowledge about antibiotics, they raised the issue of a lack of professional learning opportunities. Weak regulatory oversight of the Nepalese health system facilitated the ability to operate pharmacies without licences.

Conclusion

Antibiotic prescribing and dispensing in public and private health facilities was high compared with WHO guidelines; community people were found to lack knowledge on aspects relating to antibiotic use; and a weak regulatory environment facilitated the inappropriate use of antibiotics. Findings of this research point to the need for the government to introduce measures to both promote more appropriate prescribing and dispensing of antibiotics and raise awareness of community members about the risks of overuse and misuse of antibiotics. Given the multiple factors underlying the problem of inappropriate use of antibiotics in Nepal, a comprehensive strategy must be developed to combat the threat presented by antimicrobial resistance and drug-resistant infections.

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List of papers as part of the thesis

The following four papers were produced as part of the thesis. Three papers were published in peer-reviewed international journals and one has been accepted with minor revisions:

Paper 1: Analysis of patterns of antibiotic prescribing in public health facilities in Nepal

Nepal A, Hendrie D, Robinson S, Selvey LA. Analysis of patterns of antibiotic prescribing in public health facilities in Nepal. The Journal of Infection in Developing Countries. 2020 Jan 31;14(01):18-27. https://doi.org/10.3855/jidc.11817

Paper 2: Survey of the pattern of antibiotic dispensing in private pharmacies in Nepal

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Paper 3: Knowledge, attitudes and practices relating to antibiotic use among community members of the Rupandehi District in Nepal

Nepal A, Hendrie D, Robinson S, Selvey LA. Knowledge, attitudes and practices relating to antibiotic use among community members of the Rupandehi District in Nepal. BMC Public Health. 2019 Dec 1;19(1):1558.

Paper 4: Factors influencing the inappropriate use of antibiotics in the Rupandehi district of Nepal

Nepal A, Hendrie D, Selvey LA, Robinson S. Factors influencing the inappropriate use of antibiotics in the Rupandehi district of Nepal.

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Abbreviations

AMR	Antimicrobial Resistant
CDC	Center for Disease Control and Prevention
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DDA	Department of Drug Administration
DHO	District Health Office
DPHO	District Public Health Officer
EU	European Union
FCHV	Female Community Health Volunteer
GDP	Gross Domestic Product
HP	Health Post
ICD	International Classification of Diseases
JBI	Joanna Briggs Institute
LMIC	Low and Middle Income Country
LRTI	Lower Respiratory Tract Infection
MRSA	Methicillin-resistant Staphylococcus Aureus
NCDA	Nepal Chemist and Druggist Association
NPR	Nepalese Rupees
OR	Odds Ratio
OTC	Over-the-Counter
PCC	Population Concept Context
PHC	Primary Health Care Centre
SPSS	Statistical Package for Social Sciences
USA	United States of America
VDC	Village Development Committee
WHO	World Health Organization

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Chapter 1 Introduction

1.1 Antibiotics and their use

1.1.1 Antibiotic discovery and development

Antibiotics are one of the most successful discoveries in modern medicine (1). Since their discovery in the late 1920s, they have become a vital source of medicine and have saved millions of lives through treating previously incurable infectious diseases (1, 2) such as pneumonia, scarlet fever, smallpox, cholera, diphtheria, tuberculosis and other life-threatening infections. In addition to their use in modern medical care, antibiotics also play an important role in the prevention of infection during surgery, in organ replacements and in treating cancer (3). Additionally, in low- and middle-income countries (LMICs), antibiotics have also contributed to the decrease in morbidity and mortality caused by poor sanitation and food-borne and other poverty-related infections (4).

1.1.2 Global increase in antibiotic use

Between the years 2000 and 2010, total global antibiotic use grew by 35% from approximately 50 billion to 70 billion standard units, based on data from 71 countries including most high-population countries. This increase in use was particularly evident in the case of cephalosporins and broad-spectrum penicillins (5). Per capita consumption is generally higher in high-income countries, but the greatest increase in antibiotic use during this period was in LMICs, where use continues to rise (6). Rising incomes and a higher burden of infectious diseases with high rates of hospitalisation and a high prevalence of hospital infections are the major drivers of increased antibiotic consumption especially in LMICs (3, 7).

The period between the 1950s and 1970s has been named the golden era of discovery of novel antibiotics. Since then, very few new classes of antibiotics having been discovered. Much of the recent approach to discovery of new drugs has involved the modification of existing antibiotics (8). Despite emerging and re-emerging diseases, pharmaceutical companies have been unwilling to develop new, viable antibiotic alternatives. Antibiotics are taken for relatively short courses compared with medicines for chronic illnesses, and sold for relatively low prices, thus not providing a sufficient return on investment.

1.1.3 Understanding of antibiotic and antimicrobial

When discussing the antibiotic use, it is important to define commonly used terms. Antimicrobials refer to a group of agents that share the common aim of reducing the possibility of infection and sepsis (9). The Center for Disease Control and Prevention (CDC) defines antimicrobial agents as "a general term for the drugs, chemicals, or other substances that either kill or slow the growth of microbes" (1 p. 10). Antimicrobial medications are further specified as being antibacterial, antiviral, antifungal and antiparasitic.

As mentioned, an antibiotic is a type of antimicrobial substance, active against bacteria and is the most important type of antibacterial agent for fighting bacterial infections. Antibiotic medications are widely used in the treatment and prevention of such infections. They may either kill or inhibit the growth of bacteria. A limited number of antibiotics also possess antiprotozoal activity (11). Antibiotics are not effective against viruses such as the common cold or influenza; drugs which inhibit viruses are termed antiviral drugs or antivirals rathe r than antibiotics.

1.2 Antimicrobial resistance and the inappropriate use of antibiotic

1.2.1 Emergence of antimicrobial resistance

Antimicrobial resistance (AMR) is the ability of a microbe to resist the effects of medication that once could successfully treat the microbe (12). The resistance occurs when microbes change in some way that reduces or eliminates the effectiveness of drugs, chemicals, or other agents designed to cure or prevent infections (13). This arises through one of three mechanisms: natural resistance in certain types of bacteria, genetic mutation, or by one species acquiring resistance from another (14). All classes of microbes can develop resistance; fungi develop antifungal resistance, viruses develop antiviral resistance, protozoa develop antiprotozoal resistance, and bacteria develop antibiotic resistance (15). Resistance can appear spontaneously because of random mutations. However, extended use of antimicrobials appears to encourage selection for mutations which can render antimicrobials ineffective (16).

Since the discovery of drugs, a gradual and sustained emergence of antimicrobial resistant bacterial strains has been seen. Since the introduction in 1937 of the first effective antimicrobials, namely, the sulfonamides, the development of specific mechanisms of resistance has plagued their therapeutic use (17). The resistance has been gradually reported with the introduction of other antimicrobials such as *Staphylococcus* resistance to penicillin (1943), methicillin (1960) and linezolid (2001). Similarly,the resistance of *Enteriobacteriaceae* to cefazidime was identified in 1987, *Pneumococcus* to levofloxacin in 1996, and *Neisseria gonorrhoeae* to Ceftriaxone in 2009 (18).

Increasing trends of resistance to many pathogens has been reported over the years in different regions of the world (19). This has been attributed to changing microbial characteristics, selective pressures of antimicrobial use, and societal and technological changes that enhance the development and transmission of drug-resistant organisms (20). Although, antimicrobial resistance is a natural biological phenomenon, it often enhanced as a consequence of the adaption of infectious agents to exposure to the use of antimicrobials in humans or agriculture and the widespread use of disinfectants at the farm and the household levels (20). It is now accepted that antimicrobial use is the single most important factor responsible for increased antimicrobial resistance (19, 21).

The emergence of antimicrobial resistance has led to increasing concern about the potential impact of antibiotic resistance on the management of infectious diseases. Resistant infections are more difficult and expensive to treat, and result in increased morbidity, mortality and healthcare costs (22).

1.2.2 Burden of antibiotic resistance

As mentioned, antimicrobial resistance is now widely considered a grave threat to international public health (23, 24), with new resistance mechanisms emerging and threatening the ability to treat even common infectious diseases (25, 26). A growing list of infections, such as pneumonia, tuberculosis, gonorrhea and salmonellosis are becoming harder, and sometimes impossible, to treat as antibiotics become less effective (26). The resistant infection leads not only to increased morbidity and mortality but also to an increase in the cost of treatment (22). When infections become resistant to first-line antibiotics, more expensive second-line therapies must be used (27), resulting in a longer duration of illness and treatment in hospitals (28) as well as the economic burden on families and societies (27). Estimates have suggested an additional two million illnesses and 23,000 deaths in the United States of America (USA) (29), and 25,000 deaths in Europe (30) per year due to antibiotic resistance. The problem of resistance is worldwide, and the effects of resistance are more severe in lower- and upper middle-income countries (31). In the case of low- and middle-income countries, the resistance of pathogens to some antibiotics is higher due to rapid spread of infectious disease and increasing rates of antibiotic consumption in both humans and animals (32).

The burden of antibiotic resistance is projected to increase, with estimates of as many as 10 million extra deaths per year by 2050 if action is not taken to reduce antimicrobial resistance (33). Antibiotic-resistant infections cost the United States health care system more than US$20 billion annually, and society more than US$35 billion, and lead to more than eight million additional hospital days (34). Estimates have suggested that antimicrobial resistant infections will result in a reduction of global gross domestic product (GDP) of 2 to 3.5 percent by 2050, costing the world up to US$100 trillion per year (33).

1.2.3 Inappropriate use of antibiotic

While the terms "appropriate use" or "rational use" are used interchangeably by the World Health Organization (WHO) (22), inappropriate use of antibiotics can be defined as not completing a course, misuse and overuse (35). Overuse of antibiotics accelerates the emergence of resistance, while prudent lower use slows down this trend (36, 37).

Globally more than half of all medicines are not properly used (35) and up to half of antibiotics used in community settings are unnecessary (38). Antibiotics are effective for treating bacterial infections but not for viral infections, however, the unwarranted use of antibiotic agents for respiratory and urinary tract illnesses is noted extensively. These are among the most common illnesses experienced worldwide, accounting for numerous visits to physicians and imprudent prescriptions of antibiotic (39). Some of those infections are largely viral and self-limiting, or bacterial of minor severity, and antibiotic offer little benefit to them (40), yet antibiotics are frequently used (41).

1.2.4 Factors associated with inappropriate antibiotic use

Several factors relating to inappropriate antibiotic use have been identified, with these factors associated with both service providers and recipients (42). Patients' educational status (43, 44) and their misuse of antibiotics (45) and the competency of service providers along with behaviours such as not updating knowledge on drugs and attitudes regarding drug prescribing processes are some examples (46, 47). Another factor associated with poor prescribing practice is trade interest associated with the influence of medical representatives (48, 49). Additionally, the high prevalence of self-medication and selling antibiotics over-the-counter are of particular concern especially in LMICs (50). The non-prescription sales of antibiotics is an inappropriate practice and one of the main factors accelerating the emergence of antibiotic resistance (51).

1.3 Antimicrobial stewardship in LMICs

In 2015, the WHO released a global action plan on antimicrobial resistance, which covers antibiotic resistance in considerable detail but also refers, where appropriate, to existing action plans for viral, parasitic and bacterial diseases. The appropriate use of antibiotics in humans and animals to maximise both their current effects and their chances of being available for future generations, is one of the cornerstones of the global action plan (52). Antimicrobial stewardship interventions are aimed at various actors: prescribers, patients, drug providers, policy makers and the general public. The most evidence relating to antimicrobial stewardship interventions are for those implemented in hospital settings, which have tended to show a positive impact with reduced length of stay, shorter treatment duration without an increase in mortality and a reduction in colonisation and infection with resistant bacteria (53).

However, the evidence suggests greater success of stewardship programmes in high-income countries (54), with effective and feasible stewardship interventions in LMICs being limited and challenges faced in their implementation (55). One of the challenges in LMICs is to ensure population access to antibiotics. It is contradictory (albeit real) that not all people living in LMICs have access to antibiotics despite their high consumption at a general level. Antimicrobial stewardship programmes are a means to achieve responsible use of antimicrobial drugs, but these programmes and access to antibiotics cannot be dealt with in isolation (56). However, several barriers such as lack of infrastructure and microbiological expertise, lack of diagnostic facilities, lack of knowledge in infectious diseases and inappropriate antimicrobial prescribing are experienced in LMICs (55, 56).

Nepal has no formal antimicrobial stewardship programmes or regulation relating to the use of antibiotics, which has led to an increased prevalence of antimicrobial resistance in the community. Increased rates of antibiotics resistant to different pathogens have been shown (57) and one reason for this could be an increase in antibiotic prescribing. Providers often prescribe contrary to the clinical guidelines with one study finding 11 different antibiotics prescribed for the treatment of respiratory tract infections with duration ranging from 5 to 10 days (58). The study was conducted 13 years ago and excluded antibiotic use in the public sector. Practices of self-medication and selling antibiotic over-the-counter are also prevalent in Nepal (59). In such cases, community members are mostly reliant on the instructions of pharmacists (60, 61), thus the roles of pharmacists are not only confined to dispensing (62, 63) but also involved in prescribing (64).

Several other studies have been conducted in Nepal on issues in regards to prescribing practices (65, 66), drug utilisation (67) and knowledge of outpatients about appropriate drug use (66). However, these have all been hospital based and not included private pharmacies or the views of the general population. It is important to note that issues relating to prescribing practices are likely to differ in hospital versus community setting and the public versus private sector. Effective solutions to address the problems in regards to inappropriate antibiotic use are required, however, no published studies in Nepal have investigated the extent of antibiotic use in the general population covering both public and private health facilities or examined factors associated with inappropriate use.

1.4 Research aim and objectives

The aim of the study is to assess antibiotic use in the general population in the Rupandehi district of Nepal and factors associated with prescribing practices.

Specific objectives

- Assess the patterns of antibiotic use in the general population in the Rupandehi district of Nepal
- Examine the knowledge, attitudes and practices of community members in the Rupandehi district of Nepal in regard to the use of antibiotics
- Identify the perceptions of health providers and policy makers about factors influencing the inappropriate use of antibiotics in the Rupandehi district of Nepal

1.5 Significance of the research

The focus of this study is to assess the use of antibiotics in the general population in Nepal, covering both public and private health facilities, and to examine factors associated with prescribing practices. The study provides an evidence base about current prescribing practices in the public and private sectors, which will be useful in documenting the way antibiotics are currently being prescribed, reveal the extent of the problem of inappropriate use, and provide guidance for developing strategies to reduce inappropriate prescribing and dispensing. It also provides a baseline against which to measure the effectiveness of future policies in reducing inappropriate use.

The survey of community members exploring their knowledge, attitudes and practices in regard to the use of antibiotics, provides helpful data for future work to educate the public about the problem of antibiotic resistance and raise awareness as to how to reduce inappropriate use. Similarly, information obtained from interviews with key informants examining their perceptions of factors associated with antibiotic use complements the data collected from community members, and contribute to work targeting reduction of the antibiotic resistance problem.

By exploring and integrating multiple sources of information, this study will assist policymakers to plan and implement future effective multifaceted interventions to promote the appropriate use of antibiotics among the Nepalese population, thus helping to limit the spread of antibiotic resistance. The findings may also be applicable to other low- and middle-income countries where the health system is similar to Nepal.

1.6 Thesis outline

The thesis contains 10 chapters, and comprises three parts. The first part (Chapters 1 to 4) includes the introduction, country review, literature review, and research methodology. In the second part (Chapters 5 to 8), the thesis presents the surveys of public health facilities, private health facilities, the survey of the knowledge attitudes and practices of community members, and the survey of key informants eliciting perceptions on antibiotics use and related factors. Each of the chapters in this part includes sections covering introduction, methodology, results and discussion. The final part of the thesis draws together the research findings and presents an overall discussion and conclusions.

Chapter One has introduced the topic of this thesis, the significance of the undertaking this research in Nepal, and the aim and objectives of the research.

Chapter Two presents descriptive information on the health system in Nepal to provide a context for the study. The chapter starts with an overview of the geographic, demographic, administrative and socioeconomic characteristics of Nepal. Thereafter, a brief introduction of the Nepalese health care system is provided, followed by a discussion of the pharmaceutical sector and overview of the study area.

Chapter Three reviews the literature related to antibiotic use and factors associated with antibiotic prescribing and dispensing. This chapter focuses on three main areas, namely antibiotic use and its consequences, antibiotic prescribing practices and factors associated with antibiotic prescribing. In addition, the conceptual framework guiding the study is discussed along with knowledge and the contribution of this study.

Chapter Four presents an overview of the mixed methods design adopted in this study. The quantitative research methods used to collect data in the surveys of antibiotic use in public health facilities, antibiotic use in private health facilities and the knowledge, attitudes and practices of community members to antibiotic use are briefly discussed, together with the qualitative research methods used in the survey of the perceptions of key informants on antibiotics use.

Chapter Five discusses the details of the survey conducted in public health facilities in the Rupandehi district of Nepal. The prescription information of public health facilities were collected from administrative health data and used to identify the patterns of antibiotic prescribing in those facilities.

Chapter Six discusses the details of the survey conducted in private health facilities. Exit interviews were conducted of patients attending the private health facilities, with these data on the patterns of antibiotics dispensing in private health facilities in the Rupandehi district of Nepal complementing the data on antibiotic use in the public sector.

Chapter Seven presents the details of the survey examining the knowledge, attitudes and practices of community members among adults in the Rupandehi district of Nepal. Data collection involved conducting face-to-face interviews with an adult household member using a structured questionnaire.

Chapter Eight presents the findings of the survey of the perceptions of key informants about factors influencing the inappropriate use of antibiotics. This study applied a qualitative methodology using a semi-structured questionnaire, with interviews conducted with service providers and local policy makers.

Chapter Nine presents an overall discussion of the major findings of each study, and integrates and interprets the findings in light of what was already known about antibiotic use, in particular in the context of LMIC. The chapter describes the strength and limitations of the study and implications of the findings for policy and planning to reduce the inappropriate use of antibiotics.

Chapter 2 Country review - Nepal

2.1 Overview of Nepal

Nepal lies in the mid-belt of the Himalayas. This landlocked country, located between India in the south and China in the north (68), occupies an area of 147,181 km^2 (71) and has a population density of 180 people per square kilometre (69). Physically, it is divided into three regions, high-hill (Himalayas), hill and low-land, running east to west with a non-uniform width from north to south. One-fifth (23%) of the country in the south is plains (low-land) and the remaining areas in the north are mountainous (high-hill and hill) (70).

Nepal has a population of 26.5 million with an annual population growth rate of 1.4% (69). The distribution of the population varies among the geographic regions, with approximately half of the population living in the low-land region (70). The literacy rate is 66%, with the rate higher for males (75%) than females (58%). Life expectancy is slightly higher among females (69 years) than males (67 years) (69).

The country is a federal democratic republic, organised around three levels of government: federal, provincial, and local (71). It is divided into seven provinces with the provinces divided into districts. The districts are further divided into municipal and village councils (72).

Nepal is a land of diversity in terms of ethnicity, language and religion. More than 130 ethnic groups with 123 different languages and a number of dialects are in use in the country (69, 73). It is a secular state, provides for freedom to practice one's religion and gives equality to all religions (71) even though it has a Hindu majority (74).

Poverty is acute in Nepal and the income distribution remains grossly uneven (75). The average per-capita income was US$1,025 in 2018 (76), slightly below the threshold set by World Bank of defining low income countries as those with a per capita income of less than US$1,026 (77).

2.2 Health system and health services in Nepal

2.2.1 National health policy

The National Health Policy of Nepal (2014) is based on achieving universal health coverage through the provision of basic healthcare services free of charge to the population (78). Non-basic health services are to be provided through social health insurance, with the Health Insurance Act enacted in 2017 making enrolment in the system mandatory for all citizens in both the formal and informal sectors (79). Prior to this, the scheme was voluntary and administered only in the informal sector. It is being phased in by the Ministry of Health and Population, with 22 districts covered by the end of 2018 (80). A new national public health act was issued in early 2019, which make necessary legal provisions for implementing the right to get free basic health service and emergency health service guaranteed by the Constitution of Nepal and establishing access of the citizens to health service by making it regular, effective, qualitative and easily available (81).

2.2.2 Organisation of health system

a) Structure of public health system

The health sector has undergone a number of reforms with expansion of health facilities in rural areas ensuring a public health facility in each electoral constituency and village development committee (78). The primary health care system is comprised of more than 4000 peripheral health facilities and includes the following: health posts and primary health care centres (PHCs) that report to district (public) health offices (82). These peripheral health facilities provide direct services to their communities, as well as overseeing community-based service delivery (immunization and outreach clinics), mostly relying on nearly 50,000 female community health volunteers (FCHVs). More serious cases are referred to 83 secondary level district hospitals, 15 tertiary level hospitals and 8 specialised hospitals (83).

b) Private health system

In the wake of several policy changes in the early 1990s, the Nepalese private health sector has expanded rapidly. The private sector has over two-thirds of the hospital beds and 60% of Nepal's doctors work in this sector (84). Along with many private hospitals and nursing homes, more than 16,000 private pharmacies (85) deliver health services. Private providers are mostly located in urban areas and are used predominantly by wealthier Nepalese patients. In rural areas where public facilities are accessed more than in urban areas (86) , pharmacies are the chief private providers. People often perceive private providers to be more responsive to consumers' preferences in terms of policy and speed of services, and they are more accessible than the public sector providers. Nevertheless, the quality of services that clients are receiving from private providers are generally regarded as failing to meet international standards (87).

c) Health financing

Financing sources in Nepal can be classified by contribution mechanism as government, private (households and hospitals) and 'rest of the world'. The rest of the world refers to financial support from foreign sources (to both the public and private sector). However, out-of-pocket expenditure is the largest source of funding in Nepal, followed by government expenditure (88). Out-of-pocket expenditure comes from the 'general public' as user fees and goes directly to health providers including pharmacies. High out-of-pocket payments generate the problem of financial protection especially for the poor. As a result, patients who are poor utilise health services less than wealthier groups, despite having a higher incidence of reported illness (89).

Total health expenditure in Nepal reached 141.46 billion Nepali rupees (NPR) in 2015/16, which is 6.3% of Nepal's GDP. Health spending per capita was around US$49 per year. Out-of-pocket expenditure represented more than half (55.4%) of total health expenditure and its share of total health expenditure has shown a slightly decreasing trend from previous years (90).

d) Education and training for health professionals

Medical education is largely dominated by the private sector (91), with 18 privately run medical colleges out of 21, and the private sector producing almost 90% of all medical doctors in the country. Similarly, the majority of allied health professionals are educated in the private sector (84). The duration of doctor's training is four and a half years with one year compulsory internship (92). However, different courses with different duration (i.e. one to three years) are available for allied health professionals (93). Laboratory technicians, health assistants, nurses, pharmacy technicians, radiographers, dental assistants and ophthalmic assistants are examples of allied health professionals who directly deal with the patient in Nepal (94, 95). Prescribing is conducted by physicians and non-physicians such as health assistants (post-secondary training in diagnostics and therapeutics), nurses and other paramedics (96). The physicians are designated at hospitals and the non-physicians called health workers mainly work at health centres and health posts. The educational training along with level of prescription authorities are different among the prescribers (97).

Three levels of pharmacy personnel exist in Nepal: pharmacists who have completed a four-year Bachelor degree in pharmacy after 12 years of schooling; assistant pharmacists with a three-year diploma in pharmacy after 10 years of schooling and "professionalists" (vyabasaiin the Nepali language), who only undertake a short training course designed by the Department of Drug Administration (DDA) (98). According to the Drug Act of 1978, all three levels of pharmacy personnel can run a community pharmacy after registering the pharmacy with the DDA, which is the government body dealing with medicines and their related affairs (94). Currently, one-third (33%) of private pharmacies are run by pharmacists and assistant pharmacists, however almost two-thirds (67%) are run by "professionalists" (99).

e) Health indicators

Soon after the re-establishment of constitutional monarchy and multiparty democracy in 1990 in Nepal, the government adopted the "National Health Policy 1991", with the aim to extend the primary health care system to the rural population so that they could benefit from modern medical facilities and trained health care providers. The underlying objective was to improve the health of the most vulnerable groups, women and children, the poor and the underprivileged and marginalised population of the country (100). The government has also adopted several other health policies over time, which collectively have resulted in a rise in the health status of the population. Life expectancy at birth for both sexes increased from 54.0 years in 1991 (101) to 71.6 years in 2017 (102), a gain of 17.6 years. Notable improvements in the field of maternal and child health have also occurred. A reduction in maternal mortality from 539 to 239 per 100,000 live births was noted between 1996 and 2016, neonatal mortality has fallen from 50 to 21 deaths per 1,000 live births, infant mortality has declined from 78 to 32 deaths per 1,000 live births, and under-5 mortality has declined from 118 to 39 deaths per 1,000 live births (103).

Despite these improvements, there remain disparities between urban and rural settings and richer and poorer sectors of the society. The prevalence of disease is significantly higher in Nepal than in other LMICs, especially in rural areas (104). A large section of the population, particularly those living in rural poverty, are at risk of infection and mortality by communicable diseases, malnutrition and other health-related events (104).

Although, Nepal's human development index has improved gradually since 1990, Nepal is still behind most of the LMICs. The 2018 Statistical Update put Nepal in the medium human development category, positioning it at 149 out of 189 countries and territories with a score of 0.574 in 2017. Nepal's score is still below the average score of 0.645 for the countries which are in the medium human development category (102).

f) Constraints and challenges

Though the government has made significant progress in health care, several constraints and challenges remain in the system.

- **Lack of resources**

As discussed previously, Nepal is a low-income country with an average per capita income of US$1,025 in 2018. Although per capita income has been increasing, it is still lower than other countries in the region including Pakistan (US$1,473), Bangladesh (US$1,698) and India (US$2,016) (76).

The health expenditure as a share of GDP for Nepal was 6.3% in 2015/16 (90), an increase from 5.6% in 2000/2001 (105). This increase was mostly driven by the increase in health expenditure by the government, which increased from 16% of total health expenditure in 2001 (105) to 26% in 2015/2016 (90). However, out-of-pocket payment remained the main source of health expenditure over the period, falling from 60% in 2001 to 55% in 2015/2016 (90).

Limited resources have led to the understaffing of health facilities. Furthermore, limited resources are being inappropriately utilised due to a lack of good governance (106).

- **Workforce issues**

Many positions for medical doctors and health workers are vacant in primary health care centres and health posts (97, 107), which is a hindrance to providing even basic health care services. Health facilities are only open for certain hours (108) and low attendance of health workers at health facilities is also a concern (109). Some health workers run their own private pharmacies as a supplementary source of income, potentially compromising commitment to their main health facility responsibilities (109). District-level staff are frequently away on training workshops, which compromises their ability to supervise and monitor at the peripheral health facilities (107).

- **Medicines in public health facilities**

Some essential medicines are provided free of charge at public health outlets, however shortages occur in the peripheral health facilities (110). Timely availability of those medicines in remote areas has been another issue facing the Nepalese public health sector. The government's lengthy tendering process results in delays in the procurement process (111). Medicine procurement and supply are not well coordinated and medicines remain on hold or in storage for a considerable period of time, further contributing to the shortage of medicines. Insufficient budget allocation to purchase medicines is another reason that health facilities often experience shortages of certain types of medicines (85).

- **Governance or stewardship**

Lack of good governance is a major issue in Nepal's health system. Poor supervision and monitoring has led to an increase in absenteeism of service providers in the health facilities. Moreover, shortages of medicines, and mismatches between plans and actual health needs contribute to poor performance (82, 112, 113). Financial management has been another issue in health care authorities, with most spending occurring late in the financial year that further compromises the quality of services delivered. Additionally a few financial reports and audits have suggested problems in regard to financial management of facilities (106). Overall, the stewardship of health care of the country is becoming a growing task and a sizable challenge for the Ministry of Health and Population.

2.3 Pharmaceutical sector in Nepal

2.3.1 Legislation and regulatory agencies

Legislation related to pharmaceuticals has been enacted in Nepal in the past four decades. The Drugs Act, 2035 (1978) was enacted in 1978 and paved the way for establishing the national drug regulatory authority, the Department of Drug Administration (DDA), which is responsible for registration of all medicines and pharmacies in Nepal (114). The Nepal Pharmacy Council Act, 2057 (2000) was endorsed in 2000 in order to register pharmacists and pharmacy assistants (115). In 1995, Nepal's National Drug Policy (116) was formulated and then updated in 2007 (116) with an aim to ensure that the general population have access to safe, effective and quality medicines at an affordable price. These acts and policies are an integral part of the National Health Policy 2014 (78).

Various regulations are made under these acts, which guide and regulate the pharmaceutical functions of the country. Some trade related acts and government bills (99) are also directed at drug-related functions such as pharmaceutical production and distribution. According to these acts, the DDA under the Ministry of Health and Population (MoHP) is authorised with expanding its functions to regulate and control good pharmacy practices in the country (117). Its functions include to regulate appropriate drug use and its raw materials, and ensure access to available, safe, efficacious and quality drugs to the general public by controlling the production, marketing, distribution, sale, export, import, storage and use of drugs (116). However, given its functions, the DDA faces challenges in fulfilling all its obligations given the limited staff (85).

2.3.2 Regulation of appropriate use

As a consequence of the increasing trend of drug resistance, especially antibiotic resistance to particular microbes, monitoring of drug use patterns by public and private is equally important to understand the situation and address the issues related to inappropriate drug use. The government has developed some policies and guidelines to promote rational use of drugs. The National Drug Policy 2007 (116), Nepalese National Formulary 2010, Hospital Pharmacy Guideline 2072, Standard Treatment Guidelines (85) and some other acts (117) are available. Standard treatment guidelines for medical doctors and health workers, who have authority to prescribe, exist, however these are nominally present and are often sub-optimally implemented (85). The National Good Pharmacy Practice Guidelines are not yet published by the government (99).

2.3.3 Medicine market

The provision of affordable, high quality and appropriate essential medicines is a vital component of a well-functioning health system (118).

Nepal's health care policies promote and regulate the quality and standards of all types of medicines, including allopathic, ayurvedic, homeopathic and traditional medicines (116, 119). The Nepalese pharmaceutical sector is mainly dominated by western allopathic medicines but other medicines are also produced in the country. The government has one manufacturer, however, about 347 manufacturers (national and international) are in operation. The majority of manufacturers produce allopathic medicines but 64 manufacture ayurvedic medicines and about 30 manufacture veterinary medicines (85). All the products are available in private facilities, however only limited products are available in public health facilities.

2.3.4 Procurement system

Central and local procurement systems are embedded in the medicine procurement in the public health sector in Nepal. The logistics management division is responsible for central government procurement and supplies to the districts for use at district hospitals and lower level health facilities. Pooled donor funds are used for the free drugs supplied to districts for use at district hospitals and lower level health facilities (85). Budgets are also available for districts for local procurement. Local procurement generally occurs about twice a year. Most district purchases are small and must follow the government rules. International competitive bidding process needs to be undertaken when procuring these free drugs using pooled donor funds. Nevertheless, the lengthy tendering process results in delays in the procurement process (111).

However, Nepal has progressed towards a federalized heath care system with reform occurring in this direction, for example, the establishment of municipal hospitals and procurement systems to adjust to the new federal structure of Nepal. This has resulted in the role of the central Logistic Management Division diminishing and provincial health logistic management centres being empowered.

2.4 Overview of study area

The Rupandehi district was selected as the study area for the research. It lies in the southern lowland region of Nepal and accounts for approximately one percentage of the land area of Nepal. According to the most recent national census in 2011, the total population of the Rupandeh district was 880,196, comprising 163,916 households (69). The population density per square kilometre of land area is 647, which is 3.6 times higher than Nepal's average of 180 persons per square kilometre (69).

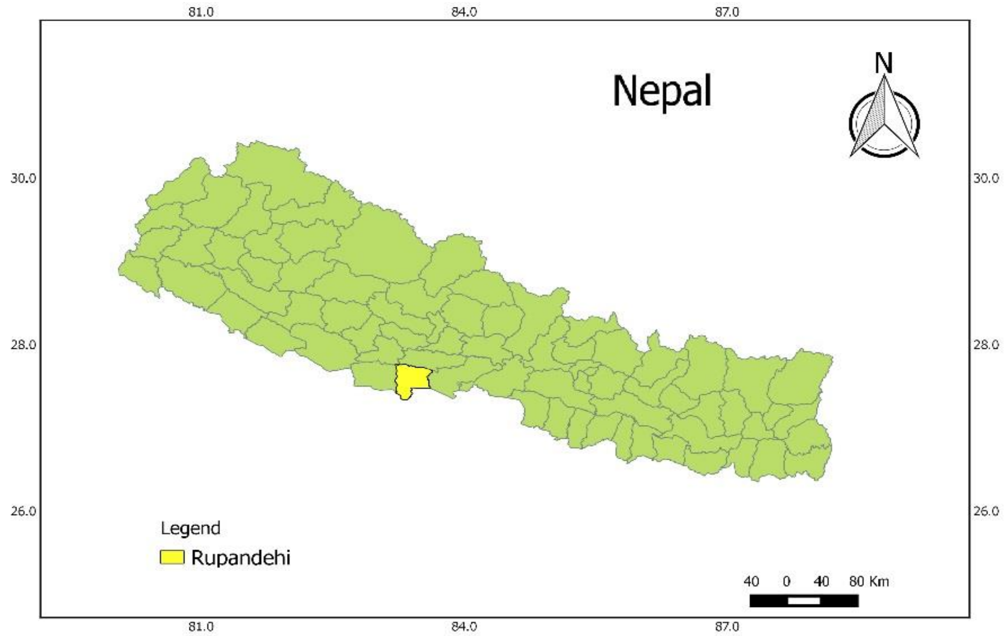

Figure 2.1 Map of Nepal indicating study district

The population is almost equally distributed in urban and rural areas. More than 63 castes/ethnicities are residing in the district (109), out of 125 castes/ethnicities in the country (69). The literacy rate of Rupandehi is slightly above the national average (69.8% versus 65.9%). Similarly, the value of the human development index (0.498) is higher than the national average (0.458) (120).

In 2015, Nepal adopted a new constitution that included the concept of local governance, and three level of governments - federal, provincial and local. As per the constitution, Nepal is divided into 7 provinces, 77 districts and 753 local government units (121). Rupandehi is one of the districts in the new structure, and is divided into 16 councils (local government unit) with nine village and seven municipal councils. However, at the time of developing the study design for this research, the re-structure had not been fully implemented. Thus, the sampling strategy was based on the earlier structure in which the district was divided into six municipalities and 42 village development committees (VDCs) (122).

In terms of health, the public sector health programmes in Rupandehi are implemented through two hospitals, five primary health care centres, 64 health posts and sub health posts and six urban health centres in the district. In the rural areas, the majority of the population have to rely on health posts and sub health posts staffed with health assistants

(36 months training), auxiliary health workers (15 months training), and auxiliary nurse midwives (18 months training) (122). In addition to the public sector facilities, two private medical college hospitals and one non-government organisation children's and women's hospital are in the district (107). A few private hospitals have recently opened in the city area. Of 449 registered private pharmacies/shops, 396 (88%) are located in urban areas and 53 (12%) are in rural areas (123). The Rupandehi district shares its border in the South with India, and the open border provides the population with access to healthcare and unregistered medicines in India, including antibiotics.

Rupandehi was selected as the study area for several reasons. It has an almost equal mix of urban and rural residents (122, 124) and a well-represented population of different castes and ethnicities with more than 63 castes/ethnicities residing in the district (73) out of 126 castes/ethnicities in the country (69). Within the district, there is varying access to transport, with good transport only available in urban areas, which is similar to other districts of Nepal.

2.5 Conclusion

This chapter has reviewed the country context of the study in terms of geographic, demographic, administrative and socio-economic characteristics. It has also presented descriptive information on the health system in Nepal including a brief discussion related to the pharmaceutical sector. An overview of the study area has also been presented.

In the next chapter, an overview of the literature on antibiotics use and prescribing practices in the healthcare sector is presented. The chapter reviews the literature relating to three specific areas: antibiotic resistance and its consequences, antibiotic use and antibiotic prescribing. It also discusses the influencing factors that are associated with inappropriate behaviour in regard to antibiotics prescribing and use.

Chapter 3 Literature review

3.1 Introduction

Antibiotic use and prescribing practices have been extensively discussed in the healthcare literature. This literature has highlighted the issue of inappropriate use of antibiotics and its impact on antibiotic resistance and other consequences. Additionally, factors associated with inappropriate prescribing and use of antibiotics has been explored.

This chapter presents a narrative review of the following areas relating to the inappropriate use of antibiotics in LMICs:

1) Antibiotic resistance and its consequences

2) Antibiotic use: appropriate and inappropriate antibiotic use, self-medication, and over-the-counter use, knowledge, attitudes and practices of community people on antibiotic use and;

3) Antibiotic prescribing: appropriate and inappropriate antibiotic prescribing, and factors associated with antibiotic prescribing.

The chapter concludes with an overview of key findings and research gaps in regard to antibiotic use in Nepal.

3.2 Methodology

This review was conducted to explore antibiotic use, prescribing practices and factors associated with antibiotic prescribing in low- and middle-income countries (LMICs). Given the far-reaching nature of the topic, a narrative review was selected as the appropriate approach to synthesise the literature (125). Narrative reviews are useful for obtaining a broad perspective on a topic and linking together heterogeneous studies to report on current knowledge relating to the issue of interest (125, 126).

To search the literature in a systematic way, the review followed the methodological framework described in the 2017 Guidance for the Conduct of Joanna Briggs Institute (JBI) Scoping Reviews (127). Articles were identified using the “population-concept-context (PCC)” framework recommended by the Joanna Briggs Institute. Key search terms for the population of interest included “health personnel”, “general population”, and “community”. For concept, search terms included “antibiotic use”, “appropriate antibiotic use”, “inappropriate antibiotic use”, “factors associated with antibiotic use/prescribing/dispensing”, “self-medication” and “over the counter purchase or sell”. The context was “low- and middle-income countries” or “developing countries” **(Table 3.1)**. A combination and variations of these terms, including appropriate MeSH terms and the Boolean operators (i.e., AND, OR) were used. The term “antibiotic” and “antimicrobial” were used interchangeably, as is done in the literature.

The following electronic databases were searched: Medline, Science Direct, Scopus, Embase and ProQuest. Additional publications were identified from a hand search of the reference lists of included studies. The exact number of articles screened was not recorded, given the narrative nature of this review.

Potential studies were identified by using inclusion and exclusion criteria. Articles published in English containing relevant data on the use of antibiotics was the major inclusion criterion. Specifically, references were included using the following criteria: i) study population included health workers, medical doctors, physicians and community members; ii) studies covering antibiotic use and misuse; iii) findings from studies conducted in LMICs; iv) English language; and v) qualitative, quantitative, or mixed-method studies; and vi) articles published from 2010 until the current period. A few studies pre-dating 2010, have also been reported if the information was relevant and identified from references lists of included studies. To provide a context, some information form official documents relating to the health system in Nepal is included.

Articles were excluded if i) the study population was a specific sex, age group or related to a specific condition or ii) the study was an animal study. The search generally excluded studies from high-income countries. However, if included studies from LMICs made reference to relevant findings from studies conducted in high-income countries, a selection of these studies were sought for inclusion. Letters, commentaries, reviews, discussion papers, editorials, and conference proceedings were also excluded.

Table 3.1 Concept grid of search terms and exclusion criteria

PCC	***Search terms***	***Exclusion criteria***
Population	*'health personnel', 'general population', community*	*Studies for which the focus was a specific sex, age or condition, and animal studies*
Concept	*'antibiotic use', 'appropriate antibiotic use, 'inappropriate antibiotic use, factors associated with antibiotics use/prescribing/dispensing', 'self-medication', 'over the counter purchase or sell'*	*Medicines other than antibiotics*
Context	*'low- and middle-income countries', 'developing countries'*	*Developed countries, high income countries**

**Selected findings relating to high-income countries were included for comparison purposes.*

Articles were reviewed at the title and abstract level, and those appearing to satisfy the inclusion criteria were obtained in full-text and screened for relevance. Data from included studies were extracted and tabulated using Microsoft Excel, with the fields in the data extraction sheet including bibliographic information (authors, title, year of publication, etc.), and study characteristics (aims and objectives, geographical scope or jurisdiction, key findings and conclusion).

3.3 Antibiotic resistance and its consequences

Since their discovery in the 1940s, antibiotics have become a vital source of medicine (2). Antibiotics are widely used as either prophylaxis or therapeutic treatment, with considerable benefits to human health (128), saving countless lives (2). However, widespread use, misuse or inappropriate prescribing has resulted in the emergence of drug resistant bacteria (128), with antibiotic resistance now a worldwide issue and a serious public health concern.

Studies have reported that the number of infections due to antibiotic-resistant bacteria is growing and outpacing the rate at which new classes of antibiotics are discovered and synthesised (38, 129). After its innovation, penicillin became a choice of antibiotic for many diseases such as venereal disease, pneumonia, and meningococcus. However, these diseases have become less responsive to antibiotic treatment. For instance, antibiotic-resistant gonorrhoea emerged in Vietnam in 1967 (130), followed by the Philippines, and the United States of America (USA) (131). Later, *Streptococcus pneumoniae* and *Meningococcus* became resistant to penicillin. Over time, many other organisms have been reported as being less responsive to antibiotics in different part of the world.

In particular, LMICs, which are tackling the convergent problem of non-communicable and infectious diseases (132) are facing particular challenges in regard to antibiotic resistance. A high proportion of the *Escherichia coli* and *Klebsiella* species has been found to be resistant to ampicillin, amoxicillin and cotrimoxazole (133, 134), as have *Vibrio cholera* strains to commonly used antibiotics (135). *Pneumococcal* has been found to be resistant to levofloxacin in Hong Kong and Korea (136). Resistance of microorganisms to ciprofloxacin has emerged in Hong Kong, and also in Sri Lanka, Philippines, Korea (137-139), and India (133).

In Nepal, studies have shown high rates of resistance to commonly used antibiotics (57, 140-143). For example, more than half of *Streptococcus pneumoniae* and *Klebsiella pneumoniae* isolates have been found to be resistant to cotrimoxazole and ciprofloxacin (140), while high rates of drug resistance of *Klebsiella pneumoniae* to cotrimoxazole, ciprofloxacin, azithromycxin and cefixime have also been identified (57). Another study conducted in Nepal reported that, out of 118 isolates, one-third were resistant to all these four antibiotics (144). In the case of *Shigella*, most isolates were resistant to ampicillin, nalidixic acid, cotrimoxazole and ciprofloxacin (141).

Infections with drug-resistant bacteria have increased not only morbidity and mortality but also duration of hospitalization and cost of treatment (22). When infections become resistant to first-line antibiotics, more expensive second-line therapies must be used, resulting in a longer duration of illness and treatment in hospitals which often increases health care costs as well as the economic burden on families and societies (145, 146). Fears about antibiotic resistance have led to several reports of the impact on humans and suggested as many as 10 million extra human deaths per year by 2050 if action is not taken to reduce antimicrobial resistance (33).

Rapidly emerging resistant bacteria threaten the health benefits that have been achieved with antibiotics (147). This crisis is global, reflecting the worldwide inappropriate use of these drugs and the lack of development of new antibiotic agents by pharmaceutical companies to address the challenge (147). Thus, these issues are important not only for the medical profession but also policy makers and the general population to understand how to better use antibiotics to optimise their beneficial effects, while minimising the risks of resistance. Nevertheless, the majority of published studies (133-135, 137, 138, 148-150) are hospital based, focusing on a particular drug resistance, with very few having examined the extent of antibiotic use in the general population and factors relating to their use.

3.4 Antibiotic use

3.4.1 Appropriate and inappropriate antibiotic use

The terms "appropriate" or "rational" drug use or prescribing are interchangeably used by the World Health Organization (WHO) (22). These terms refer to the situation in which “patients receive antibiotics appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, according to the country’s standard clinical protocol" (1 p. 151). Thus, inappropriate antibiotic use can be defined as when any of these conditions are not met and in general includes situations when a course of antibiotics is not completed or antibiotics are misused or overused.

Globally more than half of all medicines are reported as not being properly used and among them up to half of antibiotics used in community settings are unnecessary (35). Antibiotics can successfully treat bacterial infections but are useless against viral infections as viruses have a different structure and mechanism of surviving (152).

The unwarranted use of antibiotic agents for some respiratory and urinary tract illnesses is noted extensively in the literature (41, 128). These are the most common illnesses experienced worldwide (153, 154), accounting for numerous visits to physicians and imprudent prescriptions of antibiotics (39). For example, excessive use of antibiotics is found to be commonplace for cough and bronchitis (155), while these illnesses including other respiratory illnesses are largely viral and self-limiting, and antibiotics offer little or no benefit as treatment (40). Up to 75% of all antibiotic prescriptions are generated for respiratory illnesses each year in the United States, as these conditions are the most frequent reason for seeking medical care (156).

In 2011, the WHO set the theme of World Health Day as to 'Combat Antimicrobial Resistance: No Action Today, No Cure Tomorrow' (157). This reflected the seriousness of the inappropriate use of antibiotics as a global health problem and the growing consensus to urgently develop new strategies for prevention of resistance of bacteria to antibiotics. Understanding what factors may influence the inappropriate use of antibiotics is therefore important.

3.4.2 Self-medication and over-the-counter use

Self-medication has traditionally been defined as "the taking of drugs, herbs or home remedies on one's own initiative, or on the advice of another person, without consulting a doctor" (158). However, self-medication with antibiotics is a major concern, which constitutes a major form of inappropriate use of medicine and can cause significant adverse effects such as resistant microorganisms, treatment failures, drug toxicity, increase in treatment cost, prolonged hospitalization periods and an increase in morbidity (16, 159).

Similarly, selling a wide range of medicines as over-the-counter (OTC) drugs is another inappropriate drug use practice, which may have similar consequences to self-medication. The sale of antibiotics without prescriptions is a major concern in LMICs, where a clear and official list of issued OTC medications is often lacking. As a result, community pharmacies are able to sell a wide range of antibiotics as OTC products (160). Community pharmacists have increasing become involved in the self-management of minor and moderate illnesses (161), contributed to an increase in the use of non-prescription antibiotics. From a patient perspective, obtaining antibiotics from pharmacies without a prescription is easier and less expensive than having to pay to consult a physician at the health facilities (162).

A recent systematic review estimated that more than one-third of the population in LMICs used antibiotics without prescription (50), which included self-medication and OTC use. Though the prevalence of self-medication was high in LMICs (50, 159), the magnitudes varied widely with some studies reporting it to be as low as 4.0% in Yemen (163) ranging up to as high as 91.4% in Nigeria (164). For other countries the rates fell between these two extremes, such as 46% in Jordan and 74% in Sudan (165). A similar variation has been found in high income countries, with studies reporting prevalence rates ranging from 78% in Greece (166) to 3% in Denmark (167).

Several factors have been associated with self-medication practices especially in LMICs. Major factors include lack of access to health care, availability of antibiotics as OTC drugs, poor regulatory practices and the relatively higher prevalence of infectious diseases in LMICs (168-170). In addition, economic factors have been shown to be a driver of self-medication practices. For example, in a Ghanaian study, the inability to pay for hospital costs was a reason cited for self-medicating, which was considered to be cheaper (171), and other studies have also linked self-medication to high health care cost (50, 165). Lack of enforcement has been suggested as a reason for continued use of antimicrobial self-medication (172).

In Nepal, a wide range of antibiotics are available on the market and acquiring drugs OTC is a very common practice (173). This can facilitate self-medication, which is thought to be highly prevalent in the Nepalese community. Recent studies have shown a high level of drug resistance among pathogens to many of the antibiotics available on the Nepalese market (57, 140-143). This could result in treatment failures and several clinical complications for people practicing self-medication.

3.4.3 Knowledge, attitudes and practices of community people relating to antibiotic use

Existing literature has highlighted knowledge, attitudes, and practices of community members relating to antibiotic use as one of the main drivers of inappropriate antibiotic use (174-176). These studies assessing antibiotic knowledge, attitudes and practices provide a tool for identifying problems as well as possible solutions to reduce inappropriate use.

Within the context of this study, antibiotic knowledge is defined as what is known about antibiotics, attitudes to antibiotics is defined as how antibiotics are perceived, while practices refers to the act of using antibiotics.

A considerable body of recent evidence has identified widespread problems in the knowledge, attitudes and practices of community members regarding their antibiotic use (177-180). Community surveys conducted in LMICs have shown lack of knowledge (148) and inappropriate behaviour and practices such as acquiring non-prescription antibiotics, taking leftover antibiotics or those prescribed for a previous illness and not completing a course (178, 181). Although, the level of knowledge and behaviour of community members differs between LMICs and high-income countries, in both cases people living in rural areas tend to have considerably less knowledge and more inappropriate practices relating to antibiotic use (182).

Lack of knowledge about antibiotics is a contributory factor to practices leading to inappropriate antibiotic use. A study conducted in Hong Kong highlighted that lack of knowledge about antibiotics was a critical determinant of non-adherence in the community (183). Insufficient knowledge about antibiotics and problems with resistance increases the likelihood of self-perceived treatment needs (183) and the consumer tends to self-medicate or purchase over-the-counter or demand antibiotics from the physician. The physician may feel pressured by the patient's expectation of an antibiotic even in the absence of clinical indications (184). Apart from these, other factors such as, family income (185, 186), areas of residence (187), gender (188) and education (43) have been identified as being associated with inappropriate antibiotic use.

In Nepal, only a few studies have examined the knowledge, attitudes and practices of specific groups relating to antibiotic use, rather than the community more generally, with these studies often evaluating the effectiveness of an intervention. The focus of these studies was the knowledge, attitudes and practices towards antibiotics use by undergraduate (189) and high school students (190). Other studies examining knowledge, attitudes and practices have been in relation to medicines more generally with school teachers and pregnant women (191, 192) and pharmacovigilance with health professionals (193). An educational intervention to improve medicine use was also evaluated (194).

3.5 Antibiotic prescribing

3.5.1 Appropriate and inappropriate antibiotic prescribing

Inappropriate antibiotic prescribing is a major problem worldwide that has had long-standing recognition. In 1985, with the threat of drug resistance increasing, the WHO convened an international conference in Nairobi, Kenya, to develop a national essential drugs programme as a mechanism for emphasising drug selection, procurement, distribution and use under the umbrella of a national drug policy (195, 196). The concept of developing a drugs programme was to improve health status by increasing access to essential drugs and their appropriate use, with better health linked to development and economic gains in the medium and longer term (197).

In order to measure the extent of appropriate prescribing practices the following major five core drug indicators were introduced (198, 199) **(Table 3.2)**.

Table 3.2 Standards of core drug indicators

Core drug indicators	Optimal value
Percentage of prescription encounters with an antibiotic	20.0 - 26.8%
Percentage of drugs prescribed by generic	100%
Percentage of drugs prescribed from essential drugs list	100%
Average number of drugs per prescription	1.6 - 1.8
Percentage of prescription encounters with an injection	13.4 - 24.1%

Source: World Health Organization (198, 199)

As recommended by the WHO, many countries, implemented an effective national drug policy, promoting appropriate drug use (195, 196). However, inappropriate practices have continued in many countries (200) despite efforts put in place to promote better practices (201-203). Inappropriate prescribing has been found in the USA and Europe, ranging from 12% in community-dwelling elderly to 40% in nursing home residents (204), and over and under prescribing of antibiotics in primary care occurring in most European countries too (205, 206). These practices are also common in LMICs, where only around 40% of prescribing has been found to be compliant with clinical guidelines (35, 207, 208).

a) Prescription encounters with an antibiotic

Improved prescribing behaviour of health workers is one of the expected outcomes from efforts such as promoting appropriate drug use through the introduction of National Drug Policies and an Essential Medicine List. However, reports have suggested that rates of prescribing of antibiotics are high if measured against the optimal value specified by the relevant WHO indicator of 20.0 to 26.8% of prescription encounters being with an antibiotic (172). Percentages of prescriptions with an antibiotic were highest in the Eastern Mediterranean region (53.2%), the South Asian region (48.0%) and the African region (46.8% - 47%) and lower but still above the WHO recommended values in the European region (33.5%) and the Americas (39.3%) (209, 210).

On a country basis, antibiotics were generally more prevalent on prescriptions in LMICs, with the values varying across countries. In studies conducted in Nigeria (211), China (212), and Saudi Arabia (213), the rate of prescriptions encountered with antibiotics fell within WHO's recommended range (20.0 - 26.8%). Studies conducted in Egypt (214), Kuwait (215), Pakistan (216), Palestine (217), India (218, 219) and Ghana (220) have shown prescriptions of antibiotics falling within the 30 to 60% range, whereas studies conducted in Bangladesh (221) and Ethiopia (222), showed extremely high rates in the 60 to 70% range. Lower prescribing rates in Nigeria, China and Saudi Arabia could be associated with the implementation of special rectification activities for prudential use of antibacterial agents during the period (211, 212). Financial inducements and logistical benefits (e.g. gifts) from drug companies could be factors encouraging high rates of prescribing of antibiotics, even for minor ailments, in Bangladesh and Ethiopia (221, 222). High levels of antibiotic prescribing in LMICs may partly be accounted for by the high burden of infectious diseases within these countries (210, 223). In addition, antibiotic misuse may be due to lack of enforcement of regulations and to the impact of promotion of antibiotics by the pharmaceutical industry (172).

b) Antibiotic prescribing practices in Nepal

In Nepal, prescribers fall into two types: physicians who work in the hospitals and health workers who work mainly in lower level health care facilities. Both types of prescribers are authorised to prescribe antibiotics, with the guidelines limiting the authority to prescribe different types of antibiotics (224). However, such guidelines are barely used in practice nor are they monitored (225). The low number of physicians to patients (0·17 per 1000 population) (226) indicates that most Nepalese must rely on health workers as the primary source of health care. However, a perception is that the health workers have limited training on therapeutics and often give incorrect advice and dosages of antibiotics (57).

Antibiotics are the most prescribed drugs in Nepal (225). A study reported that nearly two-thirds of patients (64%) were prescribed antibiotics, with 73% receiving more than one antibiotic (227). Evidence has suggested that antibiotic prescribing patterns were often inappropriate with between 10 and 42% of patients having inappropriate prescriptions (57). Another study conducted in private pharmacies found that, contrary to clinical guidelines, 11 different antibiotics were prescribed for the treatment of respiratory tract infections with a duration ranging from 5 to 10 days (58).

Third generation cephalosporin is becoming the treatment of choice for physicians, especially in hospital settings (228), although treatment guidelines do not recommend it as a first-line treatment for several infections (224). Cotrimoxazole and amoxicillin were common choices for the prescribers in lower level health care facilities (229). A majority of antibiotics are easily available from pharmacies and used widely without prescription (59).

Some other studies conducted in Nepal have reported on issues of prescription practices (65, 66), drug utilisation (67) and knowledge of outpatients about appropriate drug use (66), however these studies have been hospital based and not covered private pharmacies or the general population. Because of the high practice of self-medication in LMICs (50), including Nepal, community members in these countries are mostly reliant on the instructions of pharmacists (60, 61). In such cases, the roles of pharmacists are not only confined to dispensing (62, 63) but also involved in prescribing (64). Limited information is available comparing (i) the prescribing and pharmacy practices of the public and private sectors and (ii) factors relating to differences in prescribing practices between hospitals and the community setting.

3.5.2 Factors associated with antibiotic prescribing

Inappropriate prescribing of antibiotics in LMICs is influenced by many factors including unavailability of updated clinical guidelines (230), lack of clinical knowledge and the behaviour of service providers (46, 47, 231), the shortages of drugs (232) and excessive pharmaceutical promotion (233).

a) Unavailability of clinical guidelines

Developing standard treatment guidelines are a strategy that can be implemented to promote prudent antibiotic prescribing (172). Treatment guidelines offer potential benefits for patients by improving their health outcomes through improving the quality of clinical decisions (234). Particularly, guidelines can assist health care professionals to provide good quality of care by decreasing inappropriate variation on prescriptions and expediting the application of effective new treatments in everyday practice (235).

Various studies have highlighted the effectiveness of treatment guidelines, outlining their contribution to significant decreases in exposure rates to antibiotics and an increase in more appropriate antibiotic prescribing. For example, in China, a considerable difference was found before and after implementation of antibiotic treatment guidelines in hospitals, with antibiotic use decreasing by a statistically significant 22.6% after implementation (236). In Serbia, a significant change was found in the prescribing patterns of antibiotic prophylaxis in Caesarean section following introduction of local guidelines, with the use of ceftriaxone (46.0%), amikacin (5.0%) and metronidazole (15.0%) decreased although statistical significance was not tested (237). In Thailand, the introduction of guidelines for acute respiratory infection was also found to lead to more appropriate prescribing in the post intervention phase (238).

Treatment guidelines are particularly useful in resource-poor countries where they can be used to streamline treatment protocols (239), however developing a guideline is not enough, rather the guidelines must be updated regularly on the basis of changes in evidence and be made available to health care facilities (240). In Nepal, the government has developed policies and guidelines such as the National Drug Policy 2007 (116), Nepalese

National Formulary 2010 and Hospital Pharmacy Guideline 2072 (117). Standard Treatment Guidelines for physicians and health workers, who are registered in their respective councils and have authority to prescribe, are also available (85). However these policies and guidelines are only nominally present and are often sub-optimally implemented (85). National Good Pharmacy Practice Guidelines are not yet published by the government (99).

b) Knowledge, attitudes and practices of service providers

Judicious selection of antimicrobial agents for infectious diseases requires healthcare providers to have detailed knowledge on bacteriological and pharmacological factors (241) and corresponding therapeutic profiles (242). Studies across several LMICs support this association between knowledge of healthcare providers on bacteriology and appropriate antibiotic prescribing. For example, a study conducted in Lesotho found healthcare providers lacking sufficient knowledge in the bacteriology of infections and principles of antibiotic prescribing, resulting in higher rates (57.0%) of inappropriate prescriptions issued (242). Similarly, a study conducted in seven countries in Latin America and the Caribbean highlighted that physicians had inconsistent and unclear knowledge on infections and empiric treatment, leading to inappropriate prescribing of antibiotics especially for acute respiratory and diarrhoeal infections (243). Studies conducted in Congo (47) and India (49) revealed the similar findings.

Attitudes and perceptions of service providers have also been shown to be related to inappropriate prescribing. Expectations of patient about receiving an antibiotic tend to place pressure on providers to prescribe antibiotics even against their clinical judgement (244, 245). A concern of prescribers is to maintain patient satisfaction at a high level (246) and avoid potential conflict in order to not lose patients to other providers (247). Additionally, in studies conducted in India, physicians have indicated they are more likely to prescribe antibiotics because patients often have to pay for the consultation and wait for a considerable time prior to the consultation (248, 249). Similar concerns on the demand and expectations have been found in the United States (250), United Kingdom (247), Malta (251) and the Netherlands (252).

The problem of over prescribing in LMICs is exacerbated by diagnostic uncertainty resulting from the unavailability of required tests (253). Syndromic management of diseases is common in health care facilities of most LMICs due to the unavailability of microbiology laboratory facilities. The WHO has reported the issue of syndromic management and its impact with disease association, including that it is often ineffective and increases the risk of antibiotic resistance (254). In conditions, such as respiratory tract infections and diarrhoea, clinicians have difficulty in diagnosing at the early stages of disease whether an infection is viral or bacterial (248). Generally, in public primary health care facilities in LMICs, microbiology laboratory facilities are not available and most patients who visit these facilities cannot afford the tests from private laboratory, thus prescribers rely mainly on their clinical acumen (248). Thus, it was suggested that lack of laboratory facility in LMICs, often a barrier to deal with major infectious diseases (255) .

Very little information is available in Nepal about clinicians' knowledge on bacteriology of infections and corresponding treatment. A study in which community pharmacists were interviewed, demonstrated an inadequate understanding of disease processes and appropriate drugs, with unnecessary antibiotics dispensed for the treatment of diarrhoea and dysuria (256). Only 25% public health facilities in Nepal, have their own microbiology laboratory and many offer a limited variety of tests (257).

c) Other factors associated with antibiotic prescribing

The promotion of drugs by pharmaceutical companies and their distributors, including medical sales representatives, induces over prescription of medicines. Interactions between physicians and the representatives of pharmaceutical companies while desirable, may create conflicts of interest (258). In many LMICs, the medical representatives are the main source of information about medicines, especially new antibiotics (259). However, they have been found to exaggerate the benefits of medicines and downplay the risks and contraindications (45, 260, 261).

Medical representatives adopt different approaches to encourage sales such as offering gifts, free samples, free lunches, plane tickets, expenses paid for conferences and research funding (262). Studies conducted in Saudi Arabia (263), India (264), Pakistan (265) and

Ethiopia (266) have all found that clinicians were influenced in their prescribing by medical representatives. In the case of Nepal, most hospitals allow free access of medical representatives to doctors, and in the majority of cases independent academic detailing is absent (267).

Pharmaceutical companies also offer good business deal to private drug sellers that put an emphasis on selling profitable antibiotics, which may impact on supplying and dispensing newer and more expensive antibiotics in the private sector (268). For example, a meta-analysis of clinical trials found that in treating uncomplicated acute bacterial sinusitis, amoxicillin and folate inhibitors are just as effective as third generation cephalosporins (269). However, third-generation cephalosporins are commonly used in the private health facilities of LMICs (270-272), with these being more expensive than the conventional antibiotics (273).

In regards to the public sector, essential medicines are free in the public facilities of some LMICs (274). However, inconsistent supply (118), over-stocked and near-expiry drugs (45) were some of the factors that have been found to promote antibiotic overuse. Medicines are suppled from central store and the supplies are sometimes erratic with no supply of some medicines (including antibiotics) for a few months and oversupply later on. To use the entire stock before it expires, prescribers prescribe these drugs even if not required by the patient (248). In Nepal, monitoring of drug supplies and ordering is still ad hoc and providers complain about medicine being unavailable and unnecessary ones being prescribed (85).

3.6 Summary

3.6.1 Key findings

The literature on antibiotic use and prescribing practices demonstrates the increased problems of overuse of antibiotics and inappropriate prescribing. Globally, antibiotic use is increasing, with much of this increases caused by a rapid increase of use in LMICs. The expansion of the economies of LMICs has increased access to medicines including to antibiotics. Antibiotic consumption rates in many LMICs are catching up with those in high-income countries, however, usage is often unnecessary due to a range of factors including the lack of supportive regulation, lack of diagnostic facilities and widespread informal use.

Globally, half of antibiotic use in humans is unnecessary and nearly one-third of antibiotics are prescribed inappropriately. The unwarranted use of antibiotic agents for some common illnesses, noted extensively in the literature, accounting for unnecessary expenditure on health services including physician visits and prescriptions.

While the WHO has recommended implementing national drug policies that promote appropriate drug use, the level of prescribing of antibiotics in many countries has been shown to exceed the thresholds set by WHO for appropriate use. Self-medication and selling medicines as OTC are also contributory factors of inappropriate use, leading incorrect medicine use and doses. Although, the prevalence of self-medication and OTC was found to be high in LMICs, the magnitudes varied widely among the countries. A clear and official list of OTC medications is lacking in some LMICs, as a result a wide range of medications including antibiotics are available as OTC products.

The literature highlighted that antibiotic use is influenced by several factors, including the behaviours of service providers and consumers. Individual knowledge about antibiotic use impacts the behaviour of consumers and contributes to inappropriate use. Likewise, inappropriate behaviour of consumers often increases the demand as a result of physician being pressurised to prescribe antibiotics. Moreover, inaccessible health care services, a weak regulatory environment and financial inducements from drug companies to the service providers also contributes to inappropriate antibiotic use.

3.6.2 Gaps in literatures

This literature review has highlighted the availability of an extensive literature on antibiotic use and prescribing in LMICs. However, studies generally focus on one aspect of the topic, rather than adopting a multi-dimensional perspective that examines antibiotic use and prescribing using data drawn from both public and private health care facilities, households, service providers and policy makers. Additionally, only limited studies are published on antibiotic prescribing and use in Nepal. Transferability of studies from one LMIC context to another can be difficult, given the unique characteristics of populations, differences in health system design, and varying regulatory environments and procurement practices.

This study has adopted a mixed methods sequential explanatory design, in which quantitative data has been collected on antibiotic prescribing and dispensing in public and private facilities in Nepal and on community knowledge, attitudes and practices about antibiotics and their use. This was followed by qualitative research using semi-structured interviews of service providers and policy makers, to gain insight into provider behaviours and factors influencing these behaviours.

Its findings provide a comprehensive evidence base on which to develop strategies to reduce the inappropriate use of antibiotics in Nepal. By exploring and integrating multiple sources of information, this study will assist policy makers to plan and implement future effective multifaceted interventions to promote the appropriate use of antibiotics among the Nepalese population, thus helping to limit the spread of antibiotic resistance.

The following chapter discusses the methodology adopted for the research.

Chapter 4 Research methodology

4.1 Introduction

This chapter explains the research methodology used in this study. First, the aim and objectives of the study are revisited. The next section then presents the study design and discusses the rationale for adopting this approach. Thereafter each stage of the research process is discussed, followed by sections describing how reliability and validity of the study were established and ethical considerations. Additional details about the methods adopted in this study are available in the relevant chapters reporting on the research conducted to achieve each objective.

4.2 Aim and objectives

The aim of this research was to assess antibiotic use in the general population in the Rupandehi district of Nepal and factors associated with prescribing practices. Its objectives were as follows:

(i) To assess the patterns of antibiotic use in the general population in the Rupandehi district of Nepal

(ii) To examine the knowledge, attitudes and practices of community members in the Rupandehi district of Nepal in regard to the use of antibiotics

(iii) To identify the perceptions of health providers and policymakers about factors influencing the inappropriate use of antibiotics in the Rupandehi district of Nepal

4.3 Methodology

4.3.1 Study design

The study adopted a mixed-methods sequential explanatory design (275), comprising three quantitative surveys and one qualitative survey. Findings from the quantitative and qualitative surveys were then integrated and interpreted to address the primary research question, which was to assess antibiotic use in the general population in the Rupandehi district of Nepal and factors associated with prescribing practices.

Most studies addressing the issue of antibiotic use and factors associated with prescribing practices have adopted a single approach, predominantly a quantitative one based on administering questionnaire surveys. In using a mixed-methods design, the current study has combined the strengths of both quantitative and qualitative methodologies to explore its research question (276). Two of the quantitative studies provide in-depth analysis of the use of antibiotics in public and private facilities respectively; with the third quantitative study involving the implementation of a knowledge, attitudes and practices survey to investigate health behaviours and health-seeking practices of community members regarding antibiotics. The qualitative phase of the study, which comprised interviews with health service providers and policymakers, was used to explore and explain the statistical results from the quantitative phase in more depth. The quantitative and qualitative findings were connected at the outset of the study in formulating the research questions, at the intermediate stage of the research process in refining the interview schedule, and integrated at the final interpretation stage of the study.

The study was conducted in the Rupandehi district of Nepal. As discussed in an earlier chapter, Rupandehi was selected as the study area for several reasons. The district has an almost equal mix of urban and rural residents (122, 124) and a well-represented population of different castes and ethnicities with more than 63 castes/ethnicities residing in the district (73) out of 126 castes/ethnicities in the country (69). Within the district, there is also varying access to transport, with good transport only available in urban areas, which is similar to other districts of Nepal.

A summary of the study design is presented below **(Table 4.1)**.

Table 4.1 Mixed-methods sequential explanatory design

Phases of mixed-methods study	Objective	Source of information	Instrument used
Quantitative	Assess the patterns of antibiotic use in the general population	Patients' administrative records from public health facilities	Electronic data collection form
		Exit interviews with consumers attending private pharmacies	Online data collection form
	Knowledge, attitudes and practices of community members in regard to the use of antibiotics	Household survey with community members	Structured questionnaire
Qualitative	Perceptions of health providers and policymakers about factors influencing the inappropriate use of antibiotics	Interviews with health care providers and policymakers	Semi-structured interview schedule

4.3.2 Data collection methods

Objective 1: Assess the patterns of antibiotic use in the general population

Two studies were conducted to address the objective of assessing patterns of antibiotic use in the general population, with both studies adopting cross sectional study designs. Data were collected from public health facility records to assess patterns of antibiotic use at these facilities, while exit interviews with consumers were conducted at private pharmacies. The cross sectional study at public health facilities was a retrospective study based on patients' administrative records; the interviews to assess antibiotic use by consumers exiting private pharmacies was prospective.

Objective 2: Knowledge, attitudes and practices of community members in regard to the use of antibiotics

Community member's knowledge, attitudes and practices relating to antibiotic use has typically been gathered through various types of cross-sectional surveys, the most popular and widely used being the knowledge, attitude, and practice (KAP) survey (277). The advantages of this method relates to characteristics such as the data collected being quantifiable, its ease of interpretation, generalisability of small sample results to a wider population, cross-cultural comparability and speed of implementation (278). In this study, a KAP survey tool was developed to assess the knowledge, attitudes and practices relating to antibiotic use of community members.

Objective 3: Perceptions of health providers and policymakers about factors influencing the inappropriate use of antibiotics

A qualitative study was conducted using a semi-structured questionnaire to assist in interpreting the findings of the qualitative phases and gain insight into factors impacting on antibiotic prescribing and dispensing practices (279).

With some components of the methodology being common across objectives, the methodology is presented sequentially by procedure (sample selection, participants, instruments, training to research assistants, data collection, data analysis and ethical consideration). Within each procedure, the approach adopted is described separately for each of the objectives where appropriate.

4.3.3 Sample selection

The method of sample selection for the quantitative phases was based on the distribution of health facilities in the Rupandehi district of Nepal. Health facilities were selected based on the WHO guidelines as presented in the following documents: "Operational package for assessing, monitoring and evaluating country pharmaceutical situations" and "Measuring medicines prices, availability, affordability and price components" (280, 281). These guidelines have been refined continuously based on the lessons learned and are widely used to generate reliable information on medicine prices and availability.

As outlined in the guidelines, six of the seven electoral areas were selected to survey. Two areas were purposively selected: one that included the largest hospital in the district and the other that represented the area with the lowest socio-economic status. An additional four areas were selected randomly from the remaining five electoral areas as recommended by the guidelines.

Objective 1: Assess the patterns of antibiotic use in the general population

A list of public health facilities and private pharmacies was obtained from available records of the District Public Health Office (DPHO), Rupandehi and the Nepal Chemists and Druggists Association, Lumbini, Nepal respectively. Among the six selected survey areas, one public health facility from each survey area was selected. In selecting the six public health facilities (one from each survey area), two of each of the following types of public health facilities were selected: hospitals, primary health care centres and health posts. Five private pharmacies from each survey area, with the three closest (within five kilometers) to each public health facility, were selected. However, three private pharmacies were added to the original sample due to refusal of the initially selected pharmacies to allow data collection on the second day. Altogether 39 health facilities (six public and 33 private) were sampled, using a simple random sampling technique **(Table 4.2)**.

Table 4.2 Number of health facilities selected for the surveys to assess antibiotic use in the general population

Survey areas	Public health facilities (n)	Private pharmacies (n)
1	1	5
2	1	6
3	1	5
4	1	6
5	1	5
6	1	6
Total	6	33

Objective 2: Knowledge, attitudes and practices of community members in regard to the use of antibiotics

The municipalities and village development committees (VDCs) from which households were selected to be surveyed were those in which the six public health facilities were located (Objective 1 above). Within municipalities and VDCs, a cluster sampling technique was applied to identify households to survey. Based on the WHO manual (282), 20 clusters from the selected municipalities and VDCs were identified. The smallest administrative unit, the "ward", was considered as a cluster. Four clusters per municipality and three clusters per VDC were selected randomly. The sample size of 220 was obtained based on an estimated prevalence of 33.7% of the population lacking knowledge on antibiotics and their role (283), a 95% confidence interval, a precision effect of 10%, a design effect of two to account for heterogeneity between clusters and an adjustment of 25% to allow for non-response (284, 285) using the formula $n = (Z^2 \times P(1 - P))/e^2$ (284).

A list of households in each cluster was obtained from the records of respective municipalities and VDC offices. This list was verified after visiting each cluster and updated by deleting any duplicate households and adding any households missing from the records. Using the updated list of households in each cluster, an equal number of subjects (eleven) was selected from each cluster applying simple random sampling techniques.

Objective 3: Perceptions of health providers and policymakers about factors influencing the inappropriate use of antibiotics

Service providers and policymakers were identified as the appropriate research participants, with participants grouped into physician, health worker, dispensers and policymaker. Health workers are health assistants and auxiliary health workers (post-secondary training in diagnostics and therapeutics) (96), who have authority to prescribe different types of antibiotics (224). Similarly, dispensers include pharmacists with a degree or diploma and "professionalists" who have only undertaken a short training course, provided by DDA (98). A mixed sampling approach was adopted (286). The chief of the District Public Health Office was the initial contact for identifying participants and a snowball method was used to select additional participants. Adopting this approach, 17 interviews were conducted. Five interviews were conducted with each of physicians and health workers, and four interviews were conducted with dispensers. One representative of each of the following organisations was interviewed in their capacity as policymakers: the District Public Health Office, the Nepal Chemists and Druggists Association and the District Pharmaceutical Association.

4.3.4 Instruments

Four instruments were used in collecting data to address the research objectives:

Objective 1: Assess the patterns of antibiotic use in the general population

Two different instruments, one for each of the public and private health facilities, were used to assess patterns of antibiotic use in the general population.

Public health facilities: An electronic data checklist was developed for extracting relevant information from patients' administrative records, including the records of inpatients and outpatients at the public health facilities. Details extracted included age and sex, disease condition and prescribed drugs **(Appendix A)**.

Private pharmacies: An online data checklist was developed to record prescription information of consumers. The checklist included similar information to the one used for public health facilities, namely age and sex of the patient, disease condition and medicines, and additionally collected information relating to prescribing status (self-medicated, recommended and supplied by a pharmacist without a prescription, or prescribed by a doctor and dispensed by a pharmacist) **(Appendix B)**.

Objective 2: Knowledge, attitudes and practices of community members in regard to the use of antibiotics

A structured questionnaire **(Appendix C)** relating to knowledge, attitudes and practices on antibiotics was used. This was developed by adapting related questionnaires including one from the United States Agency for International Development (USAID) module "Antimicrobial resistance module for population-based surveys" (287) and those used in previous studies (288, 289).

A pilot questionnaire was pre-tested with 30 respondents in urban and rural areas of the Nawalparasi district (a neighboring district of Rupandehi), Nepal, to ensure the cultural appropriateness, any problems with question wording, layout and understanding or a respondent's reaction. As a result, minor adjustments were made to the final questionnaire based on the pre-test results. The final questionnaire included twelve questions relating to knowledge, eight questions to attitudes and six questions to practices.

The questionnaire comprised four sections: socio-demographic characteristics of respondents and a section on each of knowledge, attitudes and practices relating to antibiotics and their use. Questions about knowledge were divided into four domains, namely “identification of antibiotics” (Q1-Q3), “knowledge on the role of antibiotics” (Q4-Q6), “side-effects of antibiotics” (Q7-Q9) and “antibiotic resistance” (Q10-Q12). The questions on attitudes were divided into three domains: “preference for use of antibiotics” (Q13-Q15), “antibiotic resistance and safety” (Q16-Q18), and “attitudes to doctor’s prescribing of antibiotics” (Q19-Q20). The six questions relating to practices (Q21-Q26) were not divided into domains. The English version of the questionnaire was translated into Nepali and back translated into English to ensure the accuracy of the translated text.

Objective 3: Perceptions of health providers and policymakers about factors influencing the inappropriate use of antibiotics

Two different interview schedules for the research participants were developed, one for health service providers and the other for district policymakers, with guidance on topic areas and individual questions obtained from WHO’s policy document “Promoting rational use of medicines: core components” (151) and a study on antibiotic use conducted with physicians and nurses in the Netherlands (290). Six topic areas (or components) were included: “occurrence of infectious diseases”, “prescribing or dispensing decisions”, “issues on prescribing or dispensing’, “burden of antibiotic resistance” and “current prescribing or dispensing practices”. As service providers and policymakers have different roles and responsibilities related to the use of antibiotics, only the relevant components of the interview schedule were used in interviews, with health service providers not questioned about “current prescribing or dispensing practices” and policymakers not questioned about “prescribing or dispensing decisions” or “issues on prescribing or dispensing”.

The interview schedules were drafted by the research student. The draft schedules were reviewed by the supervisory team and subsequent feedback was used to modify the questions to ensure both clarity and brevity of the questions to encourage maximum participation. The schedules were developed in the English language **(Appendix D)**, then translated into Nepali and back translated to English. The Nepali translated versions were used for interviews.

4.3.5 Training of research assistants

Six research assistants were recruited locally to help with data collection. Their qualifications were in health sciences, with all having a general background knowledge on the health system of the district. The research assistants were involved in data collection for both objective one *(assessing the patterns of antibiotic use in the general population)* and objective two *(knowledge, attitudes and practices of community members in regard to the use of antibiotics)*, as well as the pre-test activities for these objectives. The student researcher conducted all interviews with participants for objective three *(perceptions of health providers and policymakers about factors influencing the inappropriate use of antibiotics)*. A training session for research assistants was held prior to embarking on data collection to familiarise them with the data collection techniques. The training session focused on the aim of the study, the importance of quality in data collection and ethical considerations. A flow chart **(Appendix E)** illustrating the recruitment of respondents and consent process was also provided to the research assistants and used during the data collection process.

The student researcher coordinated data collection and approached respective authorities and health facilities to obtain all approvals. The research assistants were regularly monitored by the student researcher to ensure the quality of the data through observation at the study sites and crosschecking of the extracted records from public and private facilities and the household questionnaires.

4.3.6 Data collection

Objective 1: Assess the patterns of antibiotic use in the general population

Public health facilities: Administrative records for a single encounter of outpatients (general medicine outpatients at hospitals and all from other health facilities), inpatients and emergency department patients irrespective of patient age and diagnosis were collected between July 2017 and December 2017 using an electronic checklist. Data extracted from the administrative records, which were paper-based, included patient's sex, age, diagnosis and prescribed medicines. To select the administrative records, data for the most recent year (Nepali year 2073) was divided into four main climate seasons (291). Data for the middle week of each season was extracted for each site. If any public holidays were observed in the sampled week, these days were replaced with records of days following the end of the week.

Private pharmacies: Exit interviews with patients who had attended the selected pharmacies were conducted. Interviews were conducted from July 2017 to December 2017. The days allocated for data collection were based on the advice of pharmacists to obtain as representative a sample of days as possible. Interviews were conducted from 9.00 am to 5.00 pm and as many patients as possible who attended the selected pharmacies were included. Each pharmacy was surveyed for two days, other than the three that refused data to be collected on the second day and the three replacement pharmacies, which were surveyed for one day. Thus, data collection covered 60 days (2 days per pharmacy for 27 pharmacies and 1 day per pharmacy for 6 pharmacies). Individuals obtaining medicines on behalf of another person were excluded from the exit interviews, however children attending the pharmacies with their parents or caretaker were included in the survey.

Data for the exit interviews were collected using the Qualtrics Offline Surveys Application (292). In addition to data on age and sex of the patient, disease condition, medicines, and prescribing status, photographs were taken of the medicines, with no patient identifiers included in the photos. The maximum time taken for the exit interview was three minutes.

Objective 2: Knowledge, attitudes and practices of community members in regard to the use of antibiotics

Interviews were conducted in the Nepali language by two trained research assistants from September 2017 to December 2017. The research assistants went to each of 220 selected households for the interview, an equal number of subjects (eleven) from each cluster. The head of household was the preferred respondents for the study. However, if the head of household was absent at the time of interview, the most senior member of the household, who was 18 years and older, was interviewed. The average duration per interview was 20 minutes. If the participant refused to participate in the interview or no one was at home at the time of interview, the household next to the originally sampled household was used as a replacement household. Ten households were replaced in the original sample due to refusal to participate (n=7) and no one being at home at the time of interview (n=3).

Objective 3: Perceptions of health providers and policymakers about factors influencing the inappropriate use of antibiotics

Communication details of selected participants were updated from the officials of the district health office. Prior to the interview, each participant was contacted individually by telephone and briefed on the purpose of study. A convenient time and place for the interview was also arranged during the telephone conversation. The interview was conducted over the four months period from September to December 2017. The length of the interviews varied, lasting from 18 to 52 minutes. The student researcher conducted the interviews in Nepali with all interviews recorded on a digital voice recorder.

4.3.7 Data analysis

Objective 1: Assess the patterns of antibiotic use in the general population

Public health facilities: Data were entered into an Excel spreadsheet for cleaning. Analysis was done using the Statistical Package for Social Sciences (SPSS) software version 25 (IBM Analytics, Armonk, NY, USA).

The administrative records at public health facilities are populated using text fields. No additional records on provisional or final diagnoses are available, thus the recording of diagnosis in the administrative records was considered as a final diagnosis. Since the disease conditions were often described based on symptoms, similar symptoms/conditions were grouped together. Patients with no information about medicines prescribed or administered were classified as having ‘uncertain or no prescription (none)’.

A core prescribing indicator, "*the percentage of patients prescribed an antibiotic*" was computed in line with the WHO rational drug use methodology (198). Antibiotics were grouped into classes (293), and frequency distributions presented based on type of health facility. Chi square tests were performed to examine the association between the prescribing of antibiotics for selected conditions and explanatory variables including sex, age group and type of health facility. Logistic regression was also used to examine factors associated with antibiotic prescribing for selected conditions (220). Selected conditions included common ones for which a high number of antibiotics were prescribed, conditions commonly needing antibiotics and conditions for which antibiotics are not expected to be prescribed for treatment.

Private pharmacies: The data were imported from the Qualtrics Application to MSExcel spreadsheet for cleaning. The cleaned data were transferred to SPSS. Diseases or conditions collected from the interviews were generally described based on symptoms, thus similar symptoms were grouped together. For some analyses, the three most commonly occurring groups (i.e. fevers, respiratory symptoms and skin conditions) were separately analysed, with remaining groups combined into those likely to require antibiotics ("other - infectious"), and those not likely to require antibiotics ("other - non- infectious"). Similar with the data of public health facilities, antibiotics were also grouped into classes for analysis (293) and WHO's antibiotics prescribing indicator (198) was computed.

Descriptive analysis was conducted to show commonly dispensed antibiotics and antibiotic dispensing by dispensing practice, registration status of pharmacies and education of the pharmacist or drug retailer, and disease or condition. Chi square tests were performed to examine the association between antibiotic dispensing and explanatory variables including sex, age group, dispensing practices and registration status of pharmacies and education status of the pharmacist or drug retailer. Logistic regression was also used to examine factors associated with antibiotic dispensing. Additionally, an interaction term of dispensing practices with registration status and education was examined.

The significance level (α) was set at 0.05 for all statistical tests.

Objective 2: Knowledge, attitudes and practices of community members in regard to the use of antibiotics

The paper-based collected data were entered into a SPSS database for cleaning and analysis. Demographic variables and responses to the knowledge, attitudes and practices questions were analysed using descriptive statistics. Responses to the five-point Likert scale for the knowledge and attitudes questions were combined into three groups: 'strongly agree' and 'agree', 'strongly disagree' and 'disagree', and 'uncertain'. The three groups were referred to as "Yes", "No" and "Don't know", respectively (294). Questions relating to practices were assessed using the five-point Likert scales scoring scheme of 'never', 'seldom', 'sometimes', 'often' and 'always'.

Regression analysis was conducted to identify demographic factors associated with knowledge, attitudes and practices. Responses to the knowledge and attitudes questions were given a score of "1" for a correct response and "0" for an incorrect or uncertain response, and scores summed for respondents across each of the domains. For the practice questions, responses were given a score based on the five-point Likert scale, ranging from "5" for the most appropriate answer to "1" for the least appropriate answer, and summed. The median score based on responses to questions in each of the knowledge, attitudes and practice sections was used as the cut-off to dichotomize the continuous variable for use as the dependent variable in multiple logistic regression analysis. Respondents scoring higher than the median were assessed as having "better knowledge", "more appropriate attitudes" and "better practices" relating to antibiotic use (295). Spearman's rank order correlation coefficient was used to describe the strength and direction of the relationship between responses to the knowledge, attitudes and practices questions.

Objective 3: Perceptions of health providers and policymakers about factors influencing the inappropriate use of antibiotics

Prior to the interviews, all informants were assigned an identification code consisting of two parts. The first part indicated the professional status of the interviewee (PS for physicians, HW for health workers, DP for dispensers and PM for policymakers). The second part indicated interview's number within that group. For instance, PS1 corresponded to the first interview with physician. Only identification codes were used during data analysis, and all names obtained during the recorded interviews were deleted.

The recorded interviews were listened to a number of times and then translated into English. The qualitative data analysis software programme, NVivo 12 Pro, was used in the initial data coding process. The coded narrations were imported into Microsoft Word files and further analysis was conducted manually.

A combination of inductive and deductive approaches were used to analyse the data (296). For deductive coding, a codebook was developed based on the main interview questions, and for inductive coding the coding process was data-driven (297). The codes were grouped into sub-themes, which were in turn categorised into three major themes, called factors i.e. personal, organisational and regulatory factors. Lack of knowledge and financial constraints, emerged as contributory factors to each of the other personal themes. A sub-theme, professional behaviour did not fit within the three major factors, thus was presented separately.

4.4 Reliability and validity of the research

As mentioned above (section 4.3.1 and 4.3.2), the study gathered data from different sources using different instruments and data collection processes.

For the first objective, assessing the patterns of antibiotic use, two different instruments were used, namely an electronic data checklist and an online data checklist **(Appendix A and B)** for each of the public and private health facilities respectively. For the public health facilities, the checklist was developed in line with the administrative record register available for these facilities. During data collection, the research assistants were monitored by the student researcher through observation at the study sites and crosschecking of the records from public and private facilities. In the case of the private facilities, the data on dispensing of medications including antibiotics were sourced directly from patients, thus validated from the dispensed medicines. The data cleaning process included checking for any data extraction and recording errors.

Addressing the second objective, examining knowledge, attitudes and practices in regard to the use of antibiotics, a structured questionnaire **(Appendix C)** was developed by adapting related questionnaires including one from the USAID's module "Antimicrobial resistance module for population-based surveys" (287) and those used in previous studies (288, 289). Feedback for the questionnaire was obtained from the supervisory team prior to pre-testing (section 4.6), and minor adjustments were made to the final questionnaire based on pre-test results, ensuring the cultural appropriateness, problems with question wording, layout and understanding or a respondent's reaction. The reliability coefficient of responses to the final questionnaire was calculated using the Cronbach's alpha score with the following results recorded: knowledge (0.63), attitudes (0.65) and practices (0.67) **(Appendix F)**. Data collection from households by research assistants was closely monitored by the student researcher, including checking for missing data.

Moreover, to facilitate objectivity during the data entry process, the data entry into SPSS was double-checked to ensure matching between responses and the information entered into the database. To ensure objectivity during the data analysis process, the student researcher confirmed the procedures and results with supervisors and a statistician in the application of statistical methods.

Addressing the third objective, identifying the perceptions of health providers and policymakers about factors influencing the inappropriate use of antibiotics, major components in the interview schedules were adopted from a study on antibiotic use conducted with physician and nurses in the Netherlands (290) and from WHO's policy document "Promoting rational use of medicines: core components" (151). The student researcher drafted the interview schedules, which were reviewed by all supervisors and subsequent feedback was used to modify the questions, ensuring both clarity and brevity of the questions **(Appendix D)**. All interviews were conducted by the student researcher, and were recorded and transcribed prior to analysis and interpretation.

In qualitative research, important issues in regard to reliability and validity include credibility, dependability and confirmability (298, 299). Credibility is concerned with the extent that the information is accurate and reflects reality; dependability relates to whether the findings would be repeated if the study was replicated; and confirmability refers to the extent the research findings can be confirmed by others and do not reflect the biases of the researcher (298, 299). In collecting data, a range of participants were selected to collect data from health professionals with varying experiences including physicians, health workers, pharmacists and policy makers, with data collection undertaken until the point of saturation. After the data had been transcribed, the research student and one of the supervisors were involved in establishing themes and factors, with themes and factors revised following reflection and discussion as necessary. The supervisor also audited all documentation for the qualitative research.

Finally, utilising a mixed method approach combining qualitative and quantitative data for this study provided a richer and more detailed understanding of the research problem compared with using a single methodology (300). Amalgamation of both types of data (known as methodological triangulation), enhanced the rigour of the findings and increased understanding of the key research question, namely to determine antibiotic use in the general population in Nepal and identify factors associated with prescribing practices (301).

4.5 Ethical considerations

The research was conducted following the ethical and safety requirements of Curtin University as well as the Australian Code for the Responsible Conduct of Research, together with the guidelines of the Nepal Health Research Council. These guidelines require *inter alia*, free and informed consent by participants, consultation and cultural sensitivity by the researcher, minimisation of harm to participants, maintenance of confidentiality and anonymity, and a continued duty of care by the researcher to participants.

4.5.1 Ethics approval

Initially, ethics approval was obtained from the Human Research Ethics Committee, Curtin University (HRE2017-0394) **(Appendix G)**, then, an application was submitted to the ethics committee of the Nepal Health Research Council (NHRC). The approval was obtained from NHRC (Reg no.189/2017) **(Appendix H)** with the modification in the initial proposal submitted to Curtin University. In the modification, district name was added in the title as well as further description on the sample size, selection of health facilities and recruitment of research assistants were written. The amendment request to the Human Research Ethics Committee at Curtin University was approval on 03 August 2017 (HRE2017-0394-01) **(Appendix I)**. A letter of permission for collecting data in the Rupandehi district was, then obtained from District Public Health Office, Rupandehi (Dispatch no. 2193-2016/17) **(Appendix J)**.

4.5.2 Confidentiality

Confidentiality regarding respondent' identities is an essential part of all research and every effort was made to maintain this at each stage of the project. During the training of research assistants, the importance of confidentiality was emphasised and all research assistants signed the confidentiality agreement **(Appendix K)**.

While collecting patients' administrative records in the **public health facilities**, patients' names were not recorded in the electronic records, but the record indexing system used by the health facilities were adapted in generating codes that allowed only the research team to be able to link the extracted records with the source data. Once information for each patient had been checked twice by the student researcher, the indexing system was de-coded so that the extracted data could not be re-identified.

While conducting the **exit interviews** through Qualtrics Offline Surveys Application with consumers of private pharmacies, patients' names were not recorded. Along with the other demographic information, photographs of the medicines were taken and attached to the application, however no patient identifiers were included in the photographs.

To ensure anonymity, all households of interviewed in the **household survey** were assigned an identification number. Only the given name of the respondent of each household was written in the completed questionnaire. While entering the data into the SPSS database, the code of each household was used and no identifier of the respondent specified in the entry.

Prior to the qualitative **interview**, all participants were assigned an identification code. These codes were used in the analysis and no identification was recorded.

All respondents were assured that confidentiality would be maintained throughout the research process. Questionnaires used for the interviews and signed consent forms were stored in a locked cabinet at the District Public Health Office, Kathmandu Nepal. Only the Chief of the DPHO, Kathmandu and student researcher have access to a key for the cabinet. The questionnaires will be kept for seven years from the date of conducting the research and will then be destroyed indefinitely. All the recorded electronic files are stored in a password protected folder on the R-drive on the Curtin University network.

4.5.3 Informed consent

A letter of permission was obtained from the District Public Health Office, Rupandehi **(Appendix J)** for collecting patients' administrative records in public health facilities. All respondents to the exit interviews, household surveys and health service provider and policymaker interviews, were asked to sign a consent form **(Appendix L)**. Prior to the interview, they were provided with a participant information sheet which detailed information about the study's purpose, what role the interviewee would take, and the right to stop recording the interview - for the qualitative interviews – and the right to withdraw from participation at any time. Written consent was then sought to the interviews being conducted. Consent for respondents younger than 18 years, especially in the exit interview, was sought from the accompanying parent or caretaker.

4.6 Conclusion

This chapter has provided an overview of the methods adopted for this study, including its study design, sample selection, the research participants, instruments used for the research, training of the research assistants, the data collection process and data analysis. The chapter has also discussed issues relating to the reliability and validity of the research and ethical considerations.

In the next four chapters, the details of the four individual studies are presented. Three papers related to this study have been published in peer-reviewed international journals, and one paper has been accepted but with minor revisions. Links to the electronic copies of these manuscripts have been included.

Chapter 5 Antibiotic prescribing in public health facilities

The chapter presents the study analysing the patterns of antibiotic prescribing in public health facilities in the Rupandehi district, Nepal. Data were collected from the administrative records of patients who had attended six public health facilities in the district. The standard measure for antibiotic prescribing recommended by WHO, namely "*the percentage of patients prescribed an antibiotic*" was the main indicator used to assess the level of antibiotic prescribing. The study also explored the factors associated with antibiotic prescribing.

The results indicated that the proportion of patients prescribed at least one antibiotic (44.7%) was approximately twice WHO's recommended value (20.0 to 26.8%). Third-generation cephalosporins (29.9%) were the most frequently prescribed antibiotic class, despite being considered second-line treatment in most guidelines. Females and younger patients were more likely to be prescribed antibiotics. High prescribing rates of antibiotics for selected diseases appeared contrary to international recommendations. These findings suggest the need to develop and implement effective strategies to reduce the misuse of antibiotics in public health facilities in Nepal.

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Nepal A, Hendrie D, Robinson S, Selvey LA. Analysis of patterns of antibiotic prescribing in public health facilities in Nepal. *The Journal of Infection in Developing Countries*. 2020 Jan 31;14(01):18-27.

The PDF of the published paper can be found in **Appendix M**; however, for ease of reading, the paper is reproduced formatted for the thesis here.

5.1 Introduction

Increasing bacterial resistance to antibiotics is a serious threat to health care systems globally (302, 303). Antibiotic resistance occurs when bacteria change in some way that reduce the effectiveness of drugs or other agents designed to cure or prevent infections (304). Inappropriate antibiotic use is an important contributor as it clearly drives the evolution of resistance (305). Studies conducted worldwide have shown that antibiotics are frequently used inappropriately (306-308). In the United States and Canada, 30 to 50% of antibiotic prescription is inappropriate (309, 310). Similarly, in some Asian and African nations, 50% of antibiotic use has been identified as inappropriate (308).

The definition of inappropriate antibiotic prescribing varies between studies (311), making comparisons difficult. A common indicator is the prescription of an antibiotic that is not recommended in prescribing guidelines. As sufficient information about patients' conditions is often unavailable, the World Health Organization (WHO) proposed a standard measure of "*percentage of encounters with an antibiotic prescribed*" in order to assess inappropriate prescribing (312, 313). This measure has been used widely to assess the quality of antibiotic prescribing in health care delivery. However, this proportion is likely to vary according to the mix of presentations to health care. Monitoring the use of antibiotics in countries, assessing factors that promote the inappropriate use of antibiotics and developing effective interventions are important in slowing the pace of resistance development (303, 314).

Antibiotics are commonly prescribed and frequently used to treat infections (315). A substantial amount of antibiotic overuse is likely driven by over diagnosis of certain conditions, particularly when the clinical picture of viral or bacterial aetiology is similar (316). In developing countries, other factors contributing to the excessive use of antibiotics include inadequate patient education, limited diagnostic facilities, the availability of antimicrobials that can be purchased without a prescription, and lack of appropriate drug regulatory mechanisms (317). A strong policy together with strict guidelines, access to diagnostic tests and training about diagnosis and appropriate treatment are factors likely to promote more appropriate use of antibiotics (308) .

In Nepal, guidelines for the treatment of childhood illnesses, malaria, tuberculosis, leprosy and human immunodeficiency virus (HIV) infection (318) exist. The antibiotics recommended in the guidelines for those conditions are supplied through the government health system. Similarly, the Government of Nepal has also formulated the National Antibiotic Treatment Guidelines 2014 (224), however not all antibiotics listed in the guidelines are currently supplied through the government system. Thus, public health facilities have limited choices of antibiotics for different diseases. Furthermore, strict regulation and enforcement of appropriate antibiotic prescribing is lacking in the Nepalese health system, thus facilitating failure to follow the guidelines by prescribers. Similarly, several reports have suggested high (319-321) and increasing (140) prevalence of antibiotic resistance in Nepal.

Assessments of drug use within public health care facilities in Nepal have been conducted in individual studies (229, 322). However, these surveys have not assessed appropriate antibiotic use across all levels of health care facilities. In the public health system in Nepal, primary health care services are provided at district level through health posts, primary health care centres and district hospitals, and secondary and tertiary care is provided by zonal/regional hospitals and specialized tertiary facilities (104, 257). Prescribing is conducted by physicians and non-physicians such as health assistants (post-secondary training in diagnostics and therapeutics), nurses and other paramedics (96). The physicians work at hospitals and the non-physicians, who are referred to as health workers, mainly work at primary health care centres and health posts. Authorities for prescribing drugs and training differ among the prescribers (97), thus their prescribing patterns need to be monitored regularly (151). In addition to differences between prescribers, drug choice may be influenced by patients, health facilities and other factors (323). The present study examined the patterns of antibiotic prescribing across different types of public health facilities in Nepal and explored factors influencing these practices.

5.2 Methodology

5.2.1 Selection of health facilities

A cross-sectional study was conducted in the Rupandehi district of Nepal. Public health facilities were selected based on WHO guidelines (280, 281). These guidelines provide a systematic method for assessing the pharmaceutical situation, medicine prices and availability at the country, regional and facility levels. Based on these guidelines, six survey areas were selected from the seven electoral areas in the district. As in the guidelines, the district in which the major hospital is located was selected as one survey area and an area with the lowest socio-economic status as another survey area. An additional four survey areas were randomly selected. One public health facility was selected from each survey area using a list obtained from available records of the District Public Health Office. Six public health facilities were selected, two each of hospitals, primary health care centres and health posts, with the major hospital included as one of the hospitals **(Figure 5.1)**.

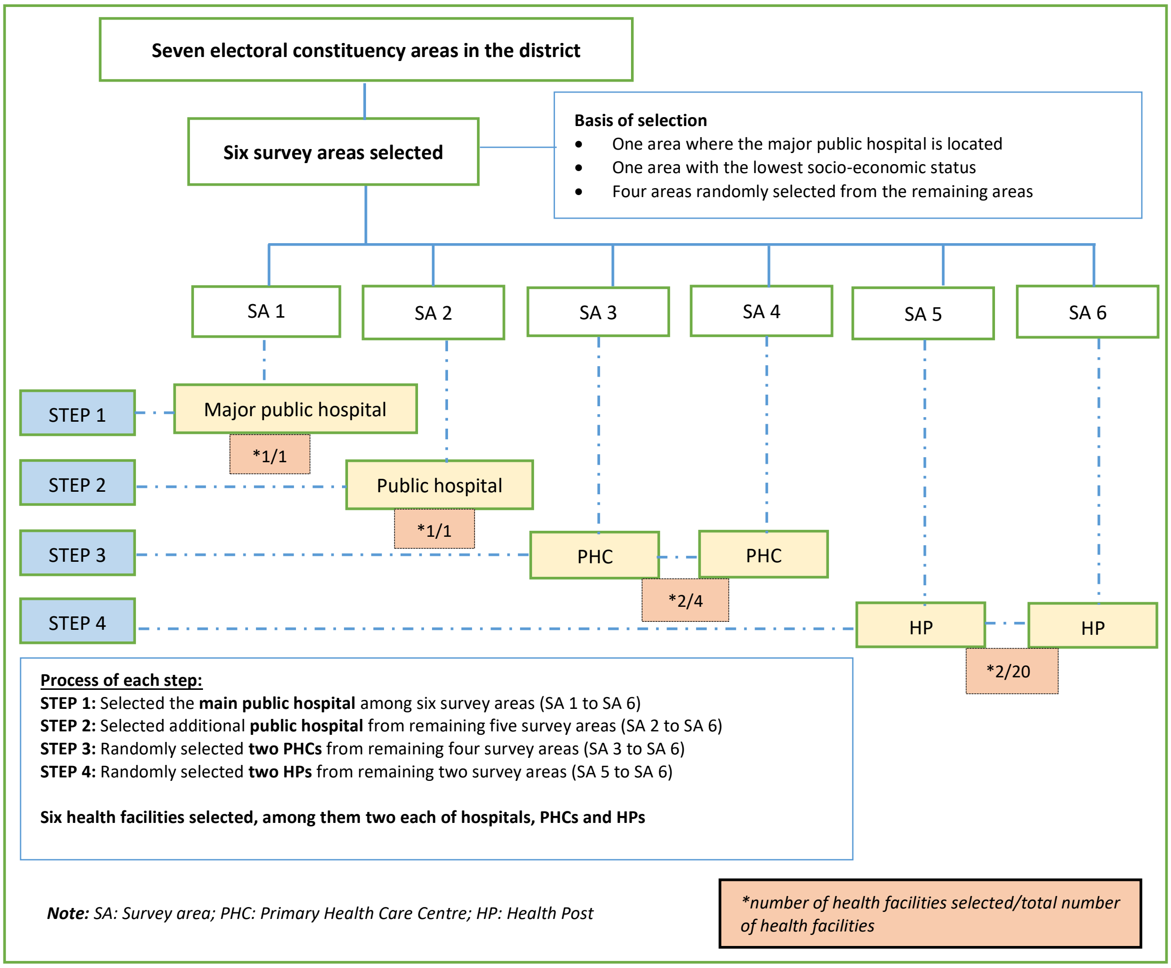

Figure 5.1 Flow chart of selection of public health facilities

5.2.2 Data collection

Administrative records for a single encounter of outpatients (outpatients of general medicine at hospitals and all from other health facilities), inpatients and emergency department patients irrespective of patient age and diagnosis were collected between July 2017 and December 2017 using a standardised data collection tool. Data extracted from the administrative records, which were paper-based, included patient's sex, age, diagnosis and prescribed medicines. To select the administrative records, data for the most recent year (Nepali year 2073) was divided into four main climate seasons (291). Data for the middle week of each season was extracted for each site. If any public holidays were observed in the sampled week, these days were replaced with records of days following the end of the week.

To ensure confidentially, patients' names were not recorded, but the record indexing system used by the health facilities were adapted in generating codes that allowed only the research team to be able to link the extracted records with the source data. Once information for each patient had been checked twice by the principal researcher (AN), the indexing system was de-coded so that the extracted data could not be re-identified.

The principal researcher coordinated data collection and approached respective authorities and health facilities to obtain approval to collect the data, and research assistants were engaged in data collection. A training session for research assistants was held prior to embarking on data collection and focused on the aim of the study, quality in the data collection and ethical considerations. The research assistants were regularly monitored by the principal researcher to ensure the quality of the data through observation at the study sites and cross-checking of the extracted records.

The study was approved by the Human Research Ethics Committee, Curtin University (HRE2017-0394) and the ethics committee of the Nepal Health Research Council (Reg no.189/2017). Permission for collecting the required administrative information of patient from public health facilities was obtained from the District Public Health Office, Rupandehi, Nepal (2193/2016-17).

5.2.3 Data analysis

Data were entered into an Excel spreadsheet for cleaning. Nearly one-fifth of the records (18.6%) had no information about medicines prescribed or administered to patients. These records were classified as having 'uncertain or no prescription (none)'. Analysis was done using Statistical Package for Social Sciences (SPSS) software version 25 (IBM Analytics, Armonk, NY, USA).

The administrative records at public health facilities are populated using text fields. No additional records on provisional or final diagnoses are available, thus the recording of diagnosis in the administrative records was considered as a final diagnosis. Since the disease were often described based on symptoms, similar symptoms or conditions were grouped together.

Antibiotics were defined as antibacterial agents, including metronidazole, irrespective of formulation. A core prescribing indicator, "*the percentage of patients prescribed an antibiotic*" was computed in line with the WHO rational drug use methodology (198). Antibiotics were grouped into classes based on the antibiotic's chemical structure or chemical class (293). Frequency distributions of these classes were presented based on type of health facility.

Chi square tests were performed to examine the association between the prescribing of antibiotics for selected disease and conditions and explanatory variables including sex, age group, and type and department of health facility. Logistic regression was also used to examine factors associated with antibiotic prescribing for selected disease and conditions (220). Selected disease and conditions included common ones for which a high number of antibiotics were prescribed, disease and conditions commonly needing antibiotics, and disease and conditions for which antibiotics are not expected to be prescribed for treatment. The significance level (α) was set at 0.05 for all statistical tests.

5.3 Results

5.3.1 Patient characteristics and prescribing indicators

In total 6,860 patient records were collected, with 1,278 (18.6%) records not having any information with regard to medicines, whether a prescribed or other medicine. Of these records, 5,582 (81.4%) had a record of medicines prescribed. Fifty-nine percent of patients were female. The highest number of records was for hospital emergency department presentations (29.9%) and hospital ambulatory visits (28.1%) with similar numbers for health post attendances (15.5%), primary health centre visits (13.8%) and hospital inpatient admissions (12.6%) **(Table 5.1)**.

The most common presenting condition was pyrexia (9.9%). At least one antibiotic was prescribed in 3064 (44.7%) patient encounters, with more than one-third of patients (35.7%) prescribed one antibiotic and almost one in ten patients (8.9%) prescribed two or more antibiotics.

Table 5.1 Patient characteristics and prescribing indicators

Variables	Percentage	n_i/n_k[a,b]
Medicine prescribed		
Yes	81.4	5582/6860
No or uncertain	18.6	1278/6860
Sex		
Male	41.3	2833/6859
Female	58.7	4026/6859
Age group		
Less than 5 years	5.2	360/6860
5 to 14 years	14.5	992/6860
15 to 24 years	20.1	1376/6860
25 to 44 years	29.9	2050/6860
45 to 64 years	18.7	1282/6860
65 and above years	11.7	800/6860
Type and department of health facility		
Inpatient hospital	12.6	865/6860
Ambulatory hospital	28.1	1928/6860
Emergency department hospital	29.9	2052/6860
Primary health centre	13.8	950/6860
Health post	15.5	1065/6860
Disease and conditions		
Fever/pyrexia	9.9	681/6860
Cellulitis/boils/impetigo/dermatitis/wound/skin infection/abscess	6.0	413/6860
Falls/injury	5.9	406/6860
Abdominal pain/nausea/vomiting/dyspepsia	5.7	388/6860
ARI/URTI/LRTI/respiratory infection/chest infection/bronchitis	4.9	337/6860
Diarrhoea/dysentery/AGE/loose motion	4.7	321/6860
Mental problem/anxiety/SOB/depression	4.7	319/6860
APD/gastritis/peptic ulcer	3.1	216/6860
Headache/migraine/TTH	3.0	204/6860
Snake bite	2.9	202/6860
Other	49.2	3373/6860
Prescribing indicator		
Percentage of patients prescribed an antibiotic	44.7	3064/6860
Number of antibiotics prescribed[c]		
Uncertain or none	55.3	3796/6860
One antibiotic	35.7	2452/6860
Two antibiotics	8.4	578/6860
Three antibiotics	0.5	32/6860
Four antibiotics	0.03	2/6860

[a]n_j numerator; [b]n_k denominator; [c]denominator for calculation of percentages is number of patient records collected.
Note: ARI: Acute respiratory tract infection, URTI: Upper respiratory tract Infection, LRTI: Lower respiratory tract infection, AGE: Acute gastroenteritis, SOB: Shortness of breath, APD: Acid peptic disease, TTH: Tension-type headache.

5.3.2 Antibiotic prescribing practices

Third-generation cephalosporins (29.9%) were the most commonly prescribed class of antibiotic, followed by penicillins (25.0%), quinolones (15.0%) and antiprotozoals (13.0%) **(Table 5.2)**. Among antibiotics, the most commonly prescribed were ceftriaxone (22.9%), amoxicillin (16.6%), metronidazole (12.5%), ciprofloxacin (11.4%) and cotrimoxazole (7.2%).

Table 5.2 Commonly prescribed antibiotics by class and name

Prescribed antibiotic's name and classes	Total no	Total share (%)	Total share within class (%)	Total share (%)
Penicillins	**926**	**24.9**		
Amoxicillin	618		66.7	16.6
Ampicillin	112		12.1	3.0
Cloxacillin	65		7.0	1.8
Amoxicillin Clavulanate	35		3.8	0.9
Other	96		10.4	2.6
Tetracyclines	**58**	**1.6**		
Doxycycline	47		81.0	1.3
Other	11		19.0	0.3
Cephalosporins	**1111**	**29.9**		
Ceftriaxone	851		76.6	22.9
Cefixime	143		12.9	3.9
Cefpodoxime	60		5.4	1.6
Other	57		5.1	1.5
Quinolones	**557**	**15.0**		
Ciprofloxacin	424		76.1	11.4
Levofloxacin	120		21.5	3.2
Other	13		2.3	0.4
Macrolides	**171**	**4.6**		
Azithromycin	163		95.3	4.4
Other	8		4.7	0.2
Sulfonamides	**267**	**7.2**		
Cotrimoxazole	267		100.0	7.2
Other	0		0.0	0.0
Antiprotozoal	**484**	**13.0**		
Metronidazole	465		96.1	12.5
Other	19		3.9	0.5
Others	**138**	**3.7**		
Amikacin	62		45.3	1.7
Fluconazole	49		35.8	1.3
Other	27		19.0	0.7
Total	**3712**	100.0		100.0

Antibiotic prescribing was highest for hospital inpatients (64.6%) and lowest for hospital ambulatory (29.7%), with approximately half of patients visiting health posts (52.2%) and primary health care centres (50.4%) prescribed an antibiotic **(Table 5.3)**. Conditions for which the antibiotic prescribing rate was highest included pneumonia (85.5%), diarrhoea and related conditions (83.2%), respiratory infections (72.4%), chronic obstructive pulmonary disease (COPD) (68.4%), pyrexia (66.1%), colds, sinusitis and rhinitis (65.3%), snake bites (64.4%) and coughs (63.1%).

The class of antibiotics prescribed varied by health facility and department. Third-generation cephalosporins were the most common antibiotics prescribed for patients presenting at emergency departments and hospital inpatients (56.8% and 49.2%, respectively), whereas penicillins (46.5%) and quinolones (23.1%) were most commonly prescribed in primary health centres. In health posts, prescribing rates of sulfonamides (28.8%), penicillins (26.0%) and quinolones (21.1%) were almost similar.

Third-generation cephalosporins were the most commonly prescribed antibiotic for the treatment of pneumonia (28.6%), COPD (41.0%), fever (40.2%), snake bite (88.6%) and abdominal pain including nausea, vomiting and dyspepsia (62.2%). Penicillins were also often prescribed for the treatment of pneumonia (27.0%) and were the most commonly used antibiotic for respiratory tract infections (43.9%), common colds (41.4%), coughs (48.6%), skin infections (56.2%), and falls and injuries (71.5%). For skin diseases and diarrhoeal cases, sulfoanmides (41.9%) and antiprotozals (57.6%) were the most commonly prescribed antibiotics respectively.

Table 5.3 Descriptive analysis of prescriptions and prescribed classes of antibiotic by types and department of health facility and selected diseases and conditions

Variables	Antibiotic prescribed (n=6860)		Classes of antibiotic prescribed (%) (n = 3712)							
	Yes, n (%)	Uncertain or none, n (%)	Penicillins	Tetracyclines	Cephalosporins	Quinolones	Macrolides	Sulfonamides	Antiprotozoal	Others
Types and department of health facility										
All	3064 (44.7)	3796 (52.2)	24.9	1.6	29.9	15.0	4.6	7.2	13.0	3.7
Inpatient hospital	559 (64.6)	306 (35.4)	14.0	1.1	49.2	13.4	1.9	0.0	12.8	7.6
Ambulatory hospital	572 (29.7)	1365 (70.3)	46.5	0.8	10.0	14.2	8.9	5.2	11.4	3.2
Emergency hospital	898 (43.8)	1154 (56.2)	15.9	0.0	56.8	9.5	2.2	0.0	13.7	2.0
Primary Health Centre	479 (50.4)	471 (49.6)	33.8	1.3	1.1	23.1	10.2	12.0	15.5	3.1
Health Post	556 (52.2)	509 (47.8)	26.0	6.3	0.2	21.1	3.3	28.8	11.6	2.7
Selected disease and conditions										
Pneumonia	46 (85.5)	6 (11.5)	27.0	0.0	28.6	14.3	6.3	15.9	1.6	6.3
Diarrhoea/dysentery/AGE/loose motion	267 (83.2)	54 (16.8)	1.7	1.2	20.0	16.5	0.5	2.2	57.6	0.2
ARI/URTI/LRTI/respiratory infection/ chest infection/bronchitis	244 (72.4)	93 (27.6)	43.9	2.7	9.8	8.2	14.5	19.2	0.8	0.8
COPD	128 (68.4)	59 (31.6)	19.7	1.1	41.0	24.2	9.0	2.2	2.2	0.6
Fever/pyrexia/PUO/FUO	450 (66.1)	231 (33.9)	23.7	1.1	40.2	19.4	4.3	2.4	3.7	5.0
Common cold/sinusitis/rhinitis	66 (65.3)	35 (34.7)	41.4	5.7	1.4	7.1	8.6	31.4	4.3	0.0
Snake bite	130 (64.4)	72 (35.6)	11.4	0.0	88.6	0.0	0.0	0.0	0.0	0.0
Cough/dry cough/allergic cough	99 (63.1)	58 (36.9)	48.6	1.8	5.5	9.2	21.1	11.9	0.0	1.8
Cellulitis/boils/impetigo/dermatitis/wound/skin infection/abscess	201 (48.7)	212 (51.3)	56.2	0.5	2.4	7.1	3.3	25.2	2.4	2.9
Falls and injury/injury/cut injury	157 (38.7)	249 (61.3)	71.5	0.0	16.3	4.7	1.2	4.7	1.7	0.0
Abdominal pain/nausea/ vomiting/dyspepsia	143 (36.9)	245 (63.1)	1.6	0.5	62.2	5.9	1.6	0.0	28.1	0.0
Skin diseases/skin allergy/sunburn/allergy/itching	59 (30.7)	133 (69.3)	37.1	3.2	3.2	4.8	6.5	41.9	3.2	0.0
Other	1074 (31.4)	2349 (68.6)	19.7	2.1	31.8	19.6	3.3	4.5	12.0	7.1

AGE: Acute Gastroenteritis, ARI: Acute Respiratory Tract Infection, URTI: Upper Respiratory Tract Infection, LRTI: Lower Respiratory Tract Infection, COPD: Chronic Obstructive Pulmonary Disease, PUO: Pyrexia of Unknown Origin, FUO: Fever of Unknown Origin.

5.3.3 Factors associated with antibiotic prescribing for selected disease and conditions

Across all disease and conditions, antibiotic prescribing was significantly associated with sex, age group and type of facility/department **(Table 5.4)**. Males were more likely to receive antibiotics than females ($p = 0.005$), patients less than 5 years were more likely than all other age groups to receive antibiotics ($p < 0.001$) and inpatients were more likely to receive antibiotics than other hospital patients and those attending primary health care facilities and health posts ($p < 0.001$).

Table 5.4 Factors associated with antibiotic prescribing (n=6860)

Variables	Antibiotic prescribing			Univariable analysis			Multiple logistic regression	
	Yes, n (%)	Uncertain or none, n (%)	χ^2 (p value)	n	OR (95% CI)	p value	OR (95% CI)	p value
Gender								
Male	1346 (47.5)	1487 (52.5)	15.753 **(< 0.001)**	2833	1	**< 0.001**	1	**0.005**
Female	1718 (42.7)	2308 (57.3)		4026	0.822 (0.747, 0.906)		0.863 (0.779, 0.956)	
Age group								
Less than 5 years	251 (69.7)	109 (30.3)	183.883 **(< 0.001)**	360	1		1	
5 to 14 years	538 (54.2)	454 (45.8)		992	0.515 (0.398, 0.666)	**< 0.001**	0.568 (0.435, 0.740)	**< 0.001**
15 to 24 years	549 (39.9)	827 (60.1)		1376	0.288 (0.225, 0.370)	**< 0.001**	0.293 (0.227, 0.379)	**< 0.001**
25 to 44 years	791 (38.6)	1259 (61.4)		2050	0.273 (0.214, 0.347)	**< 0.001**	0.298 (0.232, 0.382)	**< 0.001**
45 to 64 years	537 (41.9)	745 (58.1)		1282	0.313 (0.244, 0.402)	**< 0.001**	0.328 (0.253, 0.425)	**< 0.001**
65 and above	398 (49.8)	402 (50.3)		800	0.430 (0.330, 0.560)	**< 0.001**	0.481 (0.366, 0.631)	**< 0.001**
Type and department of health facility								
Inpatient hospital	559 (64.4)	306 (35.4)	352.791 **(< 0.001)**	865	1		1	
Ambulatory hospital	572 (29.7)	1356 (70.3)		1928	0.231 (0.195, 0.274)	**< 0.001**	0.218 (0.183, 0.259)	**< 0.001**
Emergency hospital	898 (43.8)	1154 (56.2)		2052	0.426 (0.361, 0.502)	**< 0.001**	0.416 (0.352, 0.492)	**< 0.001**
Primary Health Centre	479 (50.4)	471 (49.6)		950	0.557 (0.461, 0.672)	**< 0.001**	0.507 (0.417, 0.615)	**< 0.001**
Health Post	556 (52.2)	509 (47.8)		1065	0.598 (0.497, 0.719)	**< 0.001**	0.582 (0.482, 0.703)	**< 0.001**

OR: Odds ratio; CI: Confident intervals.

Factors associated with antibiotic prescribing varied by conditions **(Tables 5.5)**. The only condition for which the antibiotic prescribing rate differed between males and females was common colds, with males less likely to be prescribed antibiotics than females ($p = 0.023$).

Antibiotic prescribing was significantly associated with age group for several conditions. Older age groups were less likely than children less than 15 years old to receive antibiotics for skin infections ($p < 0.05$), respiratory infections ($p < 0.05$) and skin diseases ($p < 0.01$). Similarly, younger patients were less likely to receive antibiotics for diarrhoea ($p = 0.015$) and COPD ($p = 0.001$). In contrast, patients aged 45 years and above age were less likely to receive antibiotics for snake bite than those less than 25 years old ($p < 0.05$).

Antibiotic prescribing was also significantly associated with type of health facilities. Patients attending health posts and health centre were more likely to receive antibiotics for respiratory infections ($p = 0.007$) and coughs ($p = 0.002$) than those attending hospitals. On the other hand, patient attending health posts and health centre were less likely to receive antibiotics for fever ($p = 0.025$) and COPD ($p = 0.024$). Patients presenting at emergency department with snake bites were more likely to receive antibiotics than patients admitted to the hospitals ($p < 0.001$).

Table 5.5 Factors associated with antibiotic prescribing for selected diseases and conditions

Variables	Diarrhoea (n=321)						Falls and Injuries (n = 406)						Abdominal Pain (n = 388)					
	Univariable analysis			Multiple logistic regression			Univariable analysis			Multiple logistic regression			Univariable analysis			Multiple logistic regression		
	Yes = n (%)	Uncertain or none = n (%)	χ^2 (p value)	n	OR (95% CI)	p value	Yes = n (%)	Uncertain or none = n (%)	χ^2 (p value)	n	OR (95% CI)	p value	Yes = n (%)	Uncertain or none = n (%)	χ^2 (p value)	n	OR (95% CI)	p value
Gender																		
Male	103 (78.6)	28 (21.4)	3.277 (0.070)	131	0.700 (0.379, 1.292)	0.254	101 (40.9)	146 (59.1)	1.312 (0.252)	247	1	0.223	67 (38.7)	106 (61.3)	0.470 (0.493)	173	1	0.372
Female	164 (86.3)	26 (13.7)		190	1		56 (35.2)	103 (64.8)		159	0.772 (0.509, 1.170)		76 (35.3)	139 (64.7)		215	0.823 (0.536, 1.263)	
Age group																		
Less than 15 years	50 (68.5)	23 (31.5)	16.140 (**< 0.001**)	73	0.398 (0.189, 0.837)	**0.015**	42 (36.5)	73 (63.5)	1.481 (0.477)	115	0.699 (0.403, 1.212)	0.202	20 (32.3)	42 (67.7)	2.590 (0.274)	62	1	
15 to 44 years	134 (89.9)	15 (10.1)		149	1.573 (0.730, 3.390)	0.247	70 (37.2)	118 (62.8)		188	0.739 (0.451, 1.210)	0.229	93 (40.1)	139 (59.9)		232	1.407 (0.761, 2.601)	0.276
45 and above	83 (83.8)	16 (16.2)		99	1		45 (43.7)	58 (56.3)		103	1		30 (31.9)	64 (68.1)		94	0.910 (0.451, 1.836)	0.792
Type of health facilities																		
All hospital	170 (82.5)	36 (17.5)	0.175 (0.675)	206	0.754 (0.395, 1.440)	0.392	133 (37.6)	221 (62.4)	1.408 (0.235)	354	0.689 (0.381, 1.246)	0.218	134 (38.3)	216 (61.7)	3.140 (0.076)	350	1	0.077
Health post and health centre	97 (82.1)	18 (17.9)		115	1		24 (46.2)	28 (53.8)		52	1		9 (23.7)	29 (76.3)		38	0.490 (0.222, 1.081)	

OR: Odds ratio; CI: Confident intervals. Note: The following different conditions had included in the group for analysis: **Diarrhoea**: Diarrhoea/dysentery/AGE/loose motion; **Fall and Injuries**: Falls and injury/injury/cut injury; **Abdominal pain**: Abdominal pain/nausea/vomiting/dyspepsia

Variables	Skin Infection (n=413)						Fever (n=681)						ARI (n=337)					
	Univariable analysis			Multiple logistic regression			Univariable analysis			Multiple logistic regression			Univariable analysis			Multiple logistic regression		
	Yes = n (%)	Uncertain or none = n (%)	χ^2 (p value)	n	OR (95% CI)	p value	Yes = n (%)	Uncertain or none = n (%)	χ^2 (p value)	n	OR (95% CI)	p value	Yes = n (%)	Uncertain or none = n (%)	χ^2 (p value)	n	OR (95% CI)	p value
Gender																		
Male	107 (50.7)	104 (49.3)	0.720 (0.396)	211	1	0.530	212 (66.5)	107 (33.5)	0.038 (0.845)	319	0.992 (0.718, 1.369)	0.959	121 (74.2)	42 (25.8)	0.529 (0.467)	163	1	0.494
Female	94 (46.5)	108 (53.5)		202	0.881 (0.593, 1.308)		238 (65.7)	124 (34.3)		362	1		123 (70.7)	51 (29.3)		174	0.841 (0.512, 1.381)	
Age group																		
Less than 15 years	111 (58.7)	78 (41.3)	15.321 (**< 0.001**)	189	1		176 (69.3)	78 (30.7)	2.150 (0.341)	254	1		83 (82.2)	18 (17.8)	7.476 **(0.024)**	101	1	
15 to 44 years	56 (37.6)	93 (62.4)		149	0.428 (0.275, 0.665)	**< 0.001**	163 (63.2)	95 (36.8)		258	0.753 (0.519, 1.092)	0.135	95 (66.4)	48 (33.6)		143	0.437 (0.233, 0.817)	**0.009**
45 and above	34 (45.3)	41 (54.7)		75	0.586 (0.342, 1.005)	0.052	111 (65.7)	58 (34.3)		169	0.828 (0.546, 1.258)	0.377	66 (71.0)	27 (29.0)		93	0.464 (0.231, 0.930)	**0.030**
Type of health facilities																		
All hospital	100 (50.3)	99 (49.7)	0.385 (0.535)	199	1	0.766	338 (68.6)	155 (31.4)	4.902 **(0.027)**	493	1	**0.025**	91 (65.0)	49 (35.0)	6.570 **(0.010)**	140	0.503 (0.304, 0.830)	**0.007**
Health post and health centre	101 (47.2)	113 (52.8)		214	0.942 (0.634, 1.399)		112 (59.6)	76 (40.4)		188	0.671 (0.473, 0.951)		153 (77.7)	44 (22.3)		197	1	

OR: Odds ratio; CI: Confident intervals. Note: The following different conditions had included in the group for analysis: **Skin infection:** Cellulitis/boils/impetigo/dermatitis/wound/skin infection/abscess; **Fever:** Fever/pyrexia/PUO/FUO; **ARI**: ARI/URTI/LRTI/respiratory infection/chest infection/bronchitis

Variables	Cough (n=157)						Skin diseases (n=192)						Common cold (n=101)					
	Univariable analysis			Multiple logistic regression			Univariable analysis			Multiple logistic regression			Univariable analysis			Multiple logistic regression		
	Yes = n (%)	Uncertain or none = n (%)	χ^2 (p value)	n	OR (95% CI)	p value	Yes = n (%)	Uncertain or none = n (%)	χ^2 (p value)	n	OR (95% CI)	p value	Yes = n (%)	Uncertain or none = n (%)	χ^2 (p value)	n	OR (95% CI)	p value
Gender																		
Male	39 (57.4)	29 (42.6)	1.676 (0.196)	68	0.592 (0.295, 1.189)	0.141	23 (29.5)	55 (70.5)	0.095 (0.758)	78	1	0.895	16 (50.0)	16 (50.0)	4.872 **(0.027)**	32	0.332 (0.128, 0.860)	**0.023**
Female	60 (67.4)	29 (32.6)		89	1		36 (31.6)	78 (68.4)		114	0.955 (0.482, 1.893)		50 (72.5)	19 (27.5)		69	1	
Age group																		
Less than 5 years 5 to 14 years	22 (71.0)	9 (29.0)	1.038 (0.595)	31	1		32 (56.1)	25 (43.9)	24.647 (**< 0.001**)	57	1		28 (73.7)	10 (26.3)	1.893 (0.388)	38	1	
15 to 24 years 25 to 44 years	41 (61.2)	26 (38.8)		67	0.507 (0.190, 1.351)	0.174	17 (19.3)	71 (80.7)		88	0.182 (0.086, 0.386)	**< 0.001**	25 (61.0)	16 (39.0)		41	0.415 (0.145, 1.182)	0.100
45 to 64 years 65 and above	36 (61.0)	23 (39.0)		59	0.536 (0.200, 1.435)	0.215	10 (21.3)	37 (78.7)		47	0.203 (0.083, 0.498)	**< 0.001**	13 (59.1)	9 (40.9)		22	0.491 (0.151, 1.594)	0.237
Type of health facilities																		
All hospital	41 (51.2)	39 (48.8)	9.762 **(0.002)**	80	0.335 (0.168, 0.667)	0.002	18 (30.5)	41 (69.5)	0.002 (0.965)	59	1	0.581	9 (50.0)	9 (50.0)	2.278 (0.131)	18	0.600 (0.199, 1.803)	0.363
Health post and health centre	58 (75.3)	19 (24.7)		77	1		41 (30.8)	92 (69.2)		133	0.817 (0.398, 1.676)		57 (68.7)	26 (31.3)		83	1	

OR: Odds ratio; CI: Confident intervals. Note: The following different conditions had included in the group for analysis: **Cough:** Cough/dry cough/allergic cough; **Skin diseases:** Skin diseases/skin allergy/sunburn/allergy/itching; **Common cold:** Common cold/sinusitis/rhinitis

Variables	COPD (n=187)					
	Univariable analysis			Multiple logistic regression		
	Yes = n (%)	Uncertain or none = n (%)	χ^2 (p value)	n	OR (95% CI)	p value
Gender						
Male	58 (73.4)	21 (26.6)	1.564 (0.211)	79	1	0.209
Female	70 (64.8)	38 (35.2)		108	0.646 (0.327, 1.276)	
Age group						
Less than 65 years	39 (51.3)	37 (48.7)	17.404 (**< 0.001**)	76	0.287 (0.147, 0.559)	**< 0.001**
65 and above	89 (80.2)	22 (19.8)		111	1	
Type of health facilities						
All hospital	116 (73.0)	43 (27.0)	9.987 **(0.002)**	159	1	**0.024**
Health post and health centre	12 (42.9)	16 (57.1)		28	0.366 (0.153, 0.877)	

Variables	Snakebite (n=202)					
	Univariable analysis			Multiple logistic regression		
	Yes = n (%)	Uncertain or none = n (%)	χ^2 (p value)	n	OR (95% CI)	p value
Gender						
Male	53 (68.8)	24 (31.2)	1.086 (0.297)	77	1	0.193
Female	77 (61.6)	48 (38.4)		125	0.644 (0.331, 1.250)	
Age group						
Less than 25 years	62 (68.9)	28 (31.1)	4.109 (0.128)	90	1	
25 to 44 years	50 (65.8)	26 (34.2)		76	0.848 (0.419, 1.718)	0.647
45 and above	18 (50.0)	18 (50.0)		36	0.399 (0.170, 0.935)	**0.035**
Type and department						
Hospital Inpatient	25 (39.1)	39 (60.9)	26.128 (**< 0.001**)	64	0.191 (0.100, 0.367)	**< 0.001**
Hospital Emergency	105 (76.1)	33 (23.9)		138	1	

OR: Odds ratio; CI: Confident intervals.

5.4 Discussion

5.4.1 Antibiotic prescribing and associated factors

The percentage of patients prescribed at least one antibiotic (44.7%) was approximately twice the WHO recommended value of 20.0 to 26.8% (312, 313). The antibiotic prescribing rate for inpatients (64.6%) was higher than for patients in other facilities. This would be expected given the relative severity of illness of inpatients. In primary health care centres and health posts approximately half of medicines prescribed were antibiotics, possibly indicating excessive and inappropriate prescribing of antibiotics. These facilities often lack laboratory services and can be run single-handedly by a health worker who, although untrained, is expected to provide the full spectrum of services (257). While other studies have tended not to cover all types of public health facilities, our findings on antibiotic prescribing rates in specific health care settings are consistent with several other studies in low- and middle-income countries (220, 324-326).

Despite female attendance in public health facilities being higher than male attendance, consistent with reports of Nepal's Ministry of Health and Population (327), females were less likely to be prescribed antibiotics than males. This contrasts with the findings of a systematic review conducted in 10 high-income countries, which found females to be more likely to receive antibiotics (328). Being a younger age increased the possibility of an antibiotic being prescribed in our study, although this varied by disease and conditions. Younger patients visiting a public health facility for skin infection, respiratory infection, skin disease and snakebite were more likely to be prescribed an antibiotic than older patients. A reason for higher antibiotic prescribing for children may be because children tend to get more infections (329). Also infectious diseases are the leading cause of child mortality in many developing countries (330), and this may influence prescribing decisions to err on the side of caution when unsure of the underlining cause of symptoms.

Findings in our study of high prescribing rates of antibiotics for selected diseases such as diarrhoeal cases and respiratory infections suggested possible overprescribing and appear contrary to international recommendations. The WHO guidelines recommend oral rehydration solution with other supplements for non-bloody diarrhoea (331) and home care without antibiotics for children with respiratory symptoms (332).

5.4.2 Antibiotics usage patterns

Third-generation cephalosporins, penicillins and quinolones were the most frequently prescribed antibiotic classes, similar to findings of studies conducted in Pakistan (313), Saudi Arabia (271), Turkey (333) and Jordan (334). Many hospitals in high-income countries also use large amounts of the cephalosporin class of antibiotics across a wide variety of infections. Their undoubted popularity relies upon lesser allergenic and toxicity risks as well as a broad spectrum of activity (335), although guidelines including in Nepal do not recommend cephalosporins as a first-line treatment for some indications (224). Guidelines advise that cephalosporins should be avoided as a first-line treatment, when a narrower spectrum antibiotic would be effective because they increase the risk of *Clostridioides difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA) and other resistant infections (335, 336). Countries, and even individual hospitals, where cephalasporins are used more often have been shown to experience higher rates of multidrug resistant organisms, although determining if these rates result from the higher use specifically of cephalosporin antibiotics rather than all antibiotic classes is difficult (335).

5.4.3 Policy implications

Levels of antibiotic prescribing above the WHO recommended rate suggest the need to implement measures to reduce potential overprescribing. Diagnostic uncertainty is a likely factor contributing to the high prescribing rate of antibiotics, particularly at primary health care centres and health posts. Almost half of primary health care centres in Nepal do not have physicians or laboratory technicians (257), and initiatives to fill these positions could improve prescribing practices. The patient-provider relationship may also impact on prescribing (337). The expectation of patient is also a crucial factor for antibiotic prescribing and providers often prescribe antibiotics to meet their expectation (338). With primary health care centres mostly located in the villages and these populations geographically isolated (339), few other options for treatment are available. Providers and community members are known to each other and providers may be under pressure to prescribe antibiotics (326, 337, 340). A targeted intervention to provide education and training to physicians and health workers about antimicrobial resistance and prescribing antibiotics only when they are necessary, together with initiatives to monitor antimicrobial prescribing, could promote more appropriate prescribing behaviours.

Additionally, the relatively high prescribing rate of third-generation cephalosporins and quinolones in public facilities in Nepal is of concern, given that third-generation cephalosporins and quinolones are considered second-line antibiotics in most guidelines. When antibiotic therapy is necessary, the use of narrow-spectrum antibiotics should be used as first-line treatment whenever possible (341) to avoid drug-resistant bacteria developing. Therefore, any educational interventions to reduce inappropriate prescribing of antibiotics in unwarranted situations should also include education and training on the proper selection of antibiotics.

5.4.4 Strength and limitations

A strength of this study was the collection of data relating to antibiotic use across all levels of public health facilities, including hospitals, primary health care centres and health posts. At hospitals, data were separately collected for inpatients, patients attending ambulatory care clinics and those presenting at emergency departments. This enabled comparisons to be made across different levels of the public health system, and provides baseline evidence against which initiatives to improve antibiotic prescribing practices can be monitored. However, the study has several limitations. Almost one-fifth of records had no prescription information, and a medicine may have been prescribed but not recoded or a medicine may not have been prescribed at all. These cases were recorded as ‘uncertain or no prescription’. Also many recorded diagnoses were non-specific, and coded as symptoms. These cases were grouped into broad categories together with related conditions. Having such broad categories made it difficult to assess appropriate use of antibiotics. It also prevented any investigation of whether antibiotic prescribing followed the standard guidelines.

5.5 Conclusion

Current patterns of antibiotic use in public health facilities in Nepal, especially in primary health care facilities, were found to be high compared with WHO guidelines. To prevent overuse and misuse of antibiotics, antimicrobial stewardship programmes should be adopted in public health facilities in Nepal. Given the lack of data on antibiotic use in public health facilities in Nepal, the information gained from this study will help in formulating policies and guidelines to improve antibiotic use in public health facilities and limit the spread of antibiotic resistance. The findings may also be applicable to other low- and middle-income countries where the health system is similar to Nepal.

Chapter 6 Antibiotic dispensing in private pharmacies

Chapter Six presents a study that assessed the patterns of antibiotic dispensing in private pharmacies. Exit interviews were conducted with 1,537 consumers who attended 33 private pharmacies in the Rupendehi district of Nepal. The standard measure recommended by the WHO, namely *"the percentage of patients prescribed an antibiotic",* was used as the main indicator to assess the level of antibiotic use. Factors influencing dispensing practices were also examined.

The results showed that the level of antibiotic dispensing at private pharmacies (38.4%) was above than WHO's standard value (20.0 to 26.8%). The most commonly dispensed antibiotics were cefixime (16.9%) and the third-generation cephalosporins class (38.0%). High dispensing rates of antibiotics for selected conditions (e.g. respiratory infections and diarrhoea cases) were high, and appeared contrary to international guidelines. The percentage of antibiotic dispensed was highest for patients who obtained their medicines from unlicensed pharmacies (59.1%). Young patients were more likely to receive antibiotics than other age groups. The findings suggested the need for initiatives targeting private pharmacies to be implemented that promoted more appropriate use of antibiotics.

The following manuscript was accepted on 16 September 2019 and first published online on 10 October 2019 **(Appendix N)**.

Nepal A, Hendrie D, Robinson S, Selvey LA. Survey of the pattern of antibiotic dispensing in private pharmacies in Nepal. BMJ Open 2019;9:e032422. doi:10.1136/bmjopen-2019-032422

The paper is reproduced here as follows.

6.1 Introduction

The role of the private sector in health care in low- and middle-income (LMICs) countries has often been neglected by governments and international public health communities (342). However, private pharmacies are widely established in most LMICs, and usually considered as a patient's first point of contact for healthcare and the preferred channel through which to get health services and medicines (343). These pharmacies range from high-end outlets to small, rural, road side stalls and can be staffed by fully trained pharmacists or a drug retailer or seller without formal health qualifications. Because of ease of access, more flexible opening hours, availability of cheaper medicines and credit (344) and personal intimacy (345), consumers often tend to utilise private rather than public facilities (346). Further, many patients have neither the time or money to consult a physician (347) preferring over-the-counter medicines and healthcare advice. About three in four antibiotic requests and three in five consultations in community pharmacies around the world result in the sale of antibiotics without a prescription (348).

Strength and limitation of this study

- This is the first study to investigate the pattern of antibiotic dispensing in private pharmacies in Nepal.
- Data on dispensing of medications including antibiotics was sourced directly from patients and validated from the dispensed medicines.
- Data were collected from a wide range of private pharmacies including high-end outlets staffed by pharmacists and small outlets staffed by drug retailers without formal health qualifications.
- Exit interviews were based on convenience sampling with interviews conducted between 09.00 and 17.00, thus may not be representative of all patients attending private pharmacies.
- Description of diagnoses or conditions by patients were symptom-based rather than disease-specific, which made it difficult to assess appropriate use of antibiotics and whether antibiotic dispensing and prescribing followed the standard guidelines.

Non-prescription use of antibiotics is associated with the risk of inappropriate drug use, defined as patients not receiving the appropriate medicines in doses that meet their individual requirements, for an adequate duration, and at the lowest cost (349). Inappropriate use of medicines is a serious global problem occurring in both developed and developing countries (350), with the World Health Organization (WHO) estimating more than half of all medicines are inappropriately prescribed, dispensed, or sold (349). This overuse and misuse of antibiotics is one of the main causes of antibiotics becoming ineffective (351), thus posing problems relating to treatment failure and other costs to the individual and society (352-354).

In Nepal, dispensing of medicines is undertaken by pharmacists and drug retailers or sellers and many dispensers have admitted treating patients too by also prescribing medicines (98). Pharmacists have three to five years of pharmacy education (98), however, drug retailers and sellers include individuals who are only associated with private pharmacies, do not necessarily have formal education in dispensing medicines, but can undertake training and obtain a licence to own and operate a pharmacy from the Department of Drug Administration (DDA), the government body dealing with medicines and their related affairs (94, 355). Practising healthcare without a license is illegal in Nepal (99), however many unlicensed pharmacies are also operating in remote areas of Nepal (59). Little is known about the antibiotic dispensing practices from licensed or unlicensed private pharmacies in Nepal. Previous studies conducted in Nepal that have examined antibiotic dispensing practices from private pharmacies have collected data directly from pharmacists or drug sellers themselves (59, 256), which may result in inaccurate reporting of dispensing practices. This study has investigated patterns of antibiotic dispensing through exit interviews with patients by reviewing their medication information, thus ensuring collection of reliable information. The findings of this study reveal issues about inappropriate use of antibiotics and can be used as a baseline against which to evaluate initiatives to improve antibiotic dispensing and prescribing practices in the private pharmacy sector in Nepal.

6.2 Methods

The study was a cross-sectional study conducted in the Rupandehi district of Nepal. This district was selected because it has an almost equal mix of urban and rural residents (122, 124) and a well-represented population of different castes and ethnicities with more than 63 castes/ethnicities residing in the district (73) out of 126 castes/ethnicities in the country (69). Within the district, there is varying access to transport, with good transport only available in urban areas, which is similar to other districts of Nepal.

Private pharmacies were selected based on WHO guidelines (280, 281). Before deciding on the private pharmacies, six survey areas were selected from the seven electoral areas in the district. The district in which the major hospital is located was selected as one survey area and an area with the lowest socio-economic status as another survey area. An additional four survey areas were randomly selected. One public health facility was selected from each survey area using a list obtained from available records of the District Public Health Office. Altogether, six public health facilities were selected, two each from hospitals, primary healthcare centres and health posts, with the major hospital included as one of the hospitals (as per WHO guidelines). These health facilities were used as the basis for selecting the private pharmacies.

Private pharmacies to include in the study were selected from a list made available by the Nepal Chemists and Druggists Association (NCDA), Lumbini, Nepal. Separate pharmacies and pharmacies attached to private hospitals were included to represent both types. The NCDA list was verified after visiting each selected survey area and updated by deleting any duplicates in the list of pharmacies and adding any missing from the records. In total, 441 private pharmacies were in the NCDA list. Among them, 49 did not exist in the field while 31 were missing on the list. After adjusting the list for these pharmacies, 423 private pharmacies were included in the final list.

As outlined in the WHO guidelines, within each survey area, pharmacies on the final list were grouped according to whether they were located within or beyond five kilometres from each selected public health facility. Within each group in every survey area, pharmacies were assigned a number and then selected for inclusion in the study using a random number generator, with three private facilities selected from the within the five kilometres group and two selected from the greater than five kilometres group. Three private pharmacies were added to the original sample due to refusal of the initially selected pharmacies to allow data collection on the second day. Each pharmacy was surveyed for two days, other than the three that refused data to be collected on the second day and the three replacement pharmacies, which were surveyed for one day. Thus, data collection covered 60 days with 33 private pharmacies (2 days per pharmacy for 27 pharmacies and 1 day per pharmacy for 6 pharmacies).

6.2.1 Data collection

Private pharmacies in Nepal do not follow the practice of keeping patients' records, so exit interviews were conducted with patients who had attended the selected pharmacies. Interviews were conducted from July 2017 to December 2017 from 09.00 to 17.00. The days allocated for data collection were based on the advice of pharmacists to obtain as representative a sample of days as possible. Patients were invited to participate based on convenience sampling, with as many patients as possible who attended the selected pharmacies approached to participate. In total 1,554 patients were approached, with 15 (1%) patients refusing to participate and 1537 patients included in the study. Individuals obtaining medicines on behalf of another person were excluded from the exit interviews as they may not have been able to provide the relevant details about the patient or their condition. In contrast, parents have these details for their children so children attending the pharmacies with their parents were included in the survey.

Data were collected using the Qualtrics Offline Surveys Application (292). Demographic characteristics of the patients for whom the medicines had been bought (age, sex), the disease or condition and sources of antibiotic (356) (self-medicated, recommended and supplied by a pharmacist or drug retailer without a prescription, prescribed by a doctor and dispensed by a pharmacist or drug retailer, other) were collected. Photographs were taken of the medicines, with no patient identifiers included, and attached to the Application. The maximum time taken for the exit interview was three minutes. Prior to the interview, all consumers were informed of the nature of the study and written consent was sought to interviews being conducted. Consent for patients younger than 18 years was sought from the accompanying parent or caretaker.

The principal researcher coordinated data collection and approached respective authorities and health facilities to obtain approval to collect the data, and four Nepali research assistants were engaged in data collection. A training session for research assistants was held prior to embarking on data collection and focused on the aim of the study, the importance of ensuring quality in the data collection and ethical considerations. The research assistants were regularly monitored by the principal researcher to ensure the quality of the data through observation at the study sites and cross-checking of the entered records in the Qualtrics Application.

6.2.2 Data analysis

The data were imported from the Qualtrics Application to MS-Excel spreadsheet for cleaning. The cleaned data were transferred to the SPSS statistical software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: USA). Diseases or conditions collected from the interviews were generally described based on symptoms, thus similar symptoms were grouped together. For some analyses, the most commonly occurring groups (such as fever, respiratory symptoms and skin conditions) were separately analysed, with remaining groups combined into those likely to have an infectious cause ("other: infectious"), and those not likely to have an infectious cause ("other: non-infectious"). Antibiotics were also grouped into classes for analysis (293). A core prescribing indicator, "*the percentage of patients prescribed an antibiotic*" was computed in line with the WHO's standard values (199). Descriptive analysis was conducted to show commonly dispensed antibiotics, sources of antibiotic, registration status of pharmacies and education of the pharmacist or drug retailer, and disease or condition. Chi-square tests were performed to examine the association between antibiotic dispensing and explanatory variables including sex, age group of patient, sources of antibiotic and registration status of pharmacies and education status of the pharmacist or drug retailer. Logistic regression was also used to examine factors associated with antibiotic dispensing. An interaction term of sources of antibiotic with registration status and education was also examined. The significance level (α) was set at 0.05 for all statistical tests.

6.3 Results

6.3.1 Characteristics of patients and prescription information

The sample comprised a similar number of male and female respondents, with all age groups relatively well represented **(Table 6.1)**. Just over half of patients (55.2%) had a prescription from a doctor or health worker, with about one quarter not having a prescription but purchasing a medicine recommended and supplied by the pharmacist. Almost equal numbers of patients received their medicine from a pharmacist who had a diploma or bachelor's degree in pharmacy (49.6%) and drug retailers who had completed training from DDA (46.1%). The most commonly occurring diseases or conditions were fevers (18.1%), coughs (5.3%), and respiratory infection (4.9%). At least one antibiotic was dispensed in 947 (38.4%) patient encounters.

Table 6.1 Patient characteristics and information related to dispensing of medicines

Variables	Percentage	n_i/n_k[b,c]
Sex		
Male	50.5	776/1537
Female	49.5	761/1537
Age group of patient		
Less than 14 years	19.4	298/1537
15 to 24 years	20.2	310/1537
25 to 44 years	35.0	538/1537
45 and above years	25.4	391/1537
Sources of antibiotic		
Prescribed by a doctor or health worker and dispensed by a pharmacist or drug retailer	55.2	848/1537
Recommended and supplied by a pharmacist or drug retailer without a prescription	26.1	401/1537
Self-medicated	13.3	205/1537
Other (invalid prescription)	5.4	83/1537
Registration status/education		
Licensed/diploma or bachelors in pharmacy	49.6	762/1537
Licensed/training from DDA	46.1	709/1537
Unlicensed/education unknown	4.3	66/1537
Disease or condition*		
Fever	18.1	278/1537
Cough	5.3	82/1537
Respiratory infection	4.9	75/1537
Headache	4.8	74/1537
Loss of appetite	4.7	72/1537
Skin infection	4.6	70/1537
Common cold	4.4	68/1537
Injury	4.4	67/1537
Acid peptic disease	4.3	66/1537
Body ache	4.2	65/1537
Heart disease	4.2	64/1537
Fungal infection	3.8	59/1537
Skin disease	3.7	57/1537
Abdominal discomfort	3.6	55/1537
Arthritis and bone pain	3.3	50/1537
Others	21.8	335/1537
Prescribing indicator		
Percentage of patients dispensed an antibiotic	38.4	590/1537
No of antibiotics dispensed		
No antibiotic	61.6	947/1537
One antibiotic	35.8	551/1537
Two antibiotics	2.5	39/1537

[b]n_j numerator; [c]n_k denominator; DDA: Department of Drug Administration

***Diseases or conditions included:**

***Fever:** Fever and pyrexia; **Cough:** Cough, dry cough and allergic cough; **Respiratory infections:** Acute respiratory infection, respiratory infection, chest infection and bronchitis; **Loss of appetite:** Weakness, anorexia and loss of appetite; **Skin infections:** Boils, dermatitis, wound and skin infection; **Common cold:** Common cold and sinusitis; **Injury:** Injuries; **Acid peptic disease:** Acid peptic diseases, gastritis, peptic ulcer, and upper gastrointestinal bleeding; **Body ache:** Body ache and backache; **Heart disease:** Heart disease and hypertension; **Fungal infection:** Fungal infection and ring worm; **Skin disease:** Skin diseases and skin allergy; **Abdominal discomfort:** Abdominal pain, nausea, vomiting and dyspepsia; **Arthritis and bone pain:** Arthritis, joint pain, leg Pain and shoulder Pain*

6.3.2 Commonly dispensed antibiotics

Among antibiotics, the most commonly dispensed were cefixime (16.9%), amoxicillin (12.2%), cefpodoxime (10.3%), ampicillin+cloxacillin (8.7%) and ciprofloxacin (8.7%). Cephalosporins (38.0%) were the most commonly dispensed class of antibiotics, followed by penicillins (29.3%), quinolones (13.7%) and marcolides (8.1%) **(Table 6.2)**.

Table 6.2 Commonly dispensed antibiotics

	Dispensed antibiotics	No	%		Dispensed antibiotic classes	No	%
1	Cefixime	106	16.9	1	Cephalosporins	239	38.0
2	Amoxicillin	77	12.2	2	Penicillins	184	29.3
3	Cefpodoxime	65	10.3	3	Quinolones	86	13.7
4	Ampicillin+Cloxacillin	55	8.7	4	Marcolides	51	8.1
5	Ciprofloxacin	55	8.7	5	Antiprotozoal	50	7.9
6	Azithromycin	49	7.8	6	Others	19	3.0
7	Metronidazole	48	7.6		**Total**	**629**	**100**
8	Amoxicillin+Clavulanate	31	4.9				
9	Cefadroxil	16	2.5				
10	Cephalexin	16	2.5				
11	Levofloxacin	14	2.2				
12	Ofloxacin	14	2.2				
13	Amoxicillin+Cloxacillin	11	1.7				
14	Cefixime + Clavulanic Acid	11	1.7				
15	Other	61	9.7				
	Total	**629**	**99.6**				

The percentage of antibiotics dispensed was highest for those patients for whom the medicine had been prescribed by a doctor or health worker (58%). It was also highest for patients who obtained their medicines from an unlicensed pharmacy (59.1%). For several conditions, antibiotics were the most commonly dispensed medicine, including for respiratory infection (93.3%), diarrhoea and dysentery (91.3%), skin infection (87.1%), fever (70.5%) and urinary tract infection (57.9%).

The class of antibiotics dispensed was relatively similar by sources of antibiotic and registration status and education. Third generation Cephalosporins were the most common class of antibiotics recommended and supplied by a pharmacist or drug retailer without a prescription (40.7%) and prescribed by a doctor or health worker (38.1%), with Antiprotozoals the most common among patients who self-medicated (38.5%). Cephalosporins were also most commonly dispensed by both drug retailers who had training from DDA (41.3%) and those with a diploma or bachelors in pharmacy (36.1%). The highest dispensing rate of Cephalosporins was for the treatment of fever (69.5%), whereas penicillins were common for respiratory infection (60.8%), injuries (78.8%) and skin infection (67.2%) **(Table 6.3)**.

Table 6.3 Descriptive analysis of dispensed classes of antibiotics by sources of antibiotic, registration status and education, and selected diseases and conditions

Variables	Antibiotics dispensed		Classes of antibiotics dispensed (%)					
	Yes = n (%)	No = n (%)	Cephalosporins = n (%)	Penicillins = n (%)	Quinolones = n (%)	Marcolides = n (%)	Antiprotozoal = n (%)	Others = n (%)
Sources of antibiotic								
Self-medicated	12 (4.2)	276 (95.8)	2 (15.4)	2 (15.4)	2 (15.4)	1 (7.7)	5 (38.5)	1 (7.7)
Recommended and supplied by a pharmacist or drug retailer without a prescription	86 (21.4)	315 (78.6)	35 (40.7)	14 (16.3)	12 (14.0)	8 (9.3)	14 (16.3)	3 (3.5)
Prescribed by a doctor or health worker and dispensed by a pharmacist or drug retailer	492 (58.0)	356 (42.0)	202 (38.1)	168 (31.7)	72 (13.6)	42 (7.9)	31 (5.8)	15 (2.8)
Registration status/education								
Licensed/diploma and bachelors in pharmacy	260 (34.1)	502 (65.9)	101 (36.1)	81 (28.9)	35 (12.5)	33 (11.8)	24 (8.6)	6 (2.1)
Licenced/training from DDA	291 (41.0)	418 (59.0)	128 (41.3)	90 (29.0)	39 (12.6)	16 (5.2)	26 (8.4)	11 (3.5)
Unlicensed/education unknown	39 (59.1)	27 (40.0)	10 (25.6)	13 (33.3)	12 (30.8)	2 (5.1)	0 (0.0)	2 (5.1)
Disease and condition*								
Respiratory infection	70 (93.3)	5 (6.7)	12 (16.2)	45 (60.8)	3 (4.1)	13 (17.6)	0 (0.0)	1 (1.4)
Diarrhoea and dysentery	42 (91.3)	4 (8.7)	4 (7.8)	0 (0.0)	10 (19.6)	0 (0.0)	37 (72.5)	0 (0.0)
Skin Infection	61 (87.1)	9 (12.9)	12 (19.7)	41 (67.2)	1 (1.6)	2 (3.3)	0 (0.0)	5 (8.2)
Fever	196 (70.5)	82 (29.5)	141 (69.5)	29 (14.3)	21 (10.3)	11 (5.4)	1 (0.5)	0 (0.0)
Urinary tract infection	22 (57.9)	16 (42.1)	1 (4.5)	0 (0.0)	18 (81.8)	0 (0.0)	0 (0.0)	3 (13.6)
Injury	33 (49.3)	34 (50.7)	4 (12.1)	26 (78.8)	2 (6.1)	1 (3.0)	0 (0.0)	0 (0.0)
Common cold	16 (23.5)	52 (76.5)	6 (37.5)	5 (31.3)	1 (6.3)	4 (25.0)	0 (0.0)	0 (0.0)
Abdominal discomfort	10 (18.2)	45 (81.8)	3 (27.3)	0 (0.0)	4 (36.4)	0 (0.0)	4 (36.4)	0 (0.0)
Skin disease	7 (12.3)	50 (87.7)	4 (57.1)	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)
Cough	7 (8.5)	75 (91.5)	4 (40.0)	1 (10.0)	0 (0.0)	5 (50.0)	0 (0.0)	0 (0.0)
Other: infectious	104 (49.5)	106 (50.5)	38 (32.2)	29 (24.6)	23 (19.5)	14 (11.9)	6 (5.1)	8 (6.8)
Other: non-infectious	22 (4.5)	469 (95.5)	10 (43.5)	6 (26.1)	3 (13.0)	1 (4.3)	2 (8.7)	1 (4.3)

DDA: Department of Drug Administration

Diseases or conditions included:

***Respiratory infection:** Acute respiratory infection, respiratory infection, chest infection and bronchitis; **Diarrhoea and dysentery:** Diarrhoea, dysentery and loose motion; **Skin infection:** Boils, dermatitis, wound and skin infection; **Fever:** Fever and pyrexia; **Injury:** Injuries; **Common cold:** Common cold and sinusitis; **Abdominal discomfort:** Abdominal pain, nausea, vomiting and dyspepsia; **Skin disease:** Skin diseases and skin allergy; **Cough:** Cough, dry cough and allergic cough; **Other: infectious:** Likely to have an infectious cause; **Other: non-infectious:** Not likely to have an infectious cause*

6.3.3 Factors associated with antibiotic dispensing

Across all diseases and conditions, antibiotic dispensing was significantly associated with age group, sources of antibiotic, and registration status and education of pharmacists **(Table 6.4)**. Patients less than 15 years were more likely than all other age groups to receive antibiotics (p=<0.001). Those patients who attended a pharmacy without a prescription from a doctor or health worker were less likely to receive antibiotics than patients with a prescription (p=<0.001). In addition, patients were less likely to receive antibiotics from pharmacists who had a diploma or bachelors in pharmacy (p=0.001) compared to unlicensed drug retailers or licensed retailers with training from DDA only. The interaction term shows that patients who presented with no prescription were more likely to receive an antibiotic if they presented with no prescription to a pharmacy attended by a trained pharmacist.

Table 6.4 Factors associated with antibiotic dispensing

Variables	Antibiotics dispensing			Bivariable analysis			Multivariable analysis	
	Yes = n (%)	No = n (%)	X^2 (p-value)	n	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex								
Male	302 (38.9)	474 (61.1)	0.187 (0.666)	776	1	0.666	1	0.576
Female	288 (37.8)	473 (62.2)		761	0.956 (0.778, 1.174)		0.934 (0.734, 1.188)	
Age group of patient								
Less than 15 years	177 (59.4)	121 (40.6)	98.876 (<0.001)	298	1		1	
15 to 24 years	116 (37.4)	194 (62.6)		310	0.409 (0.295, 0.566)	<0.001	0.464 (0.320, 0.672)	<0.001
25 to 44 years	210 (39.0)	328 (61.0)		538	0.438 (0.328, 0.584)	<0.001	0.432 (0.311, 0.602)	<0.001
45 and above years	87 (22.3)	304 (77.7)		391	0.196 (0.140, 0.273)	0.001	0.206 (0.142, 0.299)	<0.001
Sources of antibiotic								
Recommended and supplied by a pharmacist or drug retailer without a prescription (includes self-medication)	98 (14.2)	591 (85.8)	308.278 (<0.001)	689	0.120 (0.093, 0.155)	<0.001	0.087 (0.059, 0.128)	<0.001
Prescribed by a doctor or health worker and dispensed by a pharmacist or drug retailer	492 (58.0)	356 (42.0)		848	1		1	
Registration status and education								
Licensed/diploma and bachelors in pharmacy	260 (34.1)	502 (65.9)	11.627 (0.001)	762	0.698 (0.568, 0.859)	0.001	0.617 (0.465, 0.819)	0.001
Licensed/training from DDA (Includes unlicensed)	330 (42.6)	445 (57.4)		775	1		1	
Interaction term with sources of antibiotic, and registration status and education							1.987 (1.177, 3.354)	0.010

6.4 Discussion

In most developing countries, private pharmacies or drug stores are the first point of contact for people seeking healthcare (343). Antibiotics (and other prescription medicines) are readily available with or without prescription, and self-medication by patients is common. Non-prescription use of antibiotics is associated with a risk of inappropriate use due both to failure in dispensing in accordance with clinical guidelines and patients not using the drug appropriately (357). It is also one of the drivers of the emergence of antimicrobial resistance (358).

Findings of this study show the overuse of antibiotics dispensed from private pharmacies, with the percentage of patients dispensed an antibiotic (38%) being considerably higher than the level recommended by the WHO (20 to 26.8%) (199). This finding of overuse is consistent with studies conducted in private facilities in other LMICs including 43% in both India (270) and Uganda (359) and 53% in Bangladesh (221).

Unlicensed pharmacies, especially outside of cities, often exist in low- and middle-income countries (360). These pharmacies sell medicines informally and are not legally recognised by the health system of the countries in which they operate (361). While, practicing healthcare without a license is illegal in Nepal (99), weak regulatory oversight of the Nepalese health system encourages pharmacies to operate without licences. This study found the level of dispensing of antibiotics was higher by unlicensed drug retailers and drug retailers with limited training. Interestingly the interaction term in the multivariable model suggests that, while this is the case, if patients presented to a pharmacy with a trained pharmacist without a prescription, they were more likely to receive antibiotics. It has been suggested circumstances that drug retailers may approach dispensing of medicines as any other sales job, not wanting a customer to leave without making a purchase (360). More generally, inappropriate dispensing of antibiotics may occur due to the business motive of private pharmacies with profits from antibiotics contributing to total profit (362).

Third generation cephalosporins were the most common antibiotic type recommended and dispensed with or without prescription. The finding is consistent with the studies conducted in India showing cephalosporins were the most commonly supplied class of antibiotic in private pharmacies or clinics (270) and often used by urban private health facilities (363). Guidelines often advise that cephalosporins should be avoided as a first-line treatment when a narrower spectrum antibiotic would be effective because they increase the risk of *Clostridium difficile, methicillin resistant Staphylococcus aureus (MRSA)* and other resistant infections (335, 336). Noticeably, third generation cephalosporins were dispensed to patients with minor symptoms, such as fever, which is self-limiting in most cases and could be a common symptom of several infections. The popularity of third generation cephalosporins lies in their lesser allergenic and toxicity risks as well as having a broad spectrum of activity (335). In Nepal treatment guidelines do not recommend cephalosporins as a first-line treatment for several infections such as respiratory tract infections, enteric fever, pneumonia and urinary tract infections (224).

Overprescribing and overuse of antibiotics in the treatment of respiratory infections and diarrhoea is a worldwide problem, potentially leading to widespread antimicrobial resistance (364). Contrary to international recommendations, this study found high prescribing rates of antibiotics for both conditions, suggesting possible overprescribing. The WHO guidelines recommend oral rehydration solution with other supplements for non-bloody diarrhoea (331) and home care without antibiotics for children with respiratory symptoms (332).

Across all conditions collectively, antibiotics were more likely to be dispensed to younger age groups especially less than 15 years of age compared to older groups. Respiratory diseases and diarrhoea impose a considerable health burden especially to children in LMICs (365, 366), and may lead to antibiotics being used more widely for the treatment of these diseases (367, 368). Higher self-medication practices among younger age groups could also be a factor contributing to higher antibiotic dispensing for younger age groups, with a study in Albania finding an association between self-medication and a higher use of antibiotics among younger age groups (369). Additionally increased education has been found to increase the risk of self-medication with antibiotics (370), and globally the literacy rates of young adults is higher than the elderly, with the differences is even wider in developing countries (371).

6.4.1 Policy implications

Levels of antibiotic prescribing above the WHO recommended rate suggests the need to implement measures to reduce potential inappropriate use in Nepal. Almost half of patients were dispensed antibiotics by drug retailers who, unlike pharmacists are professionally trained and do not have formal education in dispensing medicines. While this study did not examine their technical competencies, drug retailers should be encouraged to increase their skills through continued professional education.

In Nepal, prescribing is conducted by physicians and non-physicians such as auxiliary health workers and health assistants, who have 18 months to three years post-secondary training in diagnostics and therapeutics, and nurses (96). The physicians work at hospitals and non-physicians, who are referred to as health workers, mostly work in public health facilities at the community level and have their own private pharmacies. Health workers are less qualified than physicians but are authorised to prescribe medicines as outlined in the antibiotic treatment guidelines (224). However, such guidelines are barely in practice or monitored (225). WHO's guideline of good pharmacy practices confines the role of pharmacists to dispensing only (372). A general lack of enforcement of the legislation covering registration of pharmacies and the distribution of antibiotics facilitates the inappropriate use of antibiotics in Nepal. Stronger enforcement mechanisms of pharmacy registration and restricting pharmacists and drug retailers supplying antibiotics without prescription should be established.

Private pharmacies are widely established in most LMICs including Nepal. They are usually considered as a patient's first point of contact and preferred channel to receive health services (343) particularly given issues relating to the unavailability and inaccessibility of quality of care from public health facilities (373). Private pharmacists and community members are often known to each other and pharmacists can be under pressure to supply antibiotics (337). Pharmacists and drug retailers generally do not charge consultation fees and profits from selling drugs is a main source of their income (374), which could encourage the selling of antibiotics since it is one of the more profitable medicines (362). A targeted intervention to provide education and training relating to antimicrobial resistance and supplying antibiotics only with prescriptions will lead to greater consideration of antibiotic dispensing practices based on the standards of good pharmacy practices, thus contributing to a reduction in the risk of development of antibiotic resistance bacteria.

Additionally, the relatively high prescribing rate of third generation cephalosporins in private health facilities in Nepal is of concern, given that these classes are considered second-line antibiotics in most guidelines. When antibiotic therapy is necessary, the use of narrow-spectrum antibiotics should be used as first-line treatment whenever possible (341) to prevent drug-resistant bacteria developing. Educational interventions to reduce inappropriate dispensing or prescribing of antibiotics in unwarranted situations should include guidance on the proper selection of antibiotics.

6.4.2 Strengths and limitations

Limited evidence is available in regard to the pattern of antibiotic dispensing in LMICs. This study has provided an evidence base about the current pattern of antibiotic dispensing from private pharmacies in Nepal, with data on dispensing of medications including antibiotics sourced directly from patients and validated from the dispensed medicines. Data on dispensed medicines were collected from a wide range of private pharmacies including high-end outlets staffed by pharmacists and small outlets staffed by someone without formal health qualifications. The information on dispensed medicines provides a useful baseline against which to measure the effectiveness of future policies and programmes to reduce the level of inappropriate dispensing of antibiotics. The findings of the study also reinforces calls to build a strong regulatory environment in advancing prudent antibiotic use. The findings may also be applicable to other LMICs, where the health system is similar to Nepal.

However, the study has several limitations. The study covered about 8% (33/423) of private pharmacies in the Rupandehi district. While the selection process followed WHO guidelines, these guidelines do not account for the number of facilities in the district, thus the sample of pharmacies selected may not be representative. Interviews were conducted between 09.00 and 17.00 at the selected pharmacies, which excludes patients attending the pharmacies at other times, and exit interviews were based on convenience sampling. Diagnoses or conditions of patients were non-specific and recorded based on the understanding of the patients. Description of diagnoses or conditions were more symptom-based and were grouped into broad categories together with related conditions. Having such broad categories made it difficult to assess appropriate use of antibiotics. It also prevented any investigation of whether antibiotic dispensing and prescribing followed the standard guidelines. Another limitation is that the Rupandehi district lies in a low-land region of Nepal, which has a greater availability of health services than in hill and high-hill regions. Results of the study are thus more generalisable to districts falling in low-land regions than hill and high-hill regions, a factor which needs to be considered in using findings from the study in developing and implementing policy to improve pharmacy practice in Nepal and similar countries.

6.5 Conclusion

This study documents antibiotic dispensing practices in private pharmacies in Nepal that were high compared with WHO guidelines. The overuse of antibiotics has been associated with a higher prevalence of antimicrobial resistance. Given global concerns about antimicrobial resistance, evidence relating to overuse and misuse in Nepal provides a rationale to consider introducing initiatives to reduce inappropriate use of antibiotics. Additionally this evidence may be more widely generalisable to other countries with similar health system financing arrangements.

Chapter 7 Knowledge, attitudes and practices of community people

This chapter presents the study that explored the knowledge, attitudes and practices of community members to antibiotic use. Interviews were conducted with 220 community members in the Rupandehi district of Nepal using a structured questionnaire.

The study indicated that the community people had reasonably good knowledge on aspects of antibiotic use other than identifying antibiotics. The concept of antibiotic resistance was well known by the community people but imperfectly understood. Half of respondents were unsure whether skipping doses would contribute to the development of antibiotic resistance, and most respondents answered that they would go to another doctor if not prescribed an antibiotic and that antibiotics helped them get better more quickly if they had a fever. Although most respondents reported correct practices using antibiotics, however, most preferred an antibiotic when they have a cough and sore throat. Community members with higher levels of education tended to have better knowledge, more appropriate attitudes and better practices about antibiotic use. Rural respondents were less likely to have better knowledge about antibiotic use, while females were more likely to report better practices. Findings of the study will be useful in designing effective and targeted interventions to decrease misconceptions about antibiotic use and to increase people's awareness about the risks of inappropriate use of antibiotics in the community.

The following manuscript was accepted on 08 November 2019 and first published online on 26 November 2019 **(Appendix O)**.

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The paper is reproduced here as follows.

7.1 Background

Inappropriate use of antimicrobial agents and the consequences of spread of antimicrobial resistance is an increasing public health problem (316). In recent years, resistance to antimicrobial agents that were previously effective has emerged or re-emerged in many regions causing a global health threat and economic consequences. Among many other factors, behaviours of community members and their limited knowledge associated with inappropriate antibiotics use (46, 47) is contributing to antibiotic resistance. A recent review found one-third (33.7%) of the population of low and middle income countries lack knowledge about antibiotics and their role (283). A study conducted in Bhutan found unsatisfactory knowledge (52.8%) and practices (47%) on antibiotic use (375). Similarly, more than one-third (36%) of people in Kuwait reported not completing the prescribed course of antibiotics and around 28% had self-medicated with antibiotics (338).

A number of studies relating to antibiotic use in a range of different countries have investigated the knowledge, attitudes and practices of the general population (176-179, 183, 186, 283, 285, 376-378), secondary school teachers and university faculty members (379), students (171, 380-382), primary care center attendants (383) and parents (384, 385). These studies have shown patients' or parents' expectations of antibiotic therapy, or expectations as perceived by the doctor, to be a determining factor for antibiotic prescribing (338, 386, 387). The rationale for educating the public is that knowledge about antibiotic treatment and awareness of antibiotic resistance are thought to influence patient and parent demand for antibiotic prescribing (388). Because of wide cross-national differences in antibiotic use (389) tailoring of educational interventions requires determination of the needs of the audience in each country.

This paper reports on research that explores the knowledge, attitudes and practices of community members in relation to antibiotic use in the Rupandehi district in Nepal. Previous studies in Nepal have investigated surgical site infection and antibiotic use (390), antibiotic resistance (143, 319, 391, 392), antibiotic prescribing and sensitivity (393), antibiotic prescribing patterns (394, 395), antibiotic dispensing practices (256), knowledge, attitudes and practices of medical students in relation to antibiotics use (396), and dispensing practices and patients' knowledge about drug use (66). However, to our knowledge no population based studies have been conducted on knowledge, attitudes and practices relating to antibiotics use. Moreover, some studies conducted in Nepal have found that antibiotics are among the most commonly sold drug classes (256, 391, 396). Thus, it is important to measure this phenomenon, exploring the knowledge, attitudes and practices towards antibiotic usage, and awareness about anti-microbial resistance among adults of Nepal. The findings will aid in planning strategies for local health education purposes and developing intervention tools aimed at changing the practices of patients and the public.

7.2 Methods

7.2.1 Study area and sampling

A cross sectional quantitative survey of community members was conducted in the Rupandehi district of Nepal. At the time of developing the study design for this research, the administrative re-structure of Nepal had not been fully implemented. As per the earlier structure, Nepal was divided into five developmental regions and subdivided into 75 districts (120). The districts were further divided into village development committees (VDCs) and municipalities, which were divided into wards as the basic administrative units. Districts are spread across three geographic regions, high-hill, hill and low-land, with approximately half of the population living in low-land regions (397).

According to the 2011 census, the total population of Nepal was 26,494,504 with 3.3% (880,196) of the population living in the Rupandehi district (397). Almost two-thirds (66.0%, 580,688) were adults. The district is situated towards the central southern part of the country. As per the earlier structure, the district was divided into six municipalities and 42 VDCs). Municipalities and VDCs were aggregated in seven electoral areas (122).

We used guidelines developed by the World Health Organization (WHO) (280, 281) for the selection of households. Following these guidelines, public health facilities were selected as the basis of household selection. We chose six of the seven electoral areas to survey. Two were purposively selected: one that includes the largest hospital in the district and the other was the area with the lowest socio-economic status. An additional four areas were selected randomly from the remaining five electoral areas as recommended by the guidelines. One public health facility was selected from each survey area, consisting of all types of health facilities i.e. two each of hospitals (the largest as discussed above plus another), primary health care centres and health posts. The additional hospital plus other facilities were randomly selected. The VDCs and municipalities in which the public health facilities were located were used as the sampling area for selection of households. Of the total of six areas selected, four consisted of VDCs and two were municipalities.

A cluster sampling technique was applied to identify households to survey within the selected survey areas. Based on the WHO manual (282), we identified 20 clusters from the selected municipalities and VDCs. The smallest administrative unit, the "ward", was considered as a cluster. Four clusters per municipality and three clusters per VDC were selected randomly. The sample size of 220 was based on an estimated prevalence of 33.7% of the population lacking knowledge on antibiotics and their role (283), a 95% confidence interval, a precision effect of 10%, a design effect of two to account for heterogeneity between clusters and an adjustment of 25% to allow for non-response (284, 285).

A list of households in each cluster was obtained from the records of respective municipalities and VDC offices. This list was verified after visiting each cluster and updated by deleting any duplicate households and adding any households missing from the records. Using the updated list of households in each cluster, an equal number of subjects (eleven) was selected from each cluster applying simple random sampling techniques.

The head of household was the preferred respondents for the study. However, if the head of household was absent at the time of interview, the most senior member of the household, who was 18 years and older, was interviewed.

7.2.2 Data instrument and collection

A structured questionnaire was developed by adapting related questionnaires including one from the United States Agency for International Development (USAID) module "Antimicrobial resistance module for population-based surveys" (287) and those used in previous studies (288, 289).

A set of questionnaires was pre-tested with 30 respondents in urban and rural areas of the Nawalparasi district, Nepal (a neighboring district of Rupandehi), to ensure the cultural appropriateness, any problems with question wording, layout and understanding or a respondent's reaction. As a result, minor adjustments were made to the final questionnaire based on the pre-test results. With a few people not knowing what the word "antibiotics" was, the questionnaire was amended to ask if they had heard of widely used antibiotics such as penicillin or metronidazole before being asked the main questions. Similarly a few respondents were unsure of the difference between "good" and "bad" bacteria present in our bodies so this difference was explained before they answered the question. Following explanation, issues with language did not appear to cause ambiguity that might impact on interpretation of the survey and the ensuing results. The final questionnaire included twelve questions relating to knowledge, eight questions to attitudes and six questions to practices. The reliability coefficient of responses to the final questionnaire was calculated using the Cronbach's alpha score with the following results recorded: knowledge (0.63), attitudes (0.65) and practices (0.67).

The questionnaire comprised four sections: socio-demographic characteristics of respondents and a section on each of knowledge, attitudes and practices relating to antibiotics and their use. Questions about knowledge were divided into four domains, namely "identification of antibiotics" (Q1-Q3), "knowledge on the role of antibiotics" (Q4-Q6), "side-effects of antibiotics" (Q7-Q9) and "antibiotic resistance" (Q10-Q12). The questions on attitudes were divided into three domains: "preference for use of antibiotics" (Q13-Q15), "antibiotic resistance and safety" (Q16-Q18), and "attitudes to doctor's prescribing of antibiotics" (Q19-Q20). The six questions relating to practices (Q21-Q26) were not divided into domains. The English version of the questionnaire was translated into Nepali and back translated into English to ensure the accuracy of the translated text.

Interviews were conducted in the Nepali language by two trained research assistants from September 2017 to December 2017. The training of research assistants covered the objectives of the study and familiarising them with the data collection techniques. A flow chart for the recruitment of respondents and consent process was provided to the research assistants and used in the data collection process. The average duration per interview was

20 minutes. Ten households were replaced in the original sample due to refusal to participate (n=7) and no one at home at the time of interview (n=3).

All respondents were informed of the nature of the study and written consent was sought to interviews being conducted. The study was approved by the Human Research Ethics Committee, Curtin University (HRE2017-0394) and the ethics committee of the Nepal Health Research Council (Reg. no.189/2017).

7.2.3 Data management and analysis

Data were collected via paper-based questionnaires and the data were entered and analysed using the Statistical Package for the Social Sciences (SPSS) version 25.0 for Windows (IBM Corp., Armonk, NY, USA).

Demographic variables and responses to the knowledge, attitudes and practices questions were analysed using descriptive statistics. Responses to the five-point Likert scale for the knowledge and attitudes questions were combined into three groups: ‘strongly agree’ and ‘agree’, ‘strongly disagree’ and ‘disagree’, and ‘uncertain’. The three groups are referred to as “Yes”, “No” and “Don’t know”, respectively (294). Questions relating to practices were assessed using the five-point Likert scales scoring scheme of ‘never’, ‘seldom’, ‘sometimes’, ‘often’ and ‘always’.

Regression analysis was conducted to identify demographic factors associated with knowledge, attitudes and practices. Responses to the knowledge and attitudes questions were given a score of “1” for a correct response and “0” for an incorrect or uncertain response, and scores summed for respondents across each of the domains. For the practices questions, responses were given a score based on the five-point Likert scale, ranging from “5” for the most appropriate answer to “1” for the least appropriate answer, and summed. The median score based on responses to questions in each of the knowledge, attitudes and practices sections was used as the cut-off to dichotomize the continuous variable for use as the dependent variable in multiple logistic regression analysis. Respondents scoring higher than the median were assessed as having “better knowledge”, “more appropriate attitudes” and “better practices” relating to antibiotic use (295). The significance level (α) was set at

0.05 for all statistical tests. Spearman's rank order correlation coefficient was used to describe the strength and direction of the relationship between responses to the knowledge, attitudes and practices questions.

7.3 Results

7.3.1 Characteristics of respondents

The sample consisted of 220 households **(Table 7.1)**, with a response rate of 97% (n=210). Compared to the adult population of the Rupandehi district, the sample included slightly more females (54% vs 52%) and respondents from rural areas (60% vs 51%). The mean age was 38.5 years (SD 11.5). Most respondents had achieved a level of education of primary/secondary school level (31.4%) or high school/intermediate level (30.0%). The mean monthly income of respondents was Nepalese Rupees (NPR) 42,491 (SD 16,835), compared with an estimated average monthly household income for Nepal of NPR 30,121 in 2015 (398).

Table 7.1 Socio-demographic characteristics of respondents

Variables	Study, n (% distribution)	Rupandehi, n (% distribution)[a]
Gender		
Male	101 (45.9)	277,714 (47.8)[b]
Female	119 (54.1)	302,974 (52.2)[b]
Areas of residence		
Urban	88 (40.0)	(49.0)[b]
Rural	132 (60.0)	(51.0)[b]
Age (Years)		
15-24	25 (11.4)	185,430 (31.9)[b]
25-34	50 (22.7)	134,798 (23.2)[b]
35-44	81 (36.8)	99,013 (17.1)[b]
45-54	38 (17.3)	69,363 (11.9)[b]
55+	26 (11.8)	92,084 (15.9)[b]
Min=18, Max=69, Mean=38.5, SD=11.511		
Level of education		
General literate	38 (17.3)	
Primary/Secondary school	69 (31.4)	
High school/Intermediate	66 (30.0)	
Bachelors and above	47 (21.4)	
Level of Income - Quartile (NPR) (n = 210)		
First (30,000 or less)	60 (28.6)[c]	
Second (30,001 to 40,000)	46 (21.9)[c]	
Third (40,001 to 53,500)	52 (24.8)[c]	
Fourth (53,501 and above)	52 (24.8)[c]	
Min=2300, Max=110000, Mean=42491.9, SD=16835.0		

[a]*Source: CBS, 2014 (73)*
[b]*% calculated based on population of 15 years and above*
[c]*Numbers not equally distributed across quartiles due to clustering of responses at cut-off points.*

7.3.2 Knowledge, attitudes and practice relating to antibiotics use

Respondents had relatively good knowledge about three of the four knowledge domains: "knowledge about the role of antibiotics (Q4-Q6)", "side-effects of antibiotics (Q7-Q9)", and "antibiotic resistance (Q10-Q12)" **(Figure 7.1)**. While the majority of responses to questions in the three domains were correct, for questions on "side-effects of antibiotics" and "antibiotic resistance" a relatively high percentage of responses to five of the six questions fell in the "don't know" category (16-27%). Statements for which the "don't know" response was highest included that "*antibiotics can cause secondary infections after killing good bacteria present in our bodies*" (25.0%), "*many infections becoming increasingly resistant to* *treatment by antibiotics*" (25.0%) and "*misuse of antibiotics leading to antibacterial resistance*" (27.7%).

Respondents had relatively less knowledge in regard to "identification of antibiotics (Q1-Q3)". More than two-thirds (67.7%) did not answer correctly to the question that "*amoxicillin is an antibiotic*" and nearly one-third (32.7%) did not know that "*antacid is not an antibiotic*". However, most respondents (94.1% and 84.1% respectively) answered correctly that "a*ntibiotics are useful for killing germs*" and "*antibiotics are not often needed for cold and flu illness*" while more than two-thirds (71.5%) knew paracetamol was not an antibiotic.

The level of knowledge about antibiotics use was better for respondents who lived in urban compared to rural areas (X^2 = 16.257, P = <0.001), for younger respondents (X^2 = 30.696, P = <0.001) and those with higher levels of education (X^2 = 72.264, P = <0.001) **(Table 7.2)**.

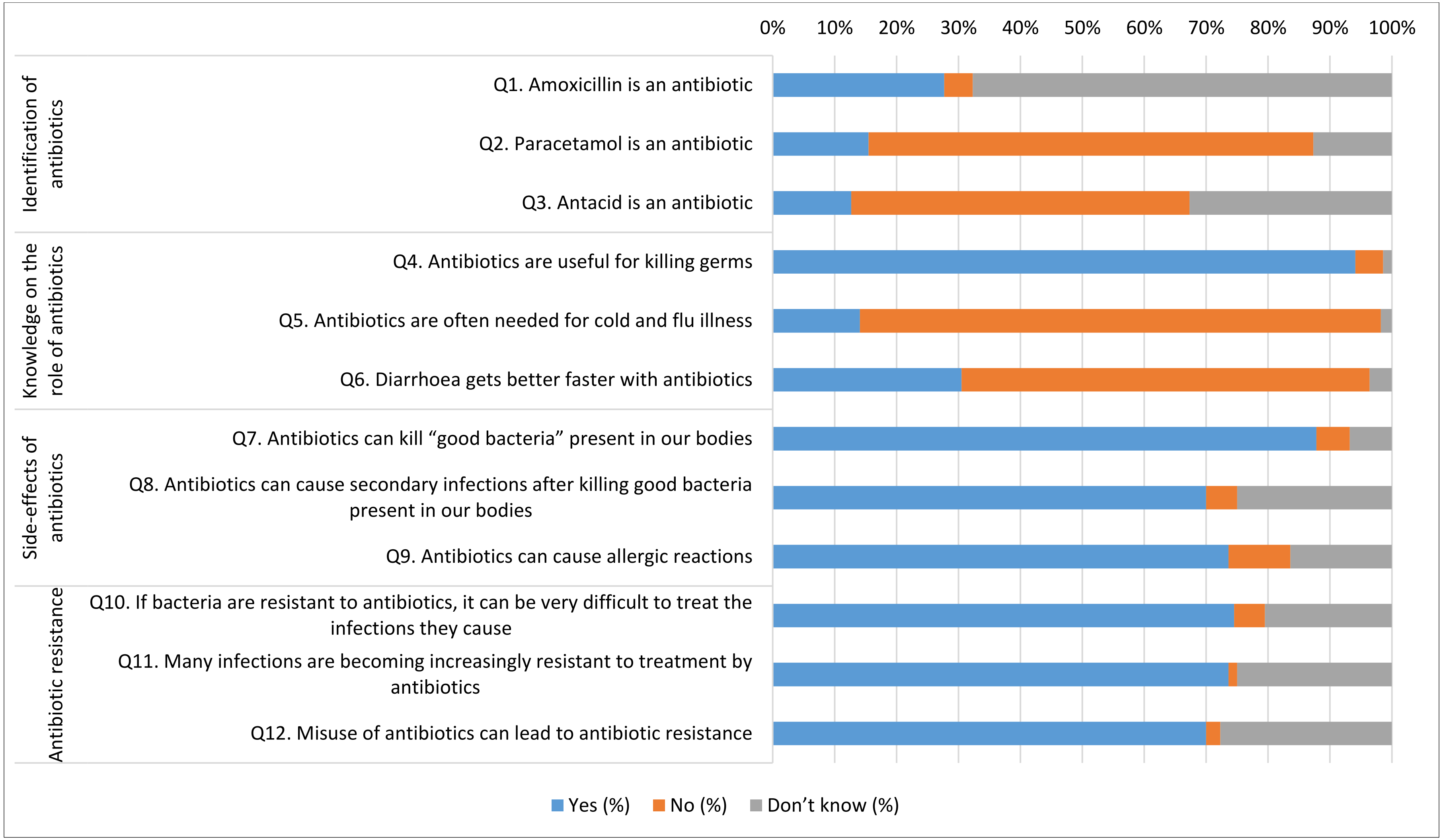

Figure 7.1 Responses to questions related to knowledge about antibiotic use

Table 7.2 Responses to questions related to knowledge, attitudes and practices in relation to antibiotics use

Variables	Knowledge level			Attitudes level			Practices level		
	Less n (%)	Better n (%)	X^2 (p=value)	Less appropriate n (%)	More appropriate n (%)	X^2 (p=value)	Poor n (%)	Better n (%)	X^2 (p=value)
Gender									
Male	55 (54.5)	46 (45.5)	0.010 (p=0.920)	61 (60.4)	40 (39.6)	3.473	76 (75.2)	25 (24.8)	5.984
Female	64 (53.8)	55 (46.2)		86 (72.3)	33 (27.7)	(p=0.062)	71 (59.7)	48 (40.3)	(p=0.014)
Areas of Residence									
Urban	33 (37.5)	55 (62.5)	16.257	51 (58.0)	37 (42.0)	5.197	46 (52.3)	42 (47.7)	13.996
Rural	86 (65.2)	46 (34.8)	(p=<0.001)	96 (72.7)	36 (27.3)	(p=0.023)	101 (76.5)	31 (23.5)	(p=<0.001)
Age Group (Yr.)									
15-24	13 (52.0)	12 (48.0)		17 (68.0)	8 (32.0)		10 (40.0)	15 (60.0)	
25-34	15 (30.0)	35 (70.0)	30.696	25 (50.0)	25 (50.0)	8.499	29 (58.0)	21 (42.0)	17.921
35-44	40 (49.4)	41 (50.6)	(p=<0.001)	58 (71.6)	23 (28.4)	(p=0.075)	55 (67.9)	26 (32.1)	(p=0.001)
45-54	28 (73.7)	10 (26.3)		28 (73.7)	10 (26.3)		30 (78.9)	8 (21.1)	
55+	23 (88.5)	3 (11.5)		19 (73.1)	7 (26.9)		23 (88.5)	3 (11.5)	
Education Level									
General literate	36 (94.7)	2 (5.3)		33 (86.8)	5 (13.2)		31 (81.6)	7 (18.4)	
Primary/Secondary School	51 (73.9)	18 (26.1)	72.264	53 (76.8)	16 (23.2)	27.306	55 (79.7)	14 (20.3)	42.452
High School/Intermediate	25 (37.9)	41 (62.1)	(p=<0.001)	43 (65.2)	23 (34.8)	(p=<0.001)	48 (72.7)	18 (27.3)	(p=<0.001)
Bachelors and above	7 (14.9)	40 (85.1)		18 (38.3)	29 (61.7)		13 (27.7)	34 (72.3)	
Income Level - Quartile (NPR)									
First (30,000 or less)	36 (60.0)	24 40.0)		44 (73.3)	16 (26.7)		38 (63.3)	22 (36.7)	
Second (30,001 to 40,000)	24 (52.2)	22 (47.8)	1.884 (p=0.597)	30 (65.2)	16 (34.8)	1.512	29 (63.0)	17 (37.0)	1.197
Third (40,001 to 53,500)	26 (50.0)	26 (50.0)		33 (63.5)	19 (36.5)	(p=0.680)	37 (71.2)	15 (28.8)	(p=0.754)
Fourth (53,501 and above)	25 (48.1)	27 (51.9)		34 (65.4)	18 (34.6)		36 (69.2)	16 (30.8)	

Responses to questions about attitudes to antibiotics reflected varying points of view **(Figure 7.2)**. In terms of having a “preference for use of antibiotics (Q13-Q15)”, most respondents were aware that they did not need to take antibiotics for a cold to prevent them getting a more serious illness (77.3%) and did not want to take an antibiotic if they did not need one (78.2%). However, almost half (47.7%) thought antibiotics would help them to get better more quickly if they had a fever.

In the domain of “antibiotic resistance and safety (Q16-Q18)”, half of respondents (50.9%) were uncertain if skipping doses would not contribute to the development of antibiotic resistance and almost one fifth (17.3%) were uncertain about if taking an antibiotic contributed to the development of antibiotic resistance. Most respondents (81.8%) agreed antibiotics should not be commonly used.

Attitudes to prescribing of antibiotics by doctors were somewhat ambivalent. Most respondents (61.8%) were not less satisfied with a doctor’s visit if they did not receive an antibiotic; however, the majority (88.2%) indicated if they were not prescribed an antibiotic when they thought one was needed, they would go to another doctor.

Attitudes to antibiotic use was significantly associated with areas of residence (X^2 = 5.197, P = 0.023) and education level (X^2 = 27.306, P = <0.001) **(Table 7.2)**. Respondents living in urban areas and those with higher levels of education had more appropriate attitudes than those living in rural areas and those with lower levels of education.

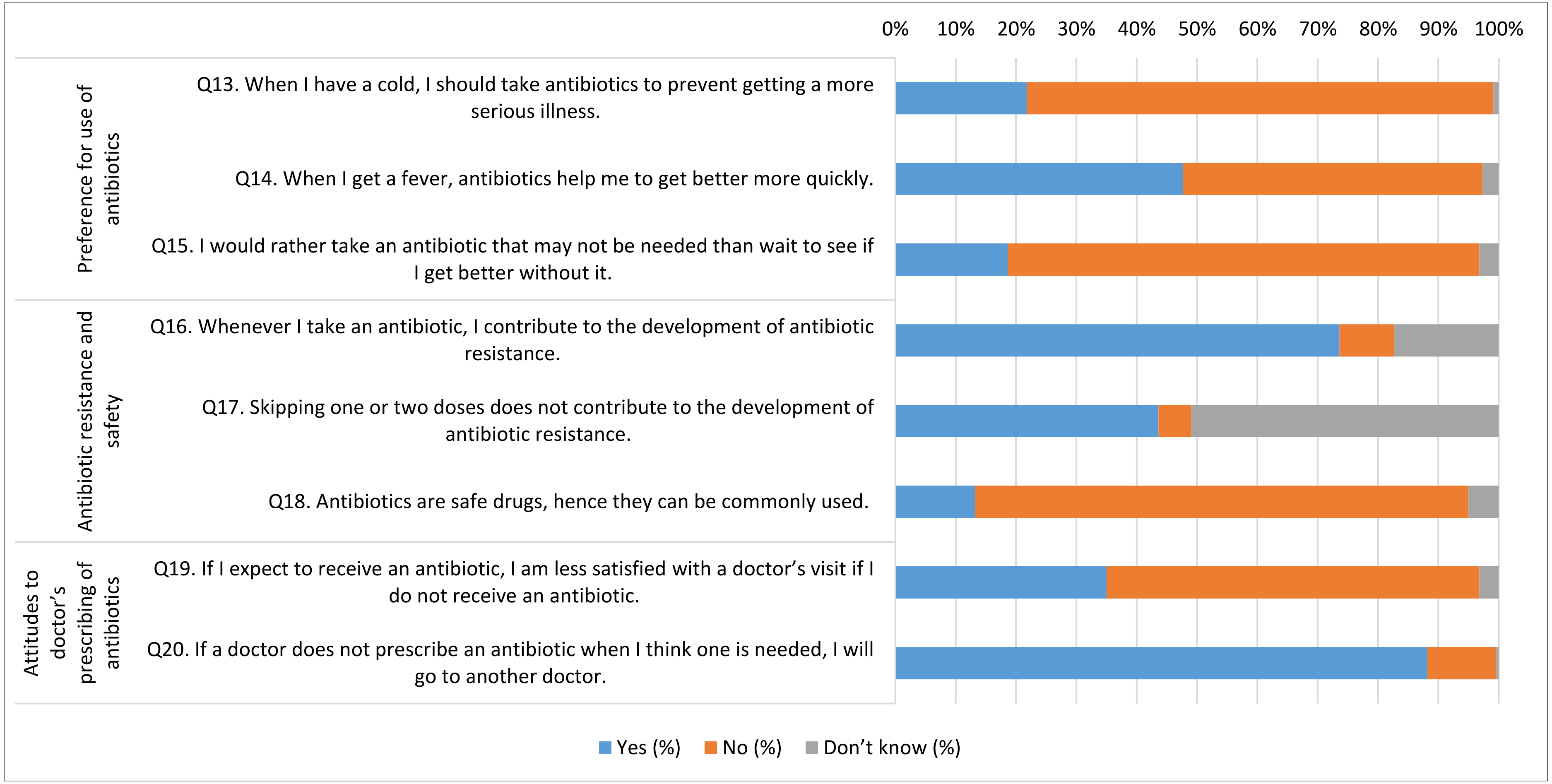

Figure 7.2 Responses to questions related to attitudes towards antibiotic use

In responding to questions about practices the majority always or often consulted a doctor before starting an antibiotic (94.5%), checked the expiry date of antibiotics before using them (85.8%) and completed the full course of treatment (81.3%), and never or seldom preferred to obtain antibiotics from the pharmacy (76.8%). However, in contrast to good practice reflected with these questions, the majority (84.6%) reported at least sometimes preferring to take an antibiotic when they have a cough or sore throat and almost a third (31.8%) to using antibiotics as a prophylaxis **(Figure 7.3)**.

Practices in relation to antibiotic use were significantly associated with gender (X^2 = 5.984; P = 0.014), areas of residence (X^2 = 13.996, P = <0.001), age group (X^2 = 17.921, P = 0.001) and education level (X^2 = 42.452; P = <0.001) **(Table 7.2)**. Female respondents, those who lived in urban areas, were younger and those with a higher level education reported better practices in regard to antibiotic use compared to male, respondents living in rural areas, older respondents and those with lower levels of education.

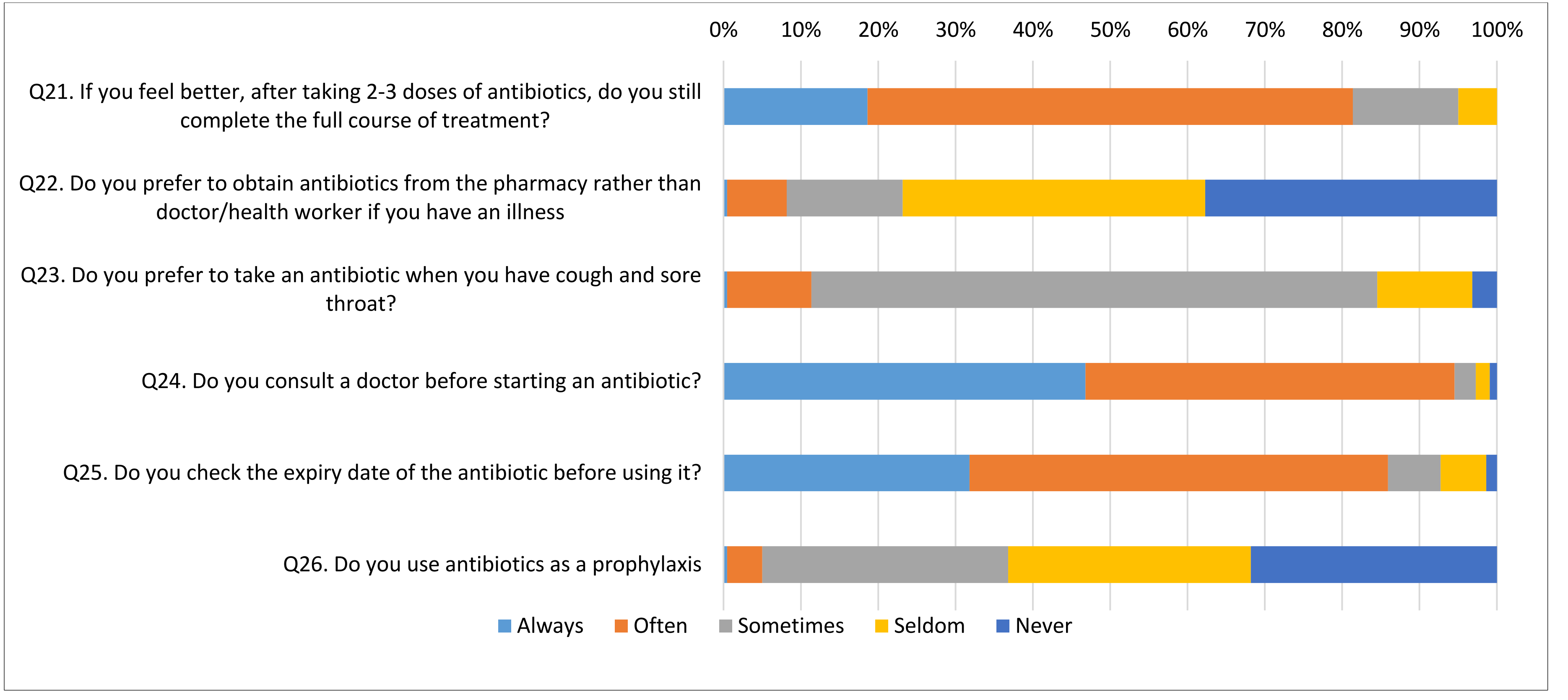

Figure 7.3 Responses to questions related to practices in relation to antibiotic use

7.3.3 Factors associated with knowledge, attitudes and practices relating to antibiotics use

In multivariable logistic regression analysis **(Table 7.3)**, after adjusting for other variables, education level was found to be significantly associated with each of knowledge, attitudes and practices, with respondents with a level of education of Bachelor degrees and above having better knowledge, more appropriate attitudes and better practices. Area of residence was significantly associated with better knowledge on antibiotics use, with rural respondents being less likely to have better knowledge compared to urban residents, and females being more likely to have better practices than males.

Table 7.3 Odds ratios (ORs) of having better knowledge, more appropriate attitudes and better practices in relation to antibiotic use

Variables	Knowledge level			Attitudes level			Practices level		
	Crude OR[a] (95% CI)	Adjusted OR[a] (95% CI)	p=value	Crude OR[a] (95% CI)	Adjusted OR[a] (95% CI)	p=value	Crude OR[a] (95% CI)	Adjusted OR[a] (95% CI)	p=value
Gender									
Male	0.973 (0.572, 1.657)	0.867 (0.404, 1.859)	0.714	1.709 (0.971, 3.009)	1.672 (0.844, 3.311)	0.141	0.487 (0.272, 0.870)	0.394 (0.187, 0.829)	0.014
Female	1	1		1	1		1	1	
Areas of Residence									
Rural	0.321 (0.183, 0.562)	0.317 (0.149, 0.676)	0.003	0.517 (0.292, 0.915)	0.587 (0.095, 1.492)	0.119	0.336 (0.188, 0.601)	0.553 (0.281, 1.085)	0.085
Urban	1	1		1	1		1	1	
Age Group (Yr.)									
15-24	3.621 (1.341, 9.777)	0.271 (0.060, 1.212)	0.088	1.301 (0.475, 3.561)	0.376 (0.95, 1.492)	0.164	7.227 (2.579, 20.254)	1.272 (0.313, 5.163)	0.736
25-34	9.154 (3.880, 21.595)	2.714 (0.861, 8.558)	0.088	2.765 (1.262, 6.057)	1.377 (0.480, 3.945)	0.552	3.489 (1.479, 8.233)	1.027 (0.324, 3.256)	0.964
35-44	4.021 (1.902, 8.502)	1.837 (0.741, 4.558)	0.189	1.096 (0.525, 2.288)	0.669 (0.278, 1.611)	0.370	2.278 (1.024, 5.067)	1.089 (0.430, 2.756)	0.858
44+	1	1		1	1		1	1	
Education Level									
Below secondary level	0.093 (0.042, 0.207)	0.035 (0.010, 0.127)	<0.001	0.152 (0.071, 0.323)	0.147 (0.053, 0.411)	<0.001	0.093 (0.042, 0.207)	0.098 (0.033, 0.293)	<0.001
High school & intermediate	0.143 (0.062, 0.331)	0.285 (0.090, 0.906)	0.033	0.332 (0.153, 0.721)	0.337 (0.140, 0.812)	0.015	0.143 (0.062, 0.331)	0.155 (0.061, 0.939)	<0.001
Bachelor degree and above	1	1		1	1		1	1	

OR: Odds ratio

[a]OR for included explanatory factors: adjusted with gender, residence, age and education.

Reference categories: 1 and better or more appropriate

Respondents scoring higher than the median were assessed as having "better knowledge", "more appropriate attitudes" and "better practices" relating to antibiotic use.

7.3.4 Relationship between knowledge, attitudes and practices

Spearman rank order correlation revealed a positive association between each pair of the knowledge, attitude and practice scores for respondents (p = <0.001) **(Table 7.4)**. The correlation was good between knowledge-attitudes and fair between knowledge-practices and attitudes-practices (399).

Table 7.4 Correlations between knowledge, attitudes, and practices

Variables	Correlation coefficient	p-value
Knowledge - Attitudes	0.649	<0.001
Knowledge - Practices	0.428	<0.001
Attitudes - Practices	0.370	<0.001

However, comparing responses to questions in different domains, a few inconsistencies were noted. For example, although most respondents (84.1%) correctly answered the question in the knowledge section that antibiotics are not often needed for cold and flu illness **(Figure 7.1)**, in the practices section the majority (84.1%), answered that sometimes or often they preferred to take an antibiotic when they had a cough or sore throat **(Figure 7.3)**. Another example was respondents seemingly having good knowledge about antibiotic resistance (correct answers of between 70.0% to 74.5% for relevant questions) **(Figure 7.1)**, however more than one-third (35.0%) were less satisfied with a doctor's visit if they did not receive an antibiotic and the majority (88.2%) would go to another doctor if a doctor did not prescribe an antibiotic when one was needed **(Figure 7.2)**.

7.4 Discussion

This is the first study to identify the knowledge, attitudes and practices of the general population in Nepal regarding antibiotic use and to identify any factors associated with these main outcomes of interest.

Overall, the respondents in our study had relatively good knowledge about antibiotic use, with an exception being in regard to identification of antibiotics. More than two-thirds of respondents (67.7%) did not know that *"amoxicillin is an antibiotic"*, a significantly higher percentage than found in a study conducted in Bhutan (32.4%) (375). Less than one-third of respondents (28.5%) did not know "*paracetamol is not an antibiotic"*, a similar result to that found in a Lebanese study (21.6%) (180). We found that 15.9% of respondents were unsure whether *"antibiotics are often needed for cold and flu illness"*, a lower percentage than was found in studies conducted in Britain (42%) (377) and Lebanon (39%) (400).

With regard to attitudes towards antibiotic use, nearly half of respondents (47.7%) still believed that *"when they get a fever, antibiotics help them to get better more quickly"*, a comparable result to that found in a study conducted in Indonesia (176). In the current study most respondents (88.2%) intended *"to go to another doctor if a doctor does not prescribe an antibiotic when they think one is needed"*. This suggests a high expectation in regard to using antibiotics for some illnesses or a low level of trust to prescribing practices of doctors. The latter was found in a Kuwaiti study, with one-third of respondents not trusting doctors who were not prescribing antibiotics (338).

Although respondents were aware that antibiotic resistance was a problem, half (50.9%) were still unsure whether "*skipping one or two doses does not contribute to the development of antibiotic resistance*". This finding is consistent with a Palestinian study that found one-third of respondents knew the meaning of antibiotic resistance, however nearly one-third of them incorrectly agreed that antibiotics' effectiveness would not be affected if antibiotics are taken less or more than the prescribed dose (401).

The only sociodemographic factor found to be associated with each of knowledge, attitudes and practices relating to antibiotics use was education. Respondents with higher education had better knowledge and more appropriate attitudes and practices, a finding consistent with other studies (43, 179, 180, 185, 186, 375, 401, 402). Our findings also suggest respondents in urban areas had better knowledge on antibiotic use than those in rural areas, a similar observation to that found in a Lithuanian study (182) but contrasting with a Polish study that found no such difference (187). We found females to have better practices with regard to antibiotic use, a comparable result to a Hong Kong study (186).

A number of implications flow from our findings. Bringing about behavioural change is never easy, especially when it is deeply entrenched (403). Our study provides an evidence base from which to develop education programmes for the community about antibiotic use. For example, given that several respondents failed to identify antibiotics, which could potentially risk antibiotics being used in a similar way to other drugs, educating the public on the roles of antibiotics and the ability to differentiate antibiotics from other drugs could help to minimise antibiotic misuse. The concept of antibiotic resistance is known but problems associated with antibiotic misuse were found to be imperfectly understood. The findings of the study also indicated that the community has high expectations with regard to being prescribed antibiotics, which increases the likelihood of non-prescription use of antibiotics. Village doctors or health workers could provide education to community members, and mass education campaigns conducted to emphasise the potential risks of resistance by using non-prescription antibiotics and the inappropriateness of using antibiotic therapy for minor ailments.

The study also identified a relationship between respondents having less knowledge, less appropriate attitudes and poor practices regarding the appropriate use of antibiotics. Groups, such as those with lower formal education, who had less knowledge and less appropriate attitudes and practices to antibiotic use and who could be targeted in education campaigns. A positive finding was females having better practices in regard to antibiotic use. In most developing countries, including Nepal, females hold the responsibility of taking care of their children and other family members, thus their better practices should contribute to some extent to the control of antimicrobial resistance.

Education of community members alone will not be enough to minimise any misuse of antibiotics. A multi-faceted approach involving policy makers, prescribers, and the general public using both educational and regulatory measures is needed. Such measures should be embedded in a general policy to change the culture of antibiotic use by improving awareness among the general public and professionals about the risks associated with antibiotic use as well as reducing public misconceptions about the benefit of taking antibiotics for minor illnesses.

This is the first known community survey conducted in Nepal to examine knowledge, attitudes and practices towards antibiotic use among the public. As such its findings provide baseline evidence about the knowledge, attitudes and practices regarding antibiotics use among the Nepalese population and offers insight in designing interventions to reduce antibiotic misuse.

The study used standard guidelines, developed by WHO (280, 281) for selecting the households. These guidelines have been refined continuously based on the lessons learned and used widely across many low and middle income countries to generate reliable information on medicines. Clustering and sampling techniques, described in the guidelines, are designed in a way to get optimum representation. Likewise, key aspects relating to antibiotics use in the community were covered by the survey questions, which were drawn from an USAID module on antimicrobial resistance (287) and previous studies (288, 289), which contributed to the validity of our study and allowed for comparison with previous results.

Another strength of the study was the high response rate (97%), which demonstrated representative results minimising the possible bias. However, the study was only conducted in one district in the low-land region of Nepal, so the results are more generalisable to districts in low-land regions. Also, surveys such as the one conducted in this study depend very much on the information given by respondents thus, the findings rely partly on the respondents' honesty and ability to recall. Moreover, it is possible that respondents may over-report socially desirable behaviours or under-report socially undesirable behaviours. A limitation of the study was not using a social desirability scale to assess the extent of these behaviours. Additionally, the survey did not identify household structure and the knowledge, attitudes and practices might differ say among households with young children compared to those with older residents.

A possible problem in studies of antibiotic use involving lay people is whether the respondents know what antibiotics are. Respondents who had not heard the word "antibiotics" were asked if they had heard of widely used antibiotics such as penicillin or metronidazole before being asked the main questions. While nearly one-fifth (17%) of respondents did not understand the word "antibiotics", all respondents were familiar with specific types of antibiotics following explanation by research assistants, thus to some extent combating this problem.

7.5 Conclusion

This study is an important step towards a better understanding of the knowledge, attitudes and practices regarding antibiotic issues in the adult population in the Rupandehi district of Nepal. Its findings may be generalisable more broadly across the country, especially low-land regions. Our findings are important to the campaign to reduce the inappropriate use of antibiotics, and its findings can be used to inform the design of effective and targeted interventions to decrease misconceptions about antibiotic use and to increase awareness regarding the risks of inappropriate use. Its findings can also be used as a baseline for monitoring future interventions. Future studies should focus on the development and implementation of such public education measures to improve antibiotic use among community members in Nepal.

Chapter 8 Perceptions of health providers and policymakers

The chapter discusses the study that explored the perceptions of health providers and policymakers about factors influencing the inappropriate use of antibiotics. A qualitative methodology was applied using a semi-structured questionnaire, with interviews conducted with 17 service providers and local policymakers in the Rupandehi district, Nepal.

The study found that the inappropriate use of antibiotics resulted from the interaction of demand and supply factors, together with a weak regulatory environment. Lack of knowledge by consumers and financial constraints resulted in practices such as self-medication and pressure being placed on providers to prescribe or dispense antibiotics. An insufficient choice of antibiotics, and health services not having investigation facilities, were also factors leading to inappropriate use of antibiotics. Additionally, in the private sector the profit motive arising from incentives provided by pharmaceutical companies contributed to prescribing or dispensing antibiotics inappropriately.

The findings of the study indicated the importance of promoting appropriate antibiotic use to reduce the growing public health threat of antibiotic resistance. Recommendations were to adopt a multi-faceted approach involving policymakers, providers, and the general public, and using both educational and regulatory measures, to improve antibiotic use in Nepal.

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Anant Nepal, Delia Hendrie, Linda A Selvey and Suzanne Robinson. Factors influencing the inappropriate use of antibiotics in the Rupandehi district of Nepal.

The submitted paper is reproduced here as follows.

8.1 Introduction

Antimicrobial resistance (AMR) is now widely considered a grave threat to international public health (24). AMR is the ability of a microbe to resist the effects of medication that once could successfully treat the microbe. The term antibiotic resistance is a subset of AMR, as it applies only to bacteria becoming resistant to antibiotics (12). International research has shown that antibiotics are commonly prescribed and dispensed, and often misused, a factor that correlates with antibiotic resistance development (305, 306). In the United States and Canada, 30 to 50% of antibiotic use has been shown to be inappropriate (309, 310). Similarly, in some Asian and African nations, 50% of antibiotic use has been identified as inappropriate (308).

Consequences of antibiotic resistance are reflected not only in an increase in the cost of health programmes but also contribute to morbidity and mortality (22). Studies have estimated that at least two million additional illnesses and 23,000 additional deaths in the United States (29), and 25,000 deaths in Europe (30) per year are due to antibiotic resistance. Due to lack of systematic surveillance, the current status of antibiotic resistance and its consequences in low- and middle-income countries (LMICs) is unknown, but likely to be considerable, given the high burden of communicable diseases (32).

Antibiotic use is a result of the behaviours of prescribers, dispensers and patients, with inappropriate use potentially attributable to any one of these groups (46, 47). Dispensers include pharmacists with a degree or diploma and “professionalists” who have only undertaken a short training course. In Nepal both pharmacists and “professionalists” can run a community pharmacy after registering the pharmacy with the Department of Drug Administration (98). Inappropriate use is facilitated by the availability of over-the-counter antibiotics without prescription and through unregulated supply chains (404). Other factors influencing inappropriate use are limited knowledge of patients and health care providers (46, 47, 405), unavailability of investigation facilities (233), lack of appropriate functioning drug regulatory mechanisms (317), excessive pharmaceutical promotion and economic incentives to prescribers (233). The social context within which prescribing decisions are made, as well as the social norms that guide them, also impact on practices (406).

Several studies conducted in Nepal have shown high rates of resistance to commonly used antibiotics (140, 141), which may be associated with inappropriate use. A few studies have focused on behavioural aspects of self-medication (173, 407), and patterns of antibiotics use (408, 409), however factors associated with decisions about prescribing and dispensing practices have not been covered. Given the importance of these practices on the use of antibiotics, gaining insight into provider behaviours and factors influencing these behaviours is an important aspect that needs to be explored in any efforts to improve antibiotic prescribing and dispensing. The purpose of this study was to identify the perception of service providers and policymakers about the inappropriate use of antibiotics in Nepal. Understanding these factors, and how they might relate to the local context, can help to tailor interventions to promote more appropriate antibiotic use in Nepal.

8.2 Methodology

8.2.1 Design

This study adopted a qualitative approach involving semi-structured interviews with service providers and policymakers in the Rupandehi district of Nepal. Its focus was to explore the perceptions of service providers and policymakers' about the dominant factors that influence inappropriate antibiotic use, as such it lends itself to a qualitative methodology. Qualitative methods allow for the exploration of context and meaning from the standpoint of the participants of interest (410).

8.2.2 Participants

The participants were selected to reflect diverse viewpoints and to represent a range of service providers working in both public and private health facilities in urban and rural areas as well as district policymakers.

Three groups of service providers were included: physicians, health workers and dispensers. In Nepal, physicians and health workers have authority to prescribe. Physicians mainly work in hospitals and sometimes primary health care centre (PHC). Health workers are health assistants and auxiliary health workers (post-secondary training in diagnostics and therapeutics) (96), and mainly work at PHCs and health posts. The third group of service providers are dispensers, who work in community pharmacies as owners or employers with roles in dispensing. Fourteen participants across the three types of service providers were selected across both urban and rural areas. In addition, three district policymakers were selected on the basis of their involvement in registration of pharmacies and monitoring the drugs and related affairs in the district. In total, 17 participants were recruited and interviewed **(Table 8.1)**.

Table 8.1 Characteristics of participants

Category	Group		Urban	Rural	Total
Service Providers	Prescribers	Physicians	2	3	5
		Health workers	2	3	5
	Dispensers (pharmacists and "professionalists")		2	2	4
Policymaker	District policymakers		3		3
Total					17

8.2.3 Participant recruitment

A mixed sampling approach was adopted (286) to recruit the research participants. The initial contact was the chief of the district public health office (DPHO), who is responsible for managing health and related affairs at the district level. Based on the criteria for selecting participants, the DPHO provided a list of 10 participants consisting of three each from the groups of physicians, health workers and dispensers, and one from the group of policymakers. A snowball method was used to select additional participants. Participants were interviewed until data saturation was reached.

8.2.4 Interview schedule

In drawing up the interview schedules, the major components adopted were from a study on antibiotic use conducted with physician and nurses in the Netherlands (290) and from WHO's policy document "Promoting rational use of medicines: core components" (151). Both sources provided useful guidance on possible factors influencing antibiotic use.

Six key components were explored in the interviews **(Table 8.2)**. The components included occurrence of infectious diseases, prescribing or dispensing decisions, issues on prescribing or dispensing antibiotics, burden of antibiotic resistance, and current prescribing or dispensing practices. As service providers and policymakers have different roles and responsibilities related to the use of antibiotics, only the relevant components of the interview schedule were used in interviews **(Appendix D: interview schedule)**.

Table 8.2 Major components included in the interview schedules

Major Components		Service Providers			District Policymakers
		Physicians	Health Workers	Dispensers	
1	Occurrence of infectious diseases	✓	✓	✓	✓
2	Prescribing or dispensing decisions	✓	✓	✓	
3	Issues on prescribing or dispensing	✓	✓	✓	
4	Burden of antibiotic resistance	✓	✓	✓	✓
5	Current prescribing or dispensing practices				✓

The interview schedules were developed in the English language, then translated into Nepali and back translated to English. The Nepali translated versions were used for the participants' interviews.

8.2.5 Data collection

Contact details of selected participants were updated with assistance from officials of the district health office. All participants who were invited for the interviews agreed to participate. Prior to the interview, each of them was contacted individually by telephone and briefed on the purpose of the study.

All interviews were conducted over a period of four months, between September and December 2017. The interviews lasted between 18 and 52 minutes. With the permission of participants, interviews were recorded.

8.2.6 Data analysis

To ensure anonymity, prior to the interviews, all participants were assigned an identification code and these codes were used during data analysis. The codes were indicated by their professional status (PS for physician, HW for health workers, DP for dispensers and PM for policymakers) and serial number within group. For instance, PS1 corresponded to the first interview with a physician.

Data analysis was guided by the steps for conducting thematic analysis outlined by Braun and Clarke (2006) (296). All recorded interviews were listened to a number of times, and then translated into English. The translated text was compared with the audio files to ensure the accuracy. The coding process was facilitated using the qualitative data analysis software programme NVivo 12 Pro. The coded narrations were imported into Microsoft Word files and further analysis was conducted manually.

The data were analysed using a combination of inductive and deductive approaches (296). For deductive coding, a codebook was developed based on the main interview questions, and for inductive coding the process was data-driven (297). Several iterations of code mapping were completed, with codes grouped into 12 higher order sub-themes. These sub-themes were categorised into three major themes (called factors) influencing the decisions by service providers to use antibiotics in Nepal **(Figure 8.1)**. These were personal factors, organisational factors and regulatory factors. Two sub-themes, lack of knowledge and financial constraints, emerged as contributory factors to each of the other personal themes. Another sub-theme, professional behaviour, did not fit within the three major factors and is separately presented. Personal, organisational and regulatory factors, including the professional behaviour sub-theme, were mapped to three underlying drivers of inappropriate use: (i) overuse or incorrect use of antibiotics (ii) prescribing of higher order antibiotics and (iii) unnecessary dispensing/prescribing of antibiotics. The accountability for overuse or incorrect use rests primarily with consumers while for prescribing of higher order antibiotics and unnecessary dispensing/prescribing the accountability is primarily with service providers.

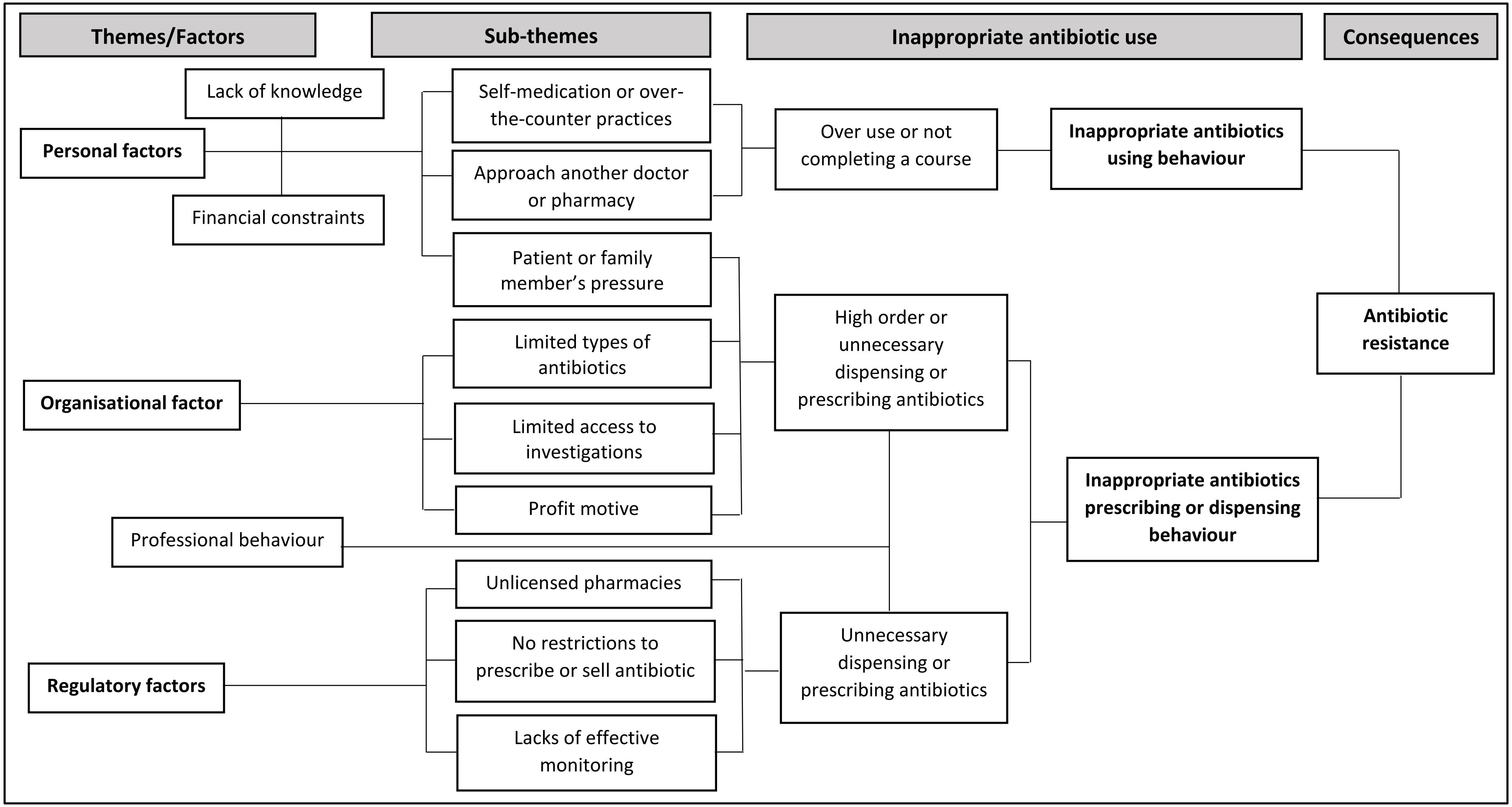


Figure 8.1 Themes - factors influencing the inappropriate use of antibiotics

8.3 Results

Factors that participants perceived as key determinants of antibiotic prescribing and dispensing in Nepal are presented below.

8.3.1 Personal factors

Purchasing behaviour is known to be influenced by personal factors such as age, income, beliefs, knowledge and education (411), and also by attributes that the consumer associates with product options. Antibiotics are perceived as 'strong medicines' in both high-income and LMICs, capable of curing almost any kind of disease (412), which often increases the demand to use antibiotics for treating many illnesses. Additionally newer, more expensive drugs are generally considered more powerful and make people willing to buy them even if they cannot afford a full course (412).

In the interviews, two key sub-themes relating to personal factors emerged as important contributors in the Nepali context, these included lack of knowledge and financial constraints.

- **Lack of knowledge**

Several studies have highlighted the impact of lack of knowledge on the appropriate use of antibiotics, and its role as a factor influencing purchasing behaviour and contributing to antibiotic misuse (413). Studies suggest that patients often lack knowledge on the aetiology of diseases, for example, believing that bacteria is a cause of the common cold, yet the common cold is usually caused by viruses (414). Not being able to differentiate between the roles of bacteria and viruses leads to the expectation by consumers of wanting to be prescribed an antibiotic from their doctor (415). In addition to poor knowledge about the cause of disease, a lack of awareness of the dangers and consequences of inappropriate use of antibiotics and misconceptions and confusion about the role of antibiotics are also factors that may lead to inappropriate use of antibiotics (416). These findings on how lack of knowledge contributes to inappropriate use of antibiotics mirror those in the present study as illustrated below.

"I think maybe because they (patients) do not have knowledge about antibiotics. The only thing they know is that it will treat them. They do not know how much of it is beneficial and how much of it is harmful". [PS4]

"Some patients pressure you to prescribe antibiotics even when they don't need them. What they do is that, in their community or village, whenever they are a little ill they used to take antibiotic capsules, thus, they insist us too." [HW3]

- **Financial constraints**

Out of pocket payments for healthcare are a significant component of health spending in most LMICs (417) and can be a major barrier to the ability to afford health care. While Nepal's Constitution guarantees every citizen with the right to free basic health services, public health facilities often face the challenge of essential medicines being out of stock (110). A social health insurance scheme is in the process of being established in Nepal, but is still in its infancy and being phased in only in a few districts (80). As such, people have to get services from private providers, which involves paying a higher cost for their health care. In many cases, people avoid visiting a doctor for a consultation or having diagnostic tests even if service providers suggest they do so.

"I say patient to go for check-up from doctor or health workers, but they make excuse that they say that they would go tomorrow or the day after tomorrow, or that they don't have enough money, and so on". [DP4]

"Sometimes there are also such patients who do not have enough money to do lab tests. Even our primary health centre (PHC), being a government facility, doesn't have everything in sufficient and not free too in terms of lab test, so some things have to be outside. In such cases, we must do an empirical therapy". [PS3]

- **Impact of lack of knowledge and financial constraints**

The participants suggested that lack of knowledge and financial constraints contribute to several factors influencing antibiotic misuse such as self-medication and over-the-counter dispensing practices, approaching another doctor or pharmacy to obtain antibiotics if refused antibiotics by service providers, and placing pressure on prescribers and dispensers to provide antibiotics.

Self-medication and over-the-counter dispensing practices: The challenges facing many LMICs in providing universal access to health care has been shown to be associated with an increase in the propensity to self-medicate (418). Self-medication is a way to save costs, and can involve directly approaching dispensers to avoid doctor consultations, saving on the cost of medicines by obtaining them from relatives, or keeping leftover medicines for future use (416). Obtaining medicines without a prescription is convenient for patients as they can purchase any doses directly from the pharmacy, which can lead to indiscriminate and incorrect use. The non-prescription use of antibiotics reflects potential poor guidance regarding their use, and can be associated with incorrect diagnosis, treatment and inappropriate choice of therapeutic class and dosage (419). Given limited knowledge on diseases and corresponding treatment, and about the potential side effects of antibiotics, people are more inclined to practice self-medication (420).

The interviews highlighted the practice of self-medication and OTC dispensing practices in Nepal, with patients often approaching the pharmacy to purchase medicines to avoid paying a doctor's consultation fee.

> *"Purchasing any medicines over-the-counter from pharmacy is common here. The patient do not have practice of consultation with the doctor working in private especially in rural areas, in which the fees of consultation and investigation could be a barrier for them". [PS1]*

> *"I must say that most of the patient prefer to buy medicine directly from us because they do not want to expense money for consultation. In fact, a full course of medicines, including antibiotics can be purchased from that amount to be paid for consultation". [DP4]*

Approach another doctor or pharmacy: A common belief is that antibiotics will prevent any disease becoming more serious, and as such antibiotics are the best option for any illnesses (412). This raises the expectation that the doctor should prescribe antibiotics for illnesses and, if this expectation is not met, encourages consumers to switch to another doctor or pharmacy to obtain antibiotics. The service providers have a strong desire to retain the person as a patient and concern about their provider-patient relationships, thus may feel pressure to supply or prescribe the antibiotic even if not required.

> *"I advise them (patient) that it is not necessary for them to have a disease to get the symptoms of fever and headaches and should not take antibiotics right away. I try to convince them in that way. Despite that, some patients are such that if they cannot get the antibiotics from my prescription, they go to meet other doctor and get it from elsewhere". [PS5]*

> *"There are many people who use antibiotics even in minor illness. I try to avoid these kind of people and advise them by telling not to require the antibiotics for such illness. Then what people do is, if they don't get it from my place, they would buy it from another place and have it". [HW1]*

Patient or family member's pressures: Prescribers have raised the issue of being pressured into prescribing antibiotics even against their clinical judgment. In one study, 74% of patients were prescribed antibiotics, with non-clinical factors influencing prescribing for 44% of those receiving antibiotics, of which patient pressure was the reason in more than half (421). Patients may perceive that every ailment needs a pill such as an antibiotic, which puts pressure on providers. The expectation of patients to be cured fast is another factor that influences prescribing of stronger medicine. Doctors often find it difficult to refuse prescribing for children, the elderly, persons well known to them, as well as individuals they like (323). In the case of children, parents become seriously concerned and worried when their children are acutely ill. This leads to frequent hospital visits and the prescribers get pressure to prescribe even high order of antibiotics (402).

In this study, participants spoke about "giving in" to patient expectations and prescribing antibiotics despite believing the presenting condition was highly likely not to be bacterial. Concern was expressed that if patients' expectations were not met, they may instead get antibiotics from another prescriber or even directly from a dispenser. Competition between private practitioners can also contribute to a dissonance between clinical judgement and prescribing practices. The practitioners may get self-pressure to cure the patient in order to maintain a good reputation in the community and encourage patients to turn up regularly.

> *"Some patient need to prescribe antibiotic even they don't need. What they say that, whenever they are ill they used to take antibiotic and insist us to prescribe antibiotic for their any illnesses." [HW3]*

> *"One person said: "Can you give me 500 mg of Azithromycin!" although he did not know the name of the company, asked with a generic name. He said, "If I take it, I will be cured. I have also had it before when I had the problem!" This is how it is!" [DP3]*

> *"Sometimes what also happens is that the patient may have come from far away where there is no health facility and no antibiotics available. They insist that they need to go back the next day because their cattle might die so they have to return to feed their cows. In such cases, we must prescribe antibiotics based on provisional diagnosis". [PS1]*

8.3.2 Organisational factors

In addition to personal factors influencing the demand for antibiotics, organisational factors influence the supply side of the market. Organisational factors that have been shown to impact on the supply of antibiotics include health system factors such as supplies of drugs, economic incentives and the fear of poor clinical outcomes (422). In this study, the three main supply side issues that participants raised were the limited availability of different types of antibiotics, the lack of diagnostic facilities in the public sector, and the profit motive. These supply side factors interact with personal factors on the demand side to influence antibiotic use.

- **Limited types of antibiotics available in public health facilities**

In some countries, medicines are provided free to patients in government-run health facilities, however, medicine supply is sometimes erratic especially in resource-poor-countries. In some instances there is a lack of supply of some medicines for months or supply can be limited in terms of types of medicines available or amounts available (248). Similarly, oversupply of drugs and sometimes supply of near-expiry drugs, leads to over-prescription as prescribers try to finish off the stock before expiry (248).

In Nepal, a significant lack of medicines has been observed in public health facilities due to improper management of procurement and supply in the publicly-funded health system (111). Facilities often experience shortages of certain types of medicines resulting in service providers being compromised in the choice of antibiotics to prescribe. Participants working in the public sector who were interviewed in this study raised this issue of the impact of shortages of antibiotics on prescribing practices.

Despite more people overall in Nepal using private facilities, most poor and underprivileged patients seek services from the public facilities (86). These groups have low purchasing capacity, thus seeking free health care. In such cases, participants suggested they did not want to disappoint patients by not providing any medication.

> *"We don't have varieties of antibiotics in the health facility. I do not just tell them to buy certain antibiotics from elsewhere, most people coming to this facilities are poor. I prescribe the ones I have, which could be choice of antibiotic, or high or low order". [HW5]*

> *"In this facility itself, we do not have all the medicines indicated by the government, you know. Among the ones available, they are also not sufficient. Like for example, if Amoxicillin is given to about 11 to 12 patients, then it runs out. That kind of a problem exists from the government side, especially in these public sectors". [PS2]*

- **Limited access to investigations**

In rural communities worldwide, health care providers often face a number of challenges and barriers when trying to provide services. Shortages of health professionals and restricted access to resources for investigations are two major challenges in rural areas (423). If appropriate investigation facilities are unavailable, prescribers mainly rely on clinical acumen, which puts pressure to prescribe antibiotics because prescribers perceive the risk of not prescribing as greater than that from unnecessary use.

Lack of investigation facilities increases the diagnostic uncertainty and many providers who were interviewed in this study said that diagnostic uncertainty makes it difficult to diagnose at the early stages whether an infection is viral or bacterial, especially in the case of upper respiratory tract infections and diarrhoea. As a result, antibiotics are often prescribed where they are not needed. In Nepal, while a variety of public health-care facilities are available, only 25% of them have access to laboratory services and many laboratories offer a limited variety of tests (257). Laboratory facilities are primarily available only in hospitals located in city areas, and service providers working in the villages often prescribe antibiotics based on clinical judgement.

> *"I do not have lab investigation in my facility. I look at the history and details of sign and symptoms and, then general investigation. If the report shows to be normal, I prescribe paracetamol for fever. If patient is serious, I prescribe antibiotics". [PS5]*

> *"The patient had some infection, such as signs on the chest; cough was continuously present and was having some difficulty with the chest; roughness. Those signs made me think that I might have to give antibiotics, so I gave it based on that". [HW4]*

> *"The centres with no investigation facilities, they provide antibiotics based on signs and symptoms; that is the main reason". [DP1]*

- **Profit motive or financial incentives**

Financial incentives are known to influence the behaviour of providers (424). As mentioned (under the sub-section *"Approach another doctor or pharmacy"*), if antibiotics are not provided when patients want them then they will go elsewhere, thus compromising provider revenue. In some LMICs, pharmaceutical companies provide incentives for selected medicines as part of their contract with prescribers and pharmacies (425). The companies are able to motivate prescribers or private dispensers with financial incentives through marketing strategies. Since antibiotics are one of the more profitable drugs (362), patients can be prescribed or dispensed considerably more antibiotics than is clinically necessary. As dispensers work within a competitive environment, they tend to adopt strategies to maximise their profits.

This prescribing or dispensing of antibiotics based on the motivation of increasing profits was commonly raised in the interviews.

> *"There have been rumours that some medicine sales people come up with schemes that provide offers for someone able to sell beyond certain limits of antibiotics. This kind of scheme is found in the market with business motive intention". [PM1]*

> *"There are many kinds of antibiotics in the market, it is up to us to choose what we want. Sometimes the companies also put more special offers on the medicines with antibiotics and sell with a larger retail price margins. Those things also cause motivate to sell the particular medicines". [PS3]*

- **Professional behaviour**

Given the rapidly advancing state of technology, continuing professional education is a necessary practice for any health professional (426). Evidence shows that the inappropriate prescribing or dispensing of medicines can result from a lack of adequate training, or there may be inadequate continuing education, resulting in the reliance on out-dated prescribing or dispensing practices (323). Many health professionals in LMICs face the challenges of a lack of opportunity for on the job training or continuing education (210).

The participants in this study discussed the lack of professional education practices available in Nepal. The government provides trainings to their service providers on some specific programmes such as tuberculosis, malaria and the management of childhood illness, however, the government does not have such training related to other diseases. In addition, training is not available for those health professionals working in the private sector. Some service providers discussed approaches used to update their knowledge and mentioned exploring the internet and textbooks, however there are some fears that these approaches can be problematic due to unreliable internet access particularly in the villages and the information in textbooks being out of date.

> *"We would perform better than our knowledge from our education. In case of any confusion, we have CIMS (Current Index of Medical Specialities - drug information resources for practicing physician and pharmacists) available and refer it. And if there*

were some organisations who give us training on how to do certain things, I think it would have been better. If someone would give us additional knowledge than what we have studied, it would have been even much better". [HW4]

"The government does provide such trainings from time to time, although they might be in small number, for the public sector regarding prevention of sexually transmitted diseases and malaria, etc. But there are no such trainings provided for the private sector". [HW1]

8.3.3 Regulatory factors

The absence of antimicrobial policy and a weak regulatory environment in the health system contributes to the inappropriate use of antibiotics (427). Without strong regulation, there are few levers available to governments to control antibiotic misuse. The Drugs Act 2035 is the only legislative instrument designed to regulate the use of drugs in Nepal (114). Specifically in regards to issues of antimicrobial resistance, the government released National Antibiotics Treatment Guidelines (224) and starting a laboratory-based antimicrobial resistance surveillance system. However, a national laboratory strategic plan to provide guidance and governance to national laboratories has not been developed.

In the interviews, three main issues regarding regulatory factors were raised, namely unlicensed pharmacies, the lack of restrictions on prescribing or selling antibiotics and the lack of effective monitoring.

- **Unlicensed pharmacies**

Private pharmacies are widely established in LMICs, and usually considered as a patients' first point of contact for health care (409). The WHO estimates that between 30% and 70% of febrile children are treated in the private sector, including pharmacies (428). Another study reports, almost half of patient consult a private health provider first (429). Despite widespread utilisation of private sector services, it is known that many of them are unlicensed and unsupervised (430). These pharmacies sell medicines informally and are not legally recognised by the health system of the countries in which they operate (361).

Whilst practicing healthcare without a license is illegal in Nepal, several unregistered pharmacies are operating in the rural areas (409). This ability to operate without licences is evidence of the weak regulatory oversight in the Nepalese health system. While the education of operators of unlicensed pharmacies is unknown, the general perception is that they are often minimally educated. In these circumstances, the drug retailers may approach dispensing of medicines as any other sales job, not wanting a customer to leave without making a purchase.

> *"I don't know if I should say it or not, but this is what I want to say if the unregistered clinics existed, the irrational use of antibiotics will occur". [HW1]*

> *"We should allow only to eligible people such as pharmacists to open clinics. Letting any unregistered people to open such clinics is to let resistance happen". [PS4]*

- **No restriction to prescribe or sell antibiotic**

Law enforcement relating to the non-prescription sale of antibiotics has existed in many developed countries, although, selected groups of antibiotics can be sold over-the-counter in some countries i.e. New Zealand and Canada (348). Some LMICs are also currently moving towards prescription-only access to antibiotics (431), however, non-prescription practices is common, where there are no regulations on the sale and distribution of medicines or the enforcement of these regulations is weak (432).

Legislation in Nepal mandates a medical prescription for the purchase of antibiotics; however, unauthorised dispensing is clearly problematic (58). Although different types of prescribers are in Nepal, the prescribing drugs including antibiotics differ among the prescribers as outlined in the guidelines (224). However, such guidelines are barely in practice or monitored. One study found that 11 different types of antibiotics were prescribed for the treatment of respiratory tract infections with duration ranging from 5 to 10 days (58). Another study found that among the prescribed drugs less than one-third were prescribed from WHO's Essential Medicines List (66).

"Variety of prescribers are in Nepal, thus most of them prescribe antibiotics without following the proper guidelines/protocols. Any prescribers can prescribe any antibiotics…". [PS5]

"The Department of Drug Administration (DDA) has announced the criteria of prescribing authorisation according to the level of services providers, but hardly to see the practices. Moreover, no any monitoring activities in regards to prescribing authorisation has been conducted [PM1]

- **Lack of effective monitoring**

Effective monitoring of prescribing and dispensing improves clinical decision making (433). It also reduces doctor shopping and the diversion of controlled substances such as prescription fraud, forgeries and improper prescribing and dispensing (434). In the current study, participants believed that many flaws existed in prescribing and dispensing practices due to the lack of regular and effective monitoring by authorities of pharmacies as well as prescribers, which encouraged overuse of antibiotics. The regulatory agency responsible for the registration and monitoring of pharmacies and prescription audits in Nepal is the Department of Drug Administration (85). However, evidence suggests that monitoring or prescription audits are not being done on a regular basis (85). The participants highlighted that the authorities had monitored some private pharmacies but no actions have been taken even in the case of dispensers having contravened the rules and regulations.

"Well, there is very less from the government level. What I would like to say is that, there should be periodic monitoring of pharmaceuticals as well. There is a system of legal penalty in the process of monitoring; but does not exist in the practice". [PM3]

"The government who needs to monitor at a deeper level about whether the clinics operating here are legal or not. In fact, in order to check this, there is a department called the Department of Drug Administration established for a long time. But what happens is, they check, but for the ones who they find to be illegal, they get bribe from them. Then they say, "You can shut down for now, after I am out of office, you

can reopen again!" I don't know if I should say it or not, but this is what we have experienced". [HW1]

8.4 Discussion

This is the first study in Nepal to explore the perceptions of service providers and policymakers about factors influencing inappropriate prescribing and dispensing of antibiotics. Its results are consistent with studies conducted in many other countries that have examined these factors. Inappropriate use of antibiotics was found to arise from the behaviour of both patients and providers. On the demand side, unaware of the negative implications, some patients choose to self-medicate, place pressure on service providers to prescribe or dispense antibiotics, and to approach another prescriber or pharmacy if not provided an antibiotic. Contributing to these, behaviours are financial constraints that make it difficult for patients to afford to pay consultation fees or the cost of investigations.

The resource-poor environment in a low-income country like Nepal also contributes to inappropriate prescribing or dispensing of antibiotics through its impact on the supply side. This study found that prescribers working in the public health sector often do not have sufficient choice of antibiotics to prescribe, despite the government of Nepal having introduced free basic healthcare services that include essential medicines (435). Other factors on the supply side include the lack of diagnostic facilities, resulting in antibiotic prescribing having to be based on clinical judgement, the limited opportunity for professional education and training, and the weak regulatory environment.

In the private sector, two further factors were found to influence antibiotic use on the supply side: the profit motive and many of the private pharmacies being unlicensed. Both factors were seen to result in patients being prescribed or dispensed considerably more antibiotics than is clinically necessary.

Other studies conducted in LMICs that have examined factors influencing the use of antibiotics have similar findings relating to both demand (412, 415, 416, 420, 421) and supply factors (210, 248, 425, 427, 432) leading to the inappropriate use of antibiotics. This widespread inappropriate use of antibiotics reflects both wasteful clinical care (436) and puts patients at risk due to its role in encouraging the development of antimicrobial resistance (305, 306). Inappropriate use of antibiotics is a complex problem and promoting effective use entails implementation of comprehensive polices targeting all key groups involved in the process of the provision and consumption of antibiotics.

In recognition of the urgency to manage the antibiotic resistance crisis, in 2015 the World Health Organization (WHO) endorsed a global action plan that comprises five strategic objectives, with the following actions of particular relevance to the findings of this study: improving awareness and understanding of antimicrobial resistance, strengthening knowledge through surveillance and research, and optimizing the use of antimicrobial agents (52). Implementation of these global strategies at a national level in Nepal can make a contribution to curbing the harm caused by inappropriate antibiotic use.

In regard to improving awareness and understanding of antimicrobial resistance, a factor that can potentially reduce inappropriate use of antibiotics is raising public awareness on antibiotic use thus promoting behaviour change (52). Programmes targeting consumers and family members that provide information on the problems associated with inappropriate use of antibiotics have been found to be successful in achieving reductions (437), and can be cost-effective and lead to lasting changes (438). These programmes should be expressed in lay terms, and convey messages relating to the consequences of inappropriate antibiotic use and its impact on their health and the economy. Inclusion of the use of antibiotics and problems relating to antimicrobial resistance in school curricula can also promote better understanding and awareness from an early age (52).

Communication training for healthcare professionals can help to improve the dialogue between patients and providers, developing skills such as being able to understand patient concerns and communicating an agreed upon treatment plan to decrease unnecessary antibiotic prescribing (439). One approach involves coaching providers to suggest "positive," non-antibiotic steps that patients can take to feel better, such as home remedies to relieve symptoms (440). Delayed prescribing techniques can also be used by healthcare professionals to reduce inappropriate use of antibiotics (441). This approach, sometimes referred to as "watchful waiting," involves a prescriber writing an antibiotic prescription but advising the patient to fill it only if symptoms persist or worsen. Although, the impact on patient satisfaction is unclear, a review of this practice has shown encouraging results (442). This approach is helpful to manage situations in which prescribers are uncertain about a patient’s diagnosis due to the unavailability of a diagnostic facility but are afraid the condition may get worse.

Continuing professional education is a necessary practice in the medical field, particularly given the rapid technological advances and an increasing evidence base (426). Antibiotic management requires effective teamwork between all health professions, regardless of who writes the prescription. It is therefore crucial to educate not only prescribers, but all other healthcare professionals in contact with the patients who are prescribed or dispensed an antibiotic (e.g., health workers, nurse and dispensers), since patients should receive consistent messages on correct and prudent antibiotic use when taking antibiotics (443). In Nepal, continuing professional education has been initiated for the physician in some health institutions, but not fully implemented (444), and gradual implementation covering other healthcare professional is required.

Enforcement of laws regulating drug distribution and use, and mandating licenses for pharmacy operation in the country is vital in achieving more appropriate use of medicines (427). Strict implementation of restrictions on over-the-counter sales of antibiotics has been shown to be effective in reducing non-prescription antibiotic consumption in some countries (418, 445). Given that many countries have laws prohibiting over-the-counter sales, there is a need to ensure that these laws are strictly enforced (348). In Nepal, a general lack of enforcement of the legislation covering registration of pharmacies and the distribution of antibiotic facilitates the inappropriate use. A stronger enforcement mechanism of pharmacy registration and restricting dispensers supplying antibiotics without prescription should also be considered.

8.4.1 Strength and limitations

A strength of the study is its coverage of a mix of health service providers, including physician, health workers and dispensers, and also policymakers. The health service providers were not only from different types of health facilities, but also from urban and rural areas. Given the diversity of participants, the survey produced a rich evidence base with which to explore factors associated with the inappropriate use of antibiotics. Insights from this evidence base, in regard to both demand and supply factors, and the regulatory environment, will be useful in developing strategies to promote the rational use of antibiotics.

The study has limitations. The primary limitation is the potential lack of response authenticity. Dispensing non-prescription antibiotics is legally unauthorised in Nepal, thus, participants may have underreported this problem and other socially undesirable activities Given the male dominance in the roles from which participants were drawn, the demographic profile of participants reflected this pattern (15 male compared with two female participants). Furthermore, the study elicited information about the behaviour of consumers from a service provider's point of view, which may not always be accurate.

8.5 Conclusion

Improving antibiotic prescribing and dispensing practices is critical to minimising the growing public health threat of antibiotic resistance. Given the findings of this study, indicating that inappropriate use results from both demand and supply factors together with a weak regulatory environment, a multi-faceted approach involving policymakers, providers, and the general public, and using both educational and regulatory measures, needs to be developed and implemented to improve antibiotic use in Nepal. The findings may also be applicable to other low-income countries where the health system is similar to Nepal.

Chapter 9 Overall discussion and conclusion

This final chapter comprises four parts. It begins with a discussion and synthesis of results previously reported in Chapters 5 to 8. With the study adopting a mixed methods design, this chapter has synthesised the results by triangulating the quantitative and qualitative findings. Discussion of the results is juxtaposed against the literature where appropriate. Following this, based on the findings of the study, a conceptual model for appropriate antibiotic use is presented. Strengths and limitations of the overall study are then dealt with, after which implications for policy and practice, including recommendations, are provided. Finally, the contribution of the study to reducing inappropriate antibiotic use is discussed along with concluding remarks.

9.1 Main findings from the mixed methods research

The extent of antibiotic use and factors impacting on their use were investigated from multiple perspectives, including of patients, community members and providers. Information about antibiotic use was obtained from administrative information recorded at public health facilities and an exit survey of patients from private pharmacies; these sources together with the perspectives of key informants provided insights into the factors associated with prescribing and dispensing practices. Furthermore, a survey of community members exploring their knowledge, attitudes and practices regarding antibiotics and their use provided additional understanding of contributory factors to antibiotic use in the Rupandehi district in Nepal.

9.1.1 Antibiotic use

Overuse of antibiotics

The problem of overuse of antibiotics including taking antibiotics when they are not the appropriate treatment was identified in Chapters 5 and 6.

In both public and private health facilities, the evidence of antibiotic overuse highlighted that at least one antibiotic was prescribed in 38 to 45% of patient encounters. Internationally the use of antibiotics varies widely, ranging from between 20 to 26% (211) to more than 65% (221). The rate of antibiotic use in the current study falls in the mid-range of these estimates, however, it is considerably higher than the WHO recommended values (20 to 26.8%) (199). Countries with a similar rate of antibiotic use to that found in this study were Ghana (220) and Uganda (359), however LMICs such as India (219), Ethiopia (222) and Bangladesh had higher rates (221). Interviews with key informants highlighted that a weak regulatory environment relating to antibiotic prescribing and dispensing in Nepal's health system facilitated inappropriate access to antibiotics in both the public and private sectors (427). Moreover, self-medication is very common world-wide (446), including in Nepal, which is also associated with overuse (357).

Most widely used antibiotics

Guidelines for antibiotic use often advise that third-generation cephalosporins should be avoided as a first-line treatment when a narrower spectrum antibiotic would be effective because they increase the risk of *Clostridium difficile, methicillin resistant Staphylococcus aureus (MRSA)* and other antibiotic-resistant infections (335, 336). However, contrary to the guidelines, this study found third-generation cephalosporins to be the most widely prescribed or dispensed class.

In both public and private health facilities, among all antibiotic classes, approximately one-third were cephalosporins (mostly third-generation cephalosporins), followed by penicillins and quinolones as the next most frequently used antibiotics. Studies in other LMICs such as India (270) and Malaysia (mostly first-generation) (447) also point to a high use of cephalasporins in public and private facilities.

In the survey of administrative records in public health facilities, conditions for which third-generation cephalosporins were mostly being used were pneumonia, Chronic Obstructive Pulmonary Disease (COPD), fever and snake bite, whereas in private pharmacies these conditions were fever, skin diseases and the common cold. The popularity of third-generation cephalosporins lies in their lesser allergenic and toxicity risks as well as having a broad spectrum of activity (335). Another reason highlighted in the key informants' interviews was that prescribing or dispensing higher order antibiotics is to cure diseases fast, with the intention to promote business in private pharmacies. There are a few infections such as some sexually transmitted diseases (448) and meningitis (449) where third-generation cephalosporins are the antibiotics of first choice, but this is not the case if a patient has minor symptoms, such as fever, which is self-limiting in most cases and could be a common symptom of several infections (450). In Nepal, the treatment guidelines do not recommend cephalosporins as a first-line treatment for infections such as respiratory tract infections, enteric fever, pneumonia and urinary tract infections (224).

Regarding specific antibiotics, in the public health facilities the most commonly prescribed were ceftriaxone, an antibiotic in the cephalosporins class, followed by amoxicillin. Although ceftriaxone is recommended as first-line treatment for some genital tract infections (451), epididymo-orchitis, and meningitis (if allergic to penicillin) (452), it was being used for several other diseases (453).

Inappropriate use

Inappropriate antibiotic use includes not completing a course, misuse and overuse (35), which may contribute to the progression of antibiotic resistance (306). If antibiotics are inappropriately used, the infections can no longer be treated by first-line antibiotics, and more expensive medicines must be used, requiring a longer duration of treatment, often in hospitals. This increases health care costs as well as the economic burden on families and societies (145, 146).

As mentioned above, some antibiotic use was inappropriate with prescribing rates above the range recommended by the WHO (199). High rates of prescribing or dispensing of cephalosporins were found for respiratory infections and diarrhoeal cases, however, this is contrary to both WHO's (331, 332) and Nepal's guidelines (454). The Nepalese guidelines - adopted from WHO's guidelines - recommend oral rehydration solution with other supplements for non-bloody diarrhoea (331) and home care without antibiotics for children with respiratory symptoms (332).

Reasons for inappropriate use were highlighted in the key informant interviews. The informants perceived that inappropriate antibiotic use could be attributed to various factors including the lack of diagnostic services at health care facilities, pressure from patients or their family members on providers to supply antibiotics, and the practice of over-the-counter sale of antibiotics. These views are supported in the literature, with consistent findings of inappropriate antibiotic use occurring if prescribers prescribe antibiotics before test results are confirmed as being a bacterial infection (248, 455), patients putting pressure on providers to receive an antibiotic (326, 421), and patients taking antibiotics they have purchased over-the-counter after self-diagnosing an illness (51, 456). Patients taking antibiotics left over from a previous prescription has also been suggested as a reason for inappropriate use (416, 457).

Dispensing without prescription

According to the Drug Act of Nepal, implemented in 1978, antibiotics are classified as prescription only drugs and may be dispensed by pharmacists or drug sellers (professional persons) only upon receipt of a valid prescription (114). In Nepal, community pharmacies are operated by pharmacists or drug sellers who are trained by the Department of Drug Administration (DDA) and obtain a licence from the national drug regulatory authority, the DDA (94). Although, the pharmacists or drug sellers currently do not have the right to prescribe (114), the sale and dispensing of antibiotics without prescription is common (59).

The key informants interviewed in this study confirmed that the practice of dispensing antibiotics without prescription is common in Nepal. One of the reasons could be that the patient often lacks money thus approaches the pharmacy or drug store to purchase antibiotics to avoid paying a doctor's consultation fee. A full course of antibiotics can be purchased with the money that would otherwise be paid for first consulting a doctor. Obtaining medicines without a prescription is also convenient for patients as they can purchase any dose directly from the pharmacy or drug store (344). This non-prescription use of antibiotics reflects poor guidance regarding their use (458), and can potentially involve incorrect diagnosis, treatment and an inappropriate choice of therapeutic class and dosage (419).

Key informants also raised the issue of dispensing without prescription being linked to the profit motive. Antibiotics are one of the more profitable medicines (362), which may provide an incentive for pharmacists and other drug sellers to dispense antibiotics without prescription and dispense more than is clinically necessary (425).

Self-medication

The WHO defines self-medication as the selection of medicines by individuals to treat self-recognised illnesses or symptoms (459). This practice is a worldwide problem, more specifically in developing countries, however, the same practice is also prevalent in developed countries (460). The scheduling of antibiotics as a prescription-only medicine does not preclude them being used for self-medication (461).

Self-medication with antibiotics is a complex phenomenon that is driven by a wide variety of determinants (462). These determinants relate to the patient level (e.g., storage of antibiotics at home, receive incomplete doses from friends/relative), the healthcare professional level (e.g., pressure from patients to sell antibiotics without a prescription) and the healthcare system level (e.g., dispensing antibiotics even for minor illnesses) (460, 461).

Despite antibiotics being classified as prescription only drugs in Nepal (114), the practice of self-medication of antibiotics is common (463), possibly due to a lack of understanding on problems associated with inappropriate use. The findings of the current study point to community people having reasonable knowledge on antibiotic use, however still preferring to use antibiotics for some illnesses such as fever, cough and sore throat. A common misconception in the community is that antibiotics are a 'strong' medicine: capable of curing almost any kind of disease (464), which encourages their use even for minor illnesses. The key informants interviewed in this study believed that community members lacked knowledge regarding antibiotics and their use, thus were inclined to self-medicate. Key informants also raised the issue that if pharmacists or drug sellers did not provide an antibiotic to patients who were pressuring them to do so, the patient would self-medicate from another pharmacy or drug store.

Other potential motives for self-medication with antibiotics, not explicitly raised in the current study are the desire to act expeditiously to treat suspected bacterial infections (464) and wanting to maintain a sense of privacy. The latter motive has been raised in the case of conditions where a social stigma is involved (for example, a sexually transmitted disease); direct purchase of an antibiotic from a pharmacy enables the patient to conceal shameful feelings that they may have by consulting a physician (51). In regard to acting expeditiously to treat a condition, people who have experienced an illness previously believe they can now handle it themselves without incurring the additional cost of consulting a physician (50).

9.1.2 Community knowledge, attitudes and practices

Previous research has identified the key role played by public knowledge and behaviour in tackling the problem of antimicrobial resistance (179, 465). Good knowledge and behaviour of the public can foster the appropriate use of antibiotics, for example by reducing the expectation of patients to receive an antibiotic, by leading to patients placing less pressure on health care professionals to prescribe or dispense antibiotics, and for encouraging medication compliance and adherence (466). In contrast, lack of knowledge about medications such as antibiotics influences the probability of misuse (467). By addressing the knowledge and beliefs of patients on aspects of appropriate antibiotic usage, the chain of misconceptions and inappropriate expectations of effectiveness of antibiotics against minor illnesses can be broken (468). In addition, improved patients' knowledge and behaviour facilitates more efficient communication between the patient and clinician (469), and contributes to appropriate decision making (470). By gaining a better understanding of the community's knowledge, attitudes and behaviours on the use of antibiotics, unmet educational needs can be identified (338) and effective public health interventions implemented (467).

The quantitative findings of the current study found that community members who participated in the household survey had relatively good knowledge about antibiotic use, which was in contrast to the views of key informants who perceived that community members lacked this knowledge. However, the household survey did suggest that the public lacked knowledge in identifying antibiotics with two-thirds (67.7%) not knowing that amoxicillin was an antibiotic. This was almost double the percentage found in similar studies conducted in Bhutan (375) and Thailand (471). Additionally, nearly half of respondents believed that antibiotics would help them to get better more quickly if they had a fever, a comparable result to the findings of a study conducted in Indonesia (62).

The current study also found the behaviour of community members towards antibiotics to be mixed. The majority of respondents indicated that they were not less satisfied with a doctor's visit if they did not receive an antibiotic, yet most respondents also indicated they would go to another doctor if not prescribed an antibiotic when they thought one was needed. The latter response supported views expressed in the key informant interviews about community members approaching another doctor or drug store if not given an antibiotic.

The concept of antibiotic resistance was well known by community members but imperfectly understood. Half of respondents were unsure whether skipping doses would contribute to the development of antibiotic resistance. The finding is consistent with a Palestinian study that found one-third of respondents knew the meaning of antibiotic resistance, however nearly one-third of them incorrectly agreed that antibiotics' effectiveness would not be affected if antibiotics were taken less or more than the prescribed dose (401).

Finding about practices relating to antibiotic use were also mixed. While community members generally followed correct practices accessing and using antibiotics, most at least sometimes preferred an antibiotic when they have a cough or sore throat, a significantly higher percentage than found in a similar study conducted in Jordan (378). Views of key informants supported the finding about community members not always following correct practices, not specifically about preferring antibiotics when not needed but regarding other practices such as self-medication and over-the-counter purchasing. These latter practices may result in incorrect self-diagnosis, delays in seeking medical advice when needed, and incorrect use such as in the administration of antibiotics and incorrect choice of therapy (472).

Findings of the current study on the knowledge, attitudes and practices of community members about antibiotic use support strategies put forward by the WHO and European Union to promote the prudent use of antibiotics among the general public (473, 474). While both organisations have emphasised the importance of adopting an interdisciplinary approach to combatting antibiotic resistance, improving the public's knowledge, attitudes and practices towards antibiotic use was acknowledge as a crucial strategy to reduce antibiotic misuse. In 2015 the World Health Assembly endorsed the Global Action Plan on Antibiotic Resistance (52), which has as a strategic objective to improve awareness and understanding of antimicrobial resistance. The World Antibiotic Awareness Week held in November each year, is one action among many that aims to raise public awareness and understanding of antibiotic resistance. Supporting national awareness-raising efforts and providing insights into reported public use of and knowledge about antibiotics has also been included in the European Union's new action plan against antimicrobial resistance (475).

9.1.3 Factors influencing antibiotics use

Demographic groups

The findings of the current study highlight the extent to which the patterns of antibiotic prescribing and dispensing vary among demographic groups in both public and private health facilities. In the public health facilities, females were less likely to be prescribed antibiotics than males, despite female attendance in public facilities being higher than male attendance. Yet, no difference was found in dispensing of antibiotics between males and females in the private health facilities. In both public and private facilities, younger age groups were more likely to be prescribed or dispensed antibiotics compared to older groups.

Females receiving fewer antibiotics than males in the public health facilities contrasts with the findings of a systematic review conducted in 10 high-income countries, which found females to be more likely to receive antibiotics than male (328). Higher antibiotic prescribing in adult women was thought to be associated with a higher consultation rate; a study conducted in the United Kingdom showed adult healthy women consulting primary care approximately 80% more than healthy adult men (476). However, social norms and gender roles, which are important determinants of health seeking behaviour, are quite different in LMICs compared to high-income countries. In the case of Nepal, gender norms have been found to be barriers to women's control over their resources and health-related decision making (477). Nepalese families are generally patriarchal, meaning that household heads are usually male, and considered as the breadwinner, with more exposure to working outside of the household (478). Women are typically involved in daily chores at home, and most women are not given sufficient decision-making power to control their own access to resources, such as information, services and money (479). These factors may hinder females seeking health care.

Higher antibiotic prescribing for children may be attributed to children tending to get more infections (329). Also infectious diseases are the leading cause of child mortality in many developing countries (330), and this may influence prescribing decisions to err on the side of caution when unsure of the underlying cause of symptoms. Similarly, higher self-medication practices among younger age groups could also be a factor contributing to higher antibiotic dispensing for younger age groups (369). Additionally increased education has been found to increase the risk of self-medication with antibiotics (370), and globally the literacy rates of young adults is higher than the elderly, with the differences even wider in developing countries (371).

Health conditions

As discussed above, the study found antibiotics were more likely to be prescribed or dispensed for some conditions, such as respiratory infections and diarrhoea. These findings were contrary to international recommendations, as the WHO guidelines recommend oral rehydration solution with other supplements for non-bloody diarrhoea (331) and home care without antibiotics for children with respiratory symptoms (332). Nepal has adopted the WHO's guidelines for the treatment of such illnesses especially for children. As per guidelines, home care without antibiotics has been recommended for respiratory illness unless any sign of infection such as pneumonia is evident. In the case of diarrhoea, level of dehydration has been classified into three categories (no, some and severe dehydration) and no antibiotic has been recommended for the first two categories (454).

Findings of this study confirm those of studies in other LMICs (480, 481) about overprescribing in the treatment of respiratory conditions and diarrhoea. However, these conditions impose a considerable health burden especially to the children in LMICs (365, 366), and may lead to antibiotics being used more widely for the treatment of these diseases (367, 368).

Conflict between knowledge and practice

A dissonance between knowledge and practices, as found in the household survey of community members, was also apparent in the qualitative interviews with the service providers. While aware of, and concerned about antimicrobial resistance, service providers acknowledged prescribing and dispensing antibiotics unnecessarily, for example for minor illnesses or when infections were likely to be viral. A factor contributing to this practice was the importance of wanting to preserve the doctor-patient relationship, with providers acquiescing to patient expectations to maintain good relationships. As found in other studies, concerns were expressed that if patient expectations were not met, they may not turn up again-and instead get antibiotics from another pharmacist (425, 482). In the private facilities, wanting to preserve the doctor-patient relationship and not lose patients to other practitioners also related to concerns about loss of revenue and wanting to maintain their reputation in the community (483).

In public health facilities, shortages of certain types of medicines result in service providers being compromised in the choice of antibiotics to prescribe (85). Patients seeking services from these facilities are often poor and have low purchasing capacity (86). To meet patient expectations, and not wanting to disappoint them, providers knowingly prescribe available antibiotics, due to the supply problems, which may not be effective for such conditions.

Uncertainty of diagnosis

Health care providers, working in the rural communities often face a number of challenges and barriers when trying to provide services such as shortages of health professionals, and restricted access to resources for diagnostic tests (423, 484). In Nepal, only 25% of the public health facilities have their own laboratory and, even when laboratories are available, the selection of diagnostic tests is limited (257). Laboratory and other diagnostic facilities are available mainly in hospitals located in urban areas, and health facilities in rural areas often lack these facilities. This lack of diagnostic facilities leads to providers having to prescribe or dispense antibiotics based on clinical observation rather than diagnostic testing, which creates pressure to prescribe antibiotics because of a perception that the risk of not prescribing is greater than that from unnecessary use (247).

In the current study, key informants expressed the difficulties in prescribing antibiotics in the absence of diagnostic tests in their facilities. Lack of diagnostic tests increased the diagnostic uncertainty, making it difficult to diagnose whether an infection was viral or bacterial (485), for example in the case of respiratory tract infections (486) and diarrhoea (487). Patients with viral and bacterial infections often have similar symptoms of congestion, cough, and sore throat making it difficult for them to differentiate between the two in the absence of a diagnostic test (488). As a result, antibiotics are prescribed when they are not needed. Even if diagnostic facilities are available, patients do not want to have a diagnostic test done because of lack of money to pay for the tests.

Unlicensed pharmacies

Private pharmacies are widely established in most LMICs, and are usually considered as a patient's first point of contact for healthcare and the preferred channel through which to get health services and medicines (343). Reasons for the popularity of private pharmacies include ease of access, more flexible opening hours, the availability of medicines on credit (344) and trusting relationships between patients and pharmacists or drug sellers (345). Private pharmacies range from high-end outlets to small, rural, road-side stalls and can be staffed by fully trained pharmacists or a drug seller without formal health qualifications (489). Unlicensed pharmacies, especially outside of cities, often exist in LMICs (360), and sell medicines informally. These unlicensed pharmacies are not legally recognised by the health system of the countries in which they operate (361).

The current study found that a number of unlicensed pharmacies existed in the Rupandehi district in Nepal, and that the level of dispensing of antibiotics was higher in these pharmacies. The key informants believed that the weak regulatory oversight of the

Nepalese health system was a contributory factor facilitating unlicensed pharmacies to operate. In this study, the education level of the operators of these unlicensed pharmacies was unknown, and the perception is they are often minimally educated (360) and that patients do not receive the appropriate medicines, in doses that meet their individual requirements, for an adequate duration, and at the lowest cost (489). It has been also suggested in these circumstances that drug sellers may approach dispensing of medicines as any other sales job, not wanting a customer to leave without making a purchase (360). More generally, inappropriate dispensing of antibiotics may occur due to the business motive of private pharmacies with profits from antibiotics contributing to total profit (362).

Lack of knowledge of community members

Factors influencing health related behaviours and people's adaptive responses to disease and treatment are becoming better understood (490). Although human behaviour can be influenced by a number of factors at a number of levels, lack of knowledge about medication increases the probability of misuse including lack of compliance (467) or poor adherence (491). In regard to antibiotics, lack of individual knowledge about antibiotic use contributes to unnecessary use, which can lead to antimicrobial resistance (175). Poor adherence to antibiotic prescriptions may also lead to worsening of the infection and selection of antimicrobial-resistant strains of bacteria (492).

As previously discussed, the household survey found that, while respondents appeared to have relatively good knowledge about antibiotic use, they were unsure about distinguishing antibiotics from other medicines and inconsistencies were apparent between knowledge and practice. These issues raise the possibility of patients stopping taking antibiotics with improving symptoms before completing the prescribed course, a practice quite acceptable with paracetamol use (375). Likewise, their lack of knowledge about the identification of antibiotics could increase the number of requests for these drugs from service providers for illnesses in which antibiotics are not effective (493).

While the respondents to the household survey recognised that antimicrobial resistance was a problem, at an individual level, self-interest drives behaviour. The findings of a systematic review were that while most people understand that resistance is driven by excessive or unnecessary antibiotic use, they tend to underestimate their own risk from resistant infections, as well as their role in, and ability to minimise, the development of antibiotic resistance (494). This finding is consistent with social cognitive theory, which suggests that, the larger the number of people that contribute to the development of a problem, and the more distant its consequences, the lower our perceived personal risk from it (495).

9.1.4 Conceptual framework

A conceptual framework has been developed based on the findings of the mixed methods research conducted in the current study. The framework is adapted from four existing theories, namely the precede-proceed planning model (496), the theory of planned behaviour (497), the diffusion of innovation theory (498) and the programme sustainability framework (499).

The framework **(Figure 9.1)** illustrates that appropriate antibiotic use is affected by both supply and demand factors, that is, the prescribing and dispensing practices of service providers and antibiotic using behaviours of patients or community members.

Prescribing or dispensing behaviours of service providers can be influenced by predisposing, reinforcing and enabling factors. The predisposing factors are any conditioning factors (500) related to attitudes, subjective norms, and perceived behavioural controls, which influence intentions and antibiotic prescription practices. Reinforcing factors are factors providing continuing reward or incentives for the persistence or repetition of behaviours (500), in the case of antibiotic prescribing practices may include patients' expectations and the relationship between service providers and patients. Enabling factors are antecedents to behavioural or environmental change that allow a motivation or environmental policy to be realised (500). In the case of antibiotic prescribing or dispensing practices, enabling factors include availability of treatment protocols and/or guidelines, the supply of different types of antibiotics to the public health facilities, the availability of diagnostic facilities and social support.

On the demand side, predisposing factors to the antibiotic use behaviours of the community relate predominately to their knowledge, attitudes and practices about antibiotics, their appropriate use and the problem of antimicrobial resistance.

The reasons for inappropriate prescribing or dispensing include poor understanding by service providers of the role of antibiotics in disease management, and pressure from patients to prescribe antibiotics. A supportive environment for local level organisations requires community involvement and input from central level authorities. Guidelines and treatment protocols are also important references for appropriate prescribing. Central level organisations are responsible to develop and revise evidence based treatment protocols and distribute them to providers and institutions as appropriate. The availability of different types of antibiotics helps prescribers to choose appropriate treatments especially in public health facilities. Diagnostic facilitates are important in correctly identifying when antibiotics are and are not needed. Effective monitoring and follow up systems by central level authorities also helps to ensure appropriate services at the local level.

On the demand side, awareness and educational activities can increase the community's knowledge and attitudes relating to antibiotic use and misuse and influence practice by reducing non-prescription antibiotics use.

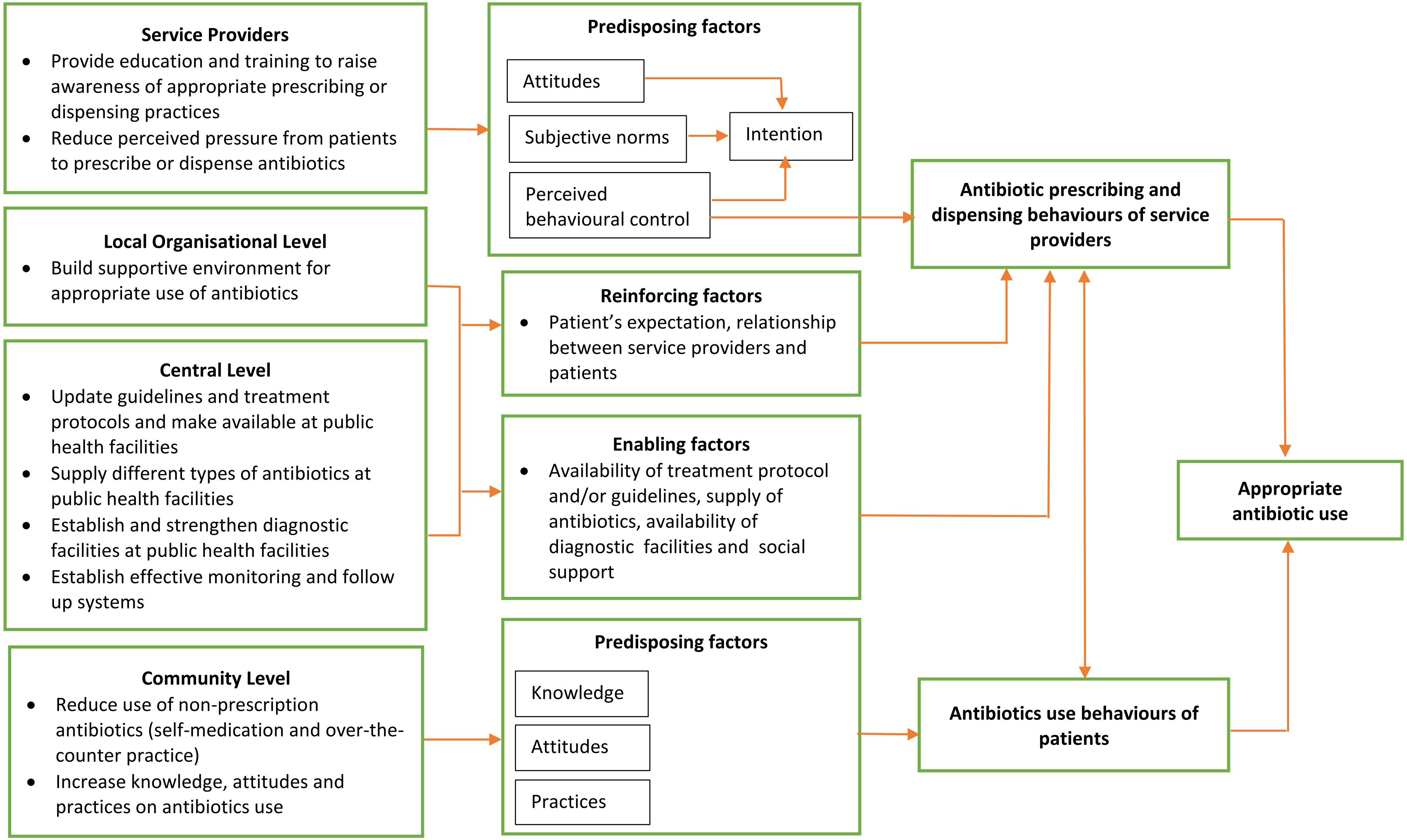


Figure 9.1 Conceptual framework for appropriate antibiotic use

9.2 Strengths and limitations of the research

The methodology chapter and each of the chapters presenting the four empirical studies have dealt with strengths and limitations. This section reflects on the strengths and limitations of the overall research.

A strength of this research lies in its design, with the study capturing a wide range of information relating to antibiotic use in the Rupandehi district of Nepal. This includes (i) the extent of antibiotic use (ii) the views of service providers about factors associated with prescribing practices, and (iii) knowledge, attitudes and practices relating to antibiotic use among community members. In capturing this information, the study collected data from four different sources: (i) patients' administrative records from public health facilities, (ii) dispensed medication information for patients collected from exit interview conducted at private pharmacies, (iii) structured interviews with community members using a household survey, and (iv) semi-structured interviews with key informants including physicians, health workers, dispensers and district policymakers. Drawing on information addressing a wide range of factors about antibiotic use, and obtaining multiple perspectives, has provided a rich evidence base regarding the inappropriate use of antibiotics. This information will be valuable in designing effective multifaceted interventions to promote prudential use of antibiotics among the Nepalese population thus helping to address the problem of antibiotic resistance.

The research adopted a mixed methods approach. Quantitative methods were used to collect information about antibiotic use in public and private facilities and the knowledge, attitudes and practices relating to antibiotic use among community members, with qualitative methods adopted for the interviews with key informants. Collecting qualitative information from the key informants provided contextual information with which the data from the administrative records, exit survey and household survey could be interpreted, and contributed to a more in-depth investigation of antibiotic use and misuse.

The study used standard guidelines, developed by WHO (280, 281) for sample selection. These guidelines have been refined continuously based on the lessons learned and used widely across many LMICs to generate reliable information on medicine use. Sampling and clustering techniques, described in the guidelines, are designed in a way to get optimum representation from respective sampling units. Although the current study collected data from multiple sources, the samples were derived from the same areas or communities, using the techniques defined in the guidelines. Consistency in the areas or communities from which data were obtained from the multiple sources enhanced the comparability of the information collected and increased confidence in the findings of the triangulation process.

The study has several limitations. While collecting the patient administrative information in both public and private health facilities, diagnoses or conditions of patients were non-specific. Records of the public health facilities were symptoms-based and the information collected in the exit interviews at private facilities was based on self-report by patients. Being symptoms-based rather than coded based on a standard classification such as the International Classification of Diseases (ICD) caused diagnoses or conditions to be grouped into broad categories together with related conditions. Such broad categories made it difficult to assess appropriate use of antibiotics. It also prevented any investigation of whether antibiotic dispensing and prescribing followed the standard guidelines.

The Rupandehi district also has an open border to India and the population has access for referral healthcare in India, where unregistered medicines, including antibiotics, are easily available. This study has not captured any information about the use of medicines obtained outside of the health care system in Nepal.

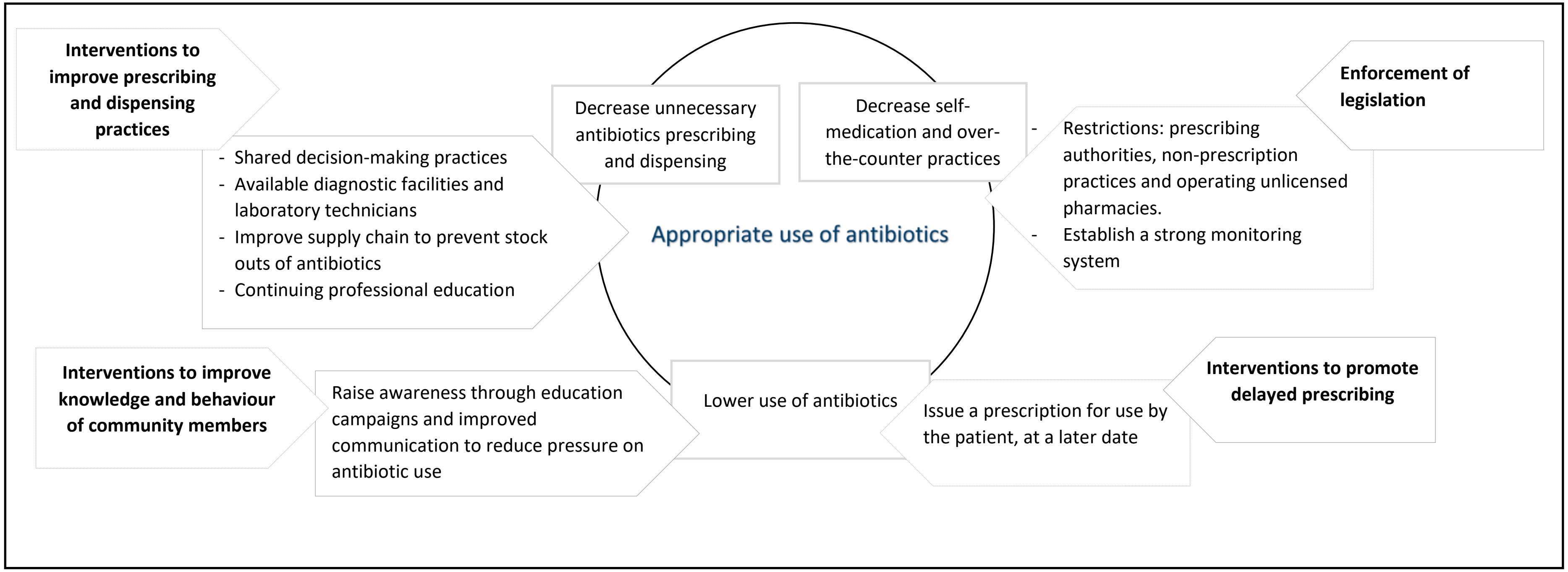
Another limitation is that the study area of Rupandehi district lies in a low-land region of Nepal, which has a greater availability of health services than the hill and high-hill regions. Results of the study are thus more generalisable to districts falling in low-land regions than hill and high-hill regions, a factor which will need to be considered in using findings from the study in developing and implementing policy to improve antibiotic use in Nepal. However, the findings are likely to be of interest to other LMICs, where the health system is similar to Nepal. For example, most of the south Asian and African countries have weak regulatory framework in relation to prescribing practices, which fail to control over-the-counter dispensing practices. Thus, some findings of this study may be applicable to these countries also.

9.3 Implications for policy and practice, and recommendations

Antibiotic use for human health is reported to be increasing substantially, with misuse and overuse adding to the increase in antibiotic resistance (52). The current study demonstrates the extent of inappropriate use of antibiotics among the general population in Nepal, and this being a multifaceted problem on both the supply and demand side of the market. Health service providers including physicians, health workers and pharmacists/dispensers play a key role in prescribing and dispensing of antibiotics, and the widespread inappropriate use of antibiotics is occurring in both public and private health facilities. Community members as patients are not only recipients of inappropriate antibiotics but also contributors to the problem through their antibiotic healthcare seeking behaviour.

The consequences of infection with resistant microorganisms increases both morbidity and mortality and treatment costs (501). In addition to increasing health risks and other public health consequences, the implications of antibiotic resistance extends more widely, contributing to economic losses due to reduced productivity caused by sickness and higher costs of treatment (52). In response to the growing problem of antibiotic resistance and its consequences, the WHO and the European Union (EU) have recommended several strategies. The global action plan developed by the WHO has five strategic objectives covering various aspects of antibiotic resistance. Among the five objectives, improving awareness and understanding of antimicrobial resistance, and optimising the use of antimicrobial agents are directly applicable to the current study (52). Similarly, one of the EU's strategies, namely multidisciplinary coordination at the community level to lower the burden of antibiotic resistance (474) is relevant to implementing a multifaceted intervention to reduce inappropriate antibiotic use.

The underlying purpose of the current study was to provide an evidence base relating to inappropriate antibiotic use that would improve understanding of the problem in Nepal and contribute to evidence-based policy to reduce the risk of antibiotic resistance in human through improving appropriate antibiotics use. Given the findings of the study, and considering international recommendations of the WHO and EU, implications for policy and practice have been illustrated in a framework **(Figure 9.2)** and are described below in detail.



Note: The figure demonstrates how to improve prudential use of antibiotics and reduce the risk of antibiotics resistance in humans and are central of the recommendations of this research.

Figure 9.2 Implications of findings of study for policy and practice on appropriate antibiotics use in Nepal

9.3.1 Improving prescribing and dispensing practices

Findings of this study have shown that both providers and patients contribute to the inappropriate use of antibiotics.

Shared decision-making, which involves patients and health providers making decisions together, is an approach that has been proposed to improve decision-making about antibiotic use (502). Having patients more involved in the decision-making process, and informing them of treatment options and risks, tends to result in more conservative choices and helps in managing patient expectations about always being provided with an antibiotic (439, 502, 503).

The availability of limited resources in health care facilities is a contributor to inappropriate prescribing. Almost half of primary health care centres in Nepal do not have physicians or laboratory technicians and more than two-thirds of health facilities do not have their own laboratory (257). An initiative to fill these positions and provide laboratory facilities would contribute to improving prescribing practices. Treatment guidelines represent the best available evidence and opinion regarding antibiotic treatment. Public health facilities do have some disease related guidelines available; private facilities do not. Making treatment guidelines available to all prescribers and health facilities and extending their availability to other diseases and conditions where necessary, may improve prescribing practices. In addition, improving the supply chain in public health facilities is critical to prevent stock outs of essential drugs, including antibiotics, which will allow providers to follow the appropriate use of antibiotics as per the guidelines.

Continuing professional education is a necessary practice in the medical field for advancing knowledge and technology (426). In relation to prescribing of antibiotics, continuing professional education has been recognised as critical to supporting and effecting a response to the global challenge of antimicrobial resistant (504). Antibiotic management requires effective teamwork between all health professions, regardless of who writes the prescription. It is therefore important to educate not only prescribers, but all other healthcare professionals in contact with patients who are prescribed or dispensed an antibiotic (e.g., health workers, nurses and pharmacists/dispensers), to ensure patients receive consistent messages on correct and prudent antibiotic use when taking antibiotics (443). In Nepal, continuing professional education has been initiated for physicians in some health facilities but not fully implemented (444), thus gradual implementation covering other healthcare professional is suggested.

9.3.2 Improving knowledge and behaviour of community members

The behaviour of both providers and patients was found to contribute to the inappropriate use of antibiotics, with lack of knowledge a predictor of these behaviours. Change in practices of the key enablers of antibiotic misuse and overuse cannot occur in the absence of awareness and knowledge (505). Education targeting prescribers and the community to raise their awareness about appropriate antibiotic use and the problem of antibiotic resistance has been shown to contribute to improving practices (404) and can be cost-effective and lead to lasting changes (438). Improving awareness and understanding of antimicrobial resistance through effective communication, education and training is a core objective of WHO's action plan to combat antibiotics resistance (52), and is an intervention supported by the findings of this study. In delivering this intervention, issues relating to over-the-counter dispensing and self-medication should also be covered.

In addition to public education and awareness campaigns, awareness of patients can be raised through better communication between patients and their family members and providers within the consultation. Effective communication within the consultation leads to patients being less likely to pressure providers for antibiotics (506), however, this type of communication is infrequent and should be encouraged (440).

9.3.3 Delayed antibiotic prescribing

Delayed prescribing of antibiotics, also referred to as 'watchful waiting', involves health care providers issuing a prescription for use by the patient at a later date, if their symptoms do not improve. Guidelines issued by the National Institute for Health and Care Excellence (NICE) have recommended this strategy as a management option for most patients presenting with respiratory tract infection (507), however, this can be used more generally for other conditions.

The impact of delayed antibiotic prescribing on patient satisfaction is unclear, however, a review showed encouraging results that this approach can reduce the number of antibiotic prescriptions filled (442). Delayed antibiotic prescriptions are as effective as immediate prescriptions in reducing complications as well as reducing the need for patient re-consultation, which suggests it offers a reasonable alternative to an immediate prescription (441). Additionally, this approach can help prescribers to manage situations in which they are uncertain about a patient's diagnosis due to unavailability of diagnostic facilities but are afraid the condition may get worse.

9.3.4 Enforcement of legislation

Enforcement of laws regulating drug distribution and use, and ensuring all pharmacy operations are licensed, is central in achieving appropriate antibiotic use (427). Strict implementation of restrictions on over-the-counter sales of antibiotics has been shown to be effective in reducing non-prescription antibiotic consumption in some countries (418, 445, 508). Given that many countries have laws prohibiting over-the-counter sales, there is a need to ensure that these laws are strictly enforced (348).

In Nepal, a general lack of enforcement of the legislation in the distribution of antibiotics and registration of pharmacies facilitates inappropriate use. The Drugs Act 1978 (published in 1986) provides the legislative power to control the use of antibiotics (114). Prescribing is allowed to be conducted by physicians and non-physicians such as auxiliary health workers and health assistants, who have 18 months to three years post-secondary training in diagnostics and therapeutics, and nurses (96). Authority to prescribe for prescribers who are not physicians should be reviewed to ensure it is limited to situations when essential. As in the Drug Act 1978, WHO's Guidelines on Good Pharmacy Practice confine the role of pharmacists to dispensing only (372). However, the laws introduced in the Drug Act 1978 and the guidelines on good pharmacy practice are barely monitored (225). Furthermore, unlicensed pharmacies operate in country areas and dispensing antibiotics without prescription occurs in both licensed and unlicensed facilities. Absence of strict enforcement of 'prescription-only' laws (509) and a weak regulatory oversight of the Nepalese health system (59) encourages these practices. A stronger enforcement mechanism to restrict antibiotic prescribing authorities, non-prescription practices, pharmacy registration and overall regulatory oversight should be initiated.

9.4 Contribution and the way forward

The research undertaken for this thesis has provided comprehensive evidence about antibiotic use in the general population in the Rupandehi district in Nepal and factors associated with inappropriate use. Multiple perspectives on these issues were obtained through collecting data from health service providers, policy makers and the community, and covering public and private sector health facilities. Additionally the integration of quantitative and qualitative data in a mixed methods research design facilitated a fuller account of the problem to be gained.

The findings confirmed previous studies of inappropriate use of antibiotics in LMICs, where the prevalence of the infectious diseases burden is aggravated by uncontrolled access to antibiotics. The situation is made worse with inappropriate self-medication and the over-the-counter sale of antibiotics. This inappropriate use of antibiotics was found to be influenced by demand and supply factors, with both the health seeking behaviour of the community and the prescribing and dispensing practices of providers contributing to the misuse and overuse of antibiotics. An additional contributory factor was the weak regulatory environment of the health system.

Policy makers in Nepal must recognise the multiple factors underlying the problem of inappropriate use of antibiotics in humans and develop a comprehensive policy to combat the threat presented by antimicrobial resistance and drug-resistant infections. While the focus of this research was on the inappropriate use of antibiotics in humans, the societal challenge of antibiotic resistance is much wider including also the overuse and misuse of antibiotics in animals and the animal-human interface (510). The Government of Nepal should consider adopting a One Health initiative as endorsed by the WHO, the Food and Agriculture Organization of the United Nations and the World Organization of Animal Health (511). This initiative advocates for the implementation of a multi-sectoral approach to encourage collaborative action for strengthening systems to minimise harmful effects of primarily infectious diseases and related issues such as antimicrobial resistance.

Although this study both confirms and adds to the evidence base for action to reduce inappropriate antibiotic use, future research is needed to address limitations of the research. First, the quantitative and qualitative studies were conducted in only one district in the low-land region of Nepal. While its findings are likely to be broadly transferable to other districts in the low-land region and also to districts in the high-hill and hill regions, the research design adopted in this study, and the data collection instruments, could be applied to other districts to explore contextual factors that might indicate the need for targeted strategies across regions. Second, informed by the findings of this study, research needs to be conducted to develop specific approaches to address its proposed recommendations, for example, how best to implement shared decision-making practices or to raise awareness through education campaigns to influence consumer behaviour.

Finally, the role of wider socio-economic factors as a driving force in inappropriate antibiotic use must be recognised. Nepal is a low-income country and, despite political commitment to social health insurance in recent years, most health care is paid out-of-pocket. For many patients, the cost of antibiotics is prohibitive and leads to inappropriate antibiotic use such as forgoing the cost of a physician consultation, self-medicating practices, not completing a course of treatment because of the inability to pay for the full cost, the sharing of medications or using old medicines for a new health problem. In recognising the resource-poor setting of the country, the role of poverty in inappropriate antibiotic use in Nepal needs further examination. Identifying poverty-related factors associated with antibiotic misuse, which are often overlooked, would inform policies to target dimensions of poverty that influence inappropriate antibiotic use but lie outside of the health system.

Appendices

Appendix A Checklist to collect public health facility records

Name of Public Health Facility: ______________________

Department: ☐ Out-patient ☐ In-patient

Serial No.	Date	Age		Provisional Diagnosis	Drugs Details					
		M	F		SN	Name	Dose	Route	Schedule	Duration
					1	x	x	x	x	x
					2					
					3					
					4					
					5					
					1					
					2					
					3					
					4					
					5					
					1					
					2					
					3					
					4					
					5					
					1					
					2					
					3					
					4					
					5					
					1					
					2					
					3					
					4					
					5					

Note:
Serial number (SN): Sequential number allocated to each patient.
Dose: Actual dose i.e. Gram (Gm) or Milligram (Mg) to be taken
Route: Mouth (PO), Per Rectum (PR), Sublingually (SL), Intramuscularly (IM), Intravenously (IV), Subcutaneously (SQ), Intranasal (IN)
Schedules: stat (immediately), p.r.n.(when required), o.d. (every day or once daily), o.n. (every night), b.d.(twice daily), t.d.s. (three times daily), q.d.s. (four times daily)
Duration: How long the medicine to be taken. For example: single dose, for two days, for one week or month
Drugs details: Use additional row if needed

Appendix B Online checklist for exit interview

Name of Pharmacy: ____________________ **Interview Date:** ________________

Patient Code: _____________

Respondents Demographic Details

No	Questions	Coding Category	Skip
101	How old are you?	Age (years)……………………………… Don't know ………………………..……	
102	What is your gender?	Male……………………..………………….1 Female………………………….…………..2 Other……………………………………… .3	

Prescription Details

<table>
<tr><th>No</th><th colspan="2">Questions</th><th colspan="6">Coding Category</th><th>Skip</th></tr>
<tr><td>103</td><td colspan="2">How did you get medicine?</td><td colspan="6">Self-medication/no prescription ……………....1
Prescribed by a doctor or health worker and dispensed by a pharmacist/dispenser…………2
Recommended and supplied by a pharmacist/ dispenser without a prescription……………… ..3
Other (invalid prescription)……………………….4</td><td>→ 105</td></tr>
<tr><td>104</td><td colspan="2">Where did you get prescription?</td><td colspan="6">Public Heath Institution. …………………………..1
Private Health Institution …………. ………………2
Name of Health Institution …………………..</td><td></td></tr>
<tr><td rowspan="8">105</td><td rowspan="8">Disease and Medicine Details</td><td>Provisional Diagnosis</td><td colspan="7">Prescribe Drugs Details</td></tr>
<tr><td rowspan="7"></td><td>SN*</td><td>Name</td><td>Dose</td><td>Route</td><td>Schedule</td><td colspan="2">Duration</td></tr>
<tr><td>1</td><td></td><td></td><td></td><td></td><td colspan="2"></td></tr>
<tr><td>2</td><td></td><td></td><td></td><td></td><td colspan="2"></td></tr>
<tr><td>3</td><td></td><td></td><td></td><td></td><td colspan="2"></td></tr>
<tr><td>4</td><td></td><td></td><td></td><td></td><td colspan="2"></td></tr>
<tr><td>5</td><td></td><td></td><td></td><td></td><td colspan="2"></td></tr>
<tr><td>6</td><td></td><td></td><td></td><td></td><td colspan="2"></td></tr>
</table>

Note:
***Serial number (SN):** Sequential number allocated to each drug.
Dose: How many tablets or Gram (Gm) or Milligram (Mg) to be taken
Route: Mouth (PO), Per Rectum (PR), Sublingually (SL), Intramuscularly (IM), Intravenously (IV), Subcutaneously (SQ), Intranasal (IN)
Schedules: stat (immediately), p.r.n.(when required), o.d. (every day or once daily), o.n. (every night), b.d.(twice daily), t.d.s. (three times daily), q.d.s. (four times daily)
Duration: How long the medicine to be taken. For example: single dose, for two days, for one week or month
Prescribe drugs details: Use additional sheet if prescribed drugs are more than six

Appendix C KAP survey questionnaire

Household Code: ______________ **Interview Date:** __________________

Municipality/Village Development Committee: _____________________ **Ward No:** _____

Section 1: Socio-Demographic

Code	Name of Respondent	Relation to Head of Household	Age	Sex	Education
101					
Note: **Sex:** 1. Male 2. Female **Education:** 1. Illiterate, 2. Literate, 3. Primary/Secondary, 4. High School, 5. Intermediate, 6. Bachelors, 7. Masters, 8. PhD					

102	What is your occupation, that is, what kind of work do you mainly do?	…………………………………
103	What is your type of family?	Nuclear……………………………1 Joint…………………………………2 Extended…………………………3
104	How many members are in your family?	Total………….. Male………….. Female ……….
105	What is your average monthly family income?	Salary: NRs………………….. Agriculture: NRs………….. Animal sales: NRs……………… Interest: NRs……………. Investments: NRs……………… Business: NRs…………………… Others (Specify…………….): NRs……… Don't Know ………………………

Section 2: Knowledge

Code	Questions	Coding Category
106	Have you ever heard of a type of medicine called antibiotics?	Yes…………………………………..1No ……………………………………..2

Note: If respondent says 'No" please ask if they have heard of a widely used antibiotic such as penicillin or metronidazole before asking the questions from 107.

Codes	Domains	Questions	Response				
			Strongly Disagree	Disagree	Uncertain	Agree	Strongly Agree
107		Amoxicillin is an antibiotic					

Codes	Domains	Questions	Response				
			Strongly Disagree	Disagree	Uncertain	Agree	Strongly Agree
	Identification of antibiotics	Paracetamol is an antibiotic					
		Aluminium hydroxide+ Magnesium hydroxide (antacid) is an antibiotic					
108	Knowledge on the role antibiotic	Antibiotics are useful for killing germs					
		Antibiotics are often needed for cold and flu illness					
		Diarrhoea gets better faster with antibiotics					
109	Side-effects of antibiotics	Antibiotics can kill “good bacteria” present in our bodies					
		Antibiotics can cause secondary infections after killing good bacteria present in our bodies					
		Antibiotics can cause allergic reactions					
110	Antibiotic resistance	If bacteria are resistant to antibiotics, it can be very difficult to treat the infections they cause					
		Many infections are becoming increasingly resistant to treatment by antibiotics					
		Misuse of antibiotics can lead to antibiotic resistance					

<u>Section 3: Attitudes and Practices</u>

Section 3A

Codes	Domains	Questions	Response				
			Strongly Disagree	Disagree	Uncertain	Agree	Strongly Agree
111	Preference for use of antibiotics	When I have a cold, I should take antibiotics to prevent getting a more serious illness.					
		When I get a fever, antibiotics help me to get better more quickly.					
		I would rather take an antibiotic that may not be needed than wait to see if I get better without it.					
112	Antibiotic resistance and safety	Whenever I take an antibiotic, I contribute to the development of antibiotic resistance.					

Codes	Domains	Questions	Response				
			Strongly Disagree	Disagree	Uncertain	Agree	Strongly Agree
		Skipping one or two doses does not contribute to the development of antibiotic resistance.					
		Antibiotics are safe drugs, hence they can be commonly used.					
113	Attitudes to doctor's prescribing of antibiotics	If I expect to receive an antibiotic, I am less satisfied with a doctor's visit if I do not receive an antibiotic.					
		If a doctor does not prescribe an antibiotic when I think one is needed, I will go to another doctor.					

Section 3B

Codes	Questions	Response				
		Almost always	Often	Sometimes	Seldom	Never
114	If you feel better, after taking 2–3 doses of antibiotics, do you still complete full course of treatment?					
115	Do you prefer to obtain antibiotics from the pharmacy rather than doctor/health worker if you have an illness					
116	Do you prefer to take an antibiotic when you have cough and sore throat?					
117	Do you consult a doctor before starting an antibiotic?					
118	Do you check the expiry date of the antibiotic before using it?					
119	Do you use antibiotics as a prophylaxis					

Appendix D Interview schedules for key informants

A. Topic List for "Physician" and "Health Worker" Interviews

Instruction: The **bold-printed** topics represent the essential elements to be covered in the interview, the remaining questions in the boxes below the main topic question can be used as prompts and to raise follow-up questions.

[Instructions to interviewer are printed in italics]

Infectious diseases

- Can you tell me something about the **occurrence of infectious diseases** in residents of this area or this facility?

  - Which types of infectious diseases occur most often?
  - How often do they occur (in comparison with other diseases)?
  - How does the occurrence of infectious diseases in this area/facility compare to the occurrence of infectious diseases in other areas/healthcare settings?

Antibiotics

- Can you describe the **most recent case in which you prescribed antibiotics**?
  Listen carefully to which of the below mentioned topics are raised, and relate to these in follow-up questions accordingly. Note: not all questions (those not bolded) need to be covered!
- What aspects of this case resulted in your decision to prescribe antibiotics? In other words, **which considerations did you make** prior to your decision to prescribe antibiotics?

In cases when the clinical presentation/status of the patient is considered in the prescribing decision: (e.g. signs and symptoms, additional diagnostic information, clinical history)

- Was the clinical presentation clear?
  Is the clinical presentation often (also) clear in other cases?
  Are there any patient groups in which the clinical presentation is often less clear?
- Do you find proper diagnosing difficult if the clinical presentation is ambiguous or not clear?
- Did you have any information about the infective agent (culture result) at the time of prescribing?

In the described case, **what information did you obtain from the patient**?

- How did you feel about the quality of the information in this case? Was this consistent with your opinion more generally?

*In case of **influence of the patient, family and/or staff** on the prescribing decision: (if this did not appear from the case description, inquire about any occurrence of influence of the patient, family and/or staff more generally, and ask for an example if applicable).*

- Which preferences for medicines were expressed by patients, family and/or staff? Are such preferences expressed more frequently?
- To what extent did these preferences concur with the treatment you would have proposed? Do they (also) concur in other cases?
- Do you experience it as 'difficult' to handle the preferences of patients, family and/or staff? Why do/don't you experience this as 'difficult'? In which situations in particular?
- Does the duration or quality of the physician/health worker-patient relationship affect the way preferences of patients and family are dealt with? And how so?

In case other factors appeared to be involved in the prescribing decision: (e.g. the risk of development of antibiotic resistance, organizational factors (time pressure, staff shortage, drug shortages, staff turnover, presence/availability of diagnostic resources, financial considerations).

Thoroughly question how and why these factors were considered

- In retrospect, do you feel that **prescribing antibiotics** was the right decision in this case?

  - Can you explain this? Why do you feel this was (not) a good decision?

  In case treatment effectiveness supported the feeling that prescribing antibiotics was the right decision:
  - On what basis did you conclude that the treatment was effective?
  - What is your understanding of a 'good/appropriate' prescribing of antibiotics?

  (Based on evidence, a formulary, routine, experience, observed effectiveness, etc.)
  - Are there any factors that encourage you to prescribe antibiotics?

  (e.g patient's pressure, unavailability of guidelines, unclear on the diagnosis, shortage of other drugs, excessive pharmaceuticals advertisement etc..)
  - Do you believe that there are opportunities to improve antibiotic prescribing by physicians/health workers (including yourself)?
    Can you give examples of such opportunities?
    How could this be achieved?
    Do you believe physicians are open to such opportunities?

- Is … [infection type case] an infection type for which you often prescribe antibiotics?
  - Why is / isn't this an infection type for which you often prescribe antibiotics?
  - For which infection types do you also frequently/more frequently prescribe antibiotics?

- So far, we have discussed situations in which antibiotics were prescribed. Can you also describe the **most recent case [with an infection] in which you did not prescribe antibiotics?**
  - Why did you decide not to prescribe antibiotics?
  - Can you describe other situations in which you do not prescribe antibiotics?
  - Are there any situations in which you find it difficult not to prescribe antibiotics? Can you describe these situations? Why do you experience it as difficult to not prescribe antibiotics in these situations? *(e.g.* ***pressure of family****, risk of negative outcome of infection etc.)*

- In your opinion, what is the effect of selling antibiotics without a prescription on the overall patient's welfare in Nepal?
  If you believe that selling antibiotics without a prescription is a problem, what are the steps that you think need to be taken to limit or eliminate this practice? *(This question will only be asked to participants who indicated that dispensing antibiotics without a prescription constitute a negative effect on the patient's welfare)*

Antibiotic resistance

- Can you tell me something about the **occurrence of antibiotic resistance in this area/facility?**
  - How often does it occur?
  - Do you believe there is an increase in antibiotic resistance? What are the causes?

  (List the causes and note that some may be already pointed out in the conversation)
  - According to you, how does the occurrence of antibiotic resistance in hospitals (public and private) compare to the occurrence in health centre/health post or the community?

- In your opinion, how large is the resistance problem in the area/health facility? And how large in Nepal in general? *(Ask the questions comparing to public and private and level of health facilities with the reasons of increasing antibiotics resistance)*
- Do you believe that you are well-aware of the developments with regard to antibiotic resistance? If not, why not?

- Do you, as a physician/health worker, **experience a personal responsibility for the emergence of antibiotic resistance** in the facility/area? And in the community in general?
    - Who is/are also/more responsible for the emergence of antibiotic resistance?

Recommendation for appropriate use of antibiotics

- How do you describe the appropriate/inappropriate use of antibiotics?
    - Are you aware of a standard definition for appropriate antibiotics use available?
    - Are you aware of any guidelines/protocol for prescribing antibiotics? *(Ask if government distributes it)*
    - How do you update your knowledge on antibiotic use? If not why not? *(If yes ask if this is a personal initiative or government's provision of training or other methods of updating knowledge)*
    - What are the main influences on inappropriate use of antibiotics – what do you think drives this? *(e.g. physicians, health workers, nurses, patients, family members, community people, drug companies, government, distributors etc.)*
    - What would be the possible intervention strategies for appropriate antibiotic use? *(e.g. possible solutions in controlling antibiotics inappropriate use and the roles of different actors)*

    (Possible strategies could be: increasing awareness among consumers, awareness and education of pharmacists, changing prescription habits of doctors, easy return policy for nearly expired antibiotics, changing pharmacists' dispensing, redefining the role of pharmacists, assessment of doctors and paramedics workload, analysis of dispensing practices, monitor prescribing and drug use as well as adverse drug reaction, develop/update standard treatment guidelines)

B. Topic List for "Dispensers" Interviews

Instruction: The **bold-printed topics** represent the essential elements to be covered in the interview, the remaining questions in the boxes below the main topic question can be used as prompts and to raise follow-up questions.

[Instructions to interviewer are printed in italics]

Infectious diseases

- Can you tell me something about the **occurrence of infectious diseases** in residents of this area?

> - Which types of infectious diseases occur most often?
> - How often do they occur (in comparison with other diseases)?
> - How does the occurrence of infectious diseases in this area compare to the occurrence of infectious diseases in other areas?

Prescribing and dispensing behaviour

- What are the roles you do in terms of **dispensing and prescribing antibiotics**?

> - Do you dispense medicine (antibiotics) without prescription? Do you also prescribe medicine (antibiotics)?
> - On an average day, how many customers ask for an antibiotic without presenting a valid prescription?
> - On an average day, how many customers do you dispense antibiotics to?
> - Are you ALWAYS aware of the indication for using the antibiotics dispensed?
> - What is the most common reason that your patients provide when they ask for an antibiotic without a prescription? *(Don't have time go to doctor? Don't have money for doctor fee? Do they only believe/trust you or your advice? Do they confidence themselves on their illnesses/diagnosis?)*
> - What is the antibiotic mostly dispensed in your pharmacy without a prescription?
> - How often do you suggest a change to the antibiotic that the patient has asked for?

Antibiotics

Dispensing practices without prescription

- *[If their role includes dispensing without prescription ask this question] Can* you describe the **most recent case in which you dispensed antibiotics without a prescription?** *Listen carefully to which of the below mentioned topics are raised, and relate to these in follow-up questions accordingly. Note: not all questions (those not bolded) need to be covered.*
- What aspects of this case resulted in your decision to prescribe antibiotics? In other words, **which considerations did you make** prior to your decision to prescribe antibiotics?

> *In cases when the clinical presentation/status of the patient is considered in the dispensing decision: (e.g. signs and symptoms, additional diagnostic information, clinical history)*
> - Was the clinical presentation clear?
>   Is the clinical presentation often (also) clear in other cases?
>   Are there any patient groups in which the clinical presentation is often less clear?
> - Do you find proper diagnosing difficult if the clinical presentation is ambiguous or not clear?
> - Did you have any information about the infective agent (culture result) at the time of dispensing?
>
> In the described case, **what information did you obtain from the patient?**
> - How did you feel about the quality of the information in this case? Was this consistent with your opinion more generally?

*In case of **influence of the patient, family and/or staff** on the dispensing decision: (if this did not appear from the case description, inquire about any occurrence of influence of the patient, family and/or staff more generally, and ask for an example if applicable).*

- Which preferences for medicines were expressed by patients, family and/or staff? Are such preferences expressed more frequently?
- To what extent did these preferences concur with the treatment you would have proposed? Do they (also) concur in other cases?
- Do you experience it as 'difficult' to handle the preferences of patients, family and/or staff? Why do/don't you experience this as 'difficult'? In which situations in particular?
- Does the duration or quality of the pharmacist-patient relationship affect the way preferences of patients and family are dealt with? And how so?

In case other factors appeared to be involved in the dispensing decision: (e.g. the risk of development of antibiotic resistance, organizational factors (time pressure, staff shortage, drug shortages, staff turnover, presence/availability of diagnostic resources, financial considerations).

Thoroughly question how and why these factors were considered

- In retrospect, do you feel that **dispensing antibiotics** was the right decision in this case?

- Can you explain this? Why do you feel this was (not) a good decision?

In case treatment effectiveness supported the feeling that dispensing antibiotics was the right decision:

- What is your understanding of a 'good/appropriate' dispensing of antibiotics?

(Based on evidence, a formulary, routine, experience, observed effectiveness, etc.)

- Are there any factors that encourage you to dispense antibiotics without a prescription?

(e.g patient's pressure, unavailability of guidelines, unclear on the diagnosis, shortage of other drugs, excessive pharmaceuticals advertisement etc..)

- So far, we discussed situations in which antibiotics were dispensed without a prescription. Can you also describe the **most recent case [with an infection] in which you did not dispense antibiotics without a prescription?**

- Why did you decide not to dispense antibiotics?
- Can you describe other situations in which you do not dispense antibiotics without a prescription?
- Are there any situations in which you find it difficult not to dispense antibiotics without a prescription? Can you describe these situations? Why do you experience it as difficult to not dispense antibiotics in these situations? (**e.g. pressure of family**, risk of negative outcome of infection etc.)

<u>Dispensing practices with prescription</u>

- Can you describe the **most recent case in which you dispensed antibiotics** with a prescription?

- Do you consider it important for information about the use of antibiotics to be conveyed to patients?
- On average, how much time do you spend in counselling each patient?
- Do you think this is sufficient for them?
- What are the most major points that you covered when you counsel patients about antibiotics?
- What are the most common side effects that patients complain about when they use antibiotics?

- In your opinion, what is the effect of selling antibiotics without a prescription on the overall patient's welfare in Nepal?
  If you believe that selling antibiotics without a prescription is a problem, what are the steps that you think need to be taken to limit or eliminate this practice? *(This question will only be asked to participants who indicated that dispensing antibiotics without a prescription constitute a negative effect on the patient's welfare)*

Antibiotic resistance

- Can you tell me something about the **occurrence of antibiotic resistance in this area?**
    - How often does it occur?
    - Do you believe there is an increase in antibiotic resistance? What are the causes? *(List the causes and note that some may be already pointed out in the conversation)*
    - According to you, how does the occurrence of antibiotic resistance in hospitals (public and private) compare to the occurrence in health centre/health post or the community?
    - In your opinion, how large is the resistance problem in the area? And how large in Nepal in general? *(Ask the questions comparing to public and private and level of health facilities with the reasons of increasing antibiotics resistance)*
    - Do you believe that you are well-aware of the developments with regard to antibiotic resistance? If not, why not?

- Do you, as a dispenser, **experience a personal responsibility for the emergence of antibiotic resistance** in the area? And in the community in general?
    - Who is/are also/more responsible for the emergence of antibiotic resistance?

Recommendation for appropriate use of antibiotics

- How do you describe the appropriate/inappropriate use of antibiotics?
    - Are you aware of a standard definition for appropriate antibiotics use available?
    - Are you aware of any guidelines/protocol for dispensing antibiotics? *(Ask if government distributes it)*
    - How do you update your knowledge on antibiotic use and dispensing practices? If not why not? *(If yes ask if this is a personal initiative or government's provision of training or other methods of updating knowledge)*
    - What are the main influences on inappropriate use of antibiotics – what do you think drives this? *(e.g. physicians, health workers, nurses, patients, family members, community people, drug companies, government, distributors etc.)*
    - What would be the possible intervention strategies for appropriate antibiotic use? *(e.g. possible solutions in controlling antibiotics inappropriate use and the roles of different actors)*

    (Possible strategies could be: increasing awareness among consumers, awareness and education of dispensers/pharmacists, changing prescription habits of doctors, easy return policy for nearly expired antibiotics, changing dispensers'/pharmacists' dispensing, redefining the role of dispensers/pharmacists, assessment of doctors and paramedics workload, analysis of dispensing practices, monitor prescribing and drug use as well as adverse drug reaction, develop/update standard treatment guidelines)

C. Topic List for “District Policymakers” Interviews

Instruction: The bold-printed topics represent the essential elements to be covered in the interview, the remaining questions in the boxes below the main topic question can be used as prompts and to raise follow-up questions.

[Instructions to interviewer are printed in italics]

Infectious diseases

- Can you tell me something about the **occurrence of infectious diseases** in residents of this area or this facility?
  Which types of infectious diseases occur most often?
  How often do they occur (in comparison with other diseases)?
  How does the occurrence of infectious diseases in this area/facility compare to the occurrence of infectious diseases in other areas/healthcare settings?

Antibiotic resistance

- Can you tell me something about the **occurrence of antibiotic resistance in this area/facility?**

  How often does it occur?
  Do you believe there is an increase in antibiotic resistance? What are the causes? *(List the causes and note that some may be already pointed out in the conversation)*
  According to you, how does the occurrence of antibiotic resistance in hospitals (public and private) compare to the occurrence in health centre/health post or the community?
  In your opinion, how large is the resistance problem in the area/health facility? And how large in Nepal in general? *(Ask the questions comparing to public and private and level of health facilities with the reasons of increasing antibiotics resistance)*
- Do you believe that you are well-aware of the developments with regard to antibiotic resistance? If not, why not?
- Do you, as a policy maker, **experience a personal responsibility for the emergence of antibiotic resistance** in the facility/area? And in the community in general?
  Who is/are also/more responsible for the emergence of antibiotic resistance?

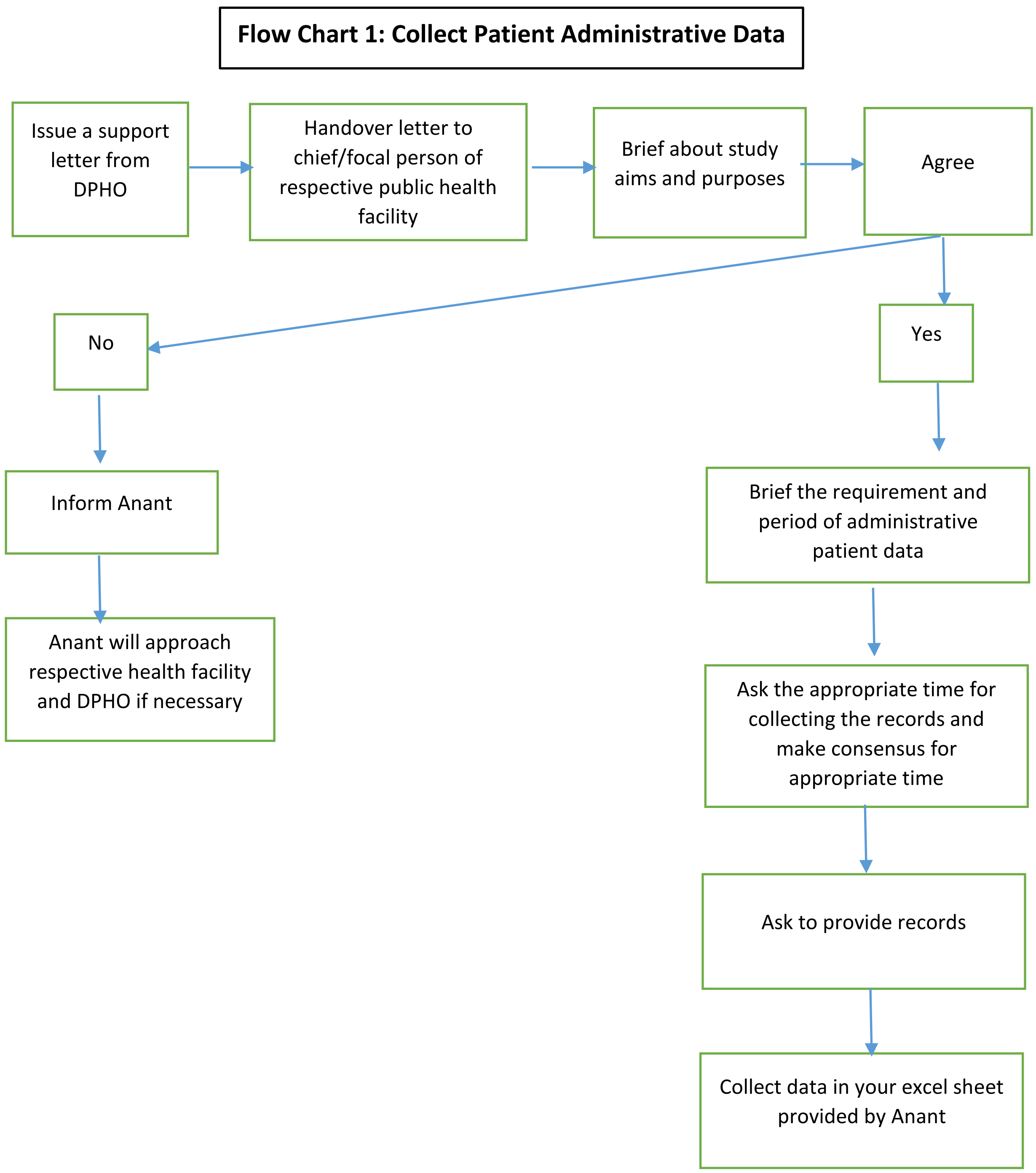
Current prescribing and dispensing behaviour

- Do you have contact with physician/health worker? *(for what purposes?)*
- How frequently do you have contact with them?
- When you have contact, what do you do? *(i.e. monitoring or observation or discussion?)*
- Do you think that physician/health worker currently prescribe or dispense appropriate antibiotic?
- Do you provide any suggestion in regards to antibiotic prescribing or dispensing decision?

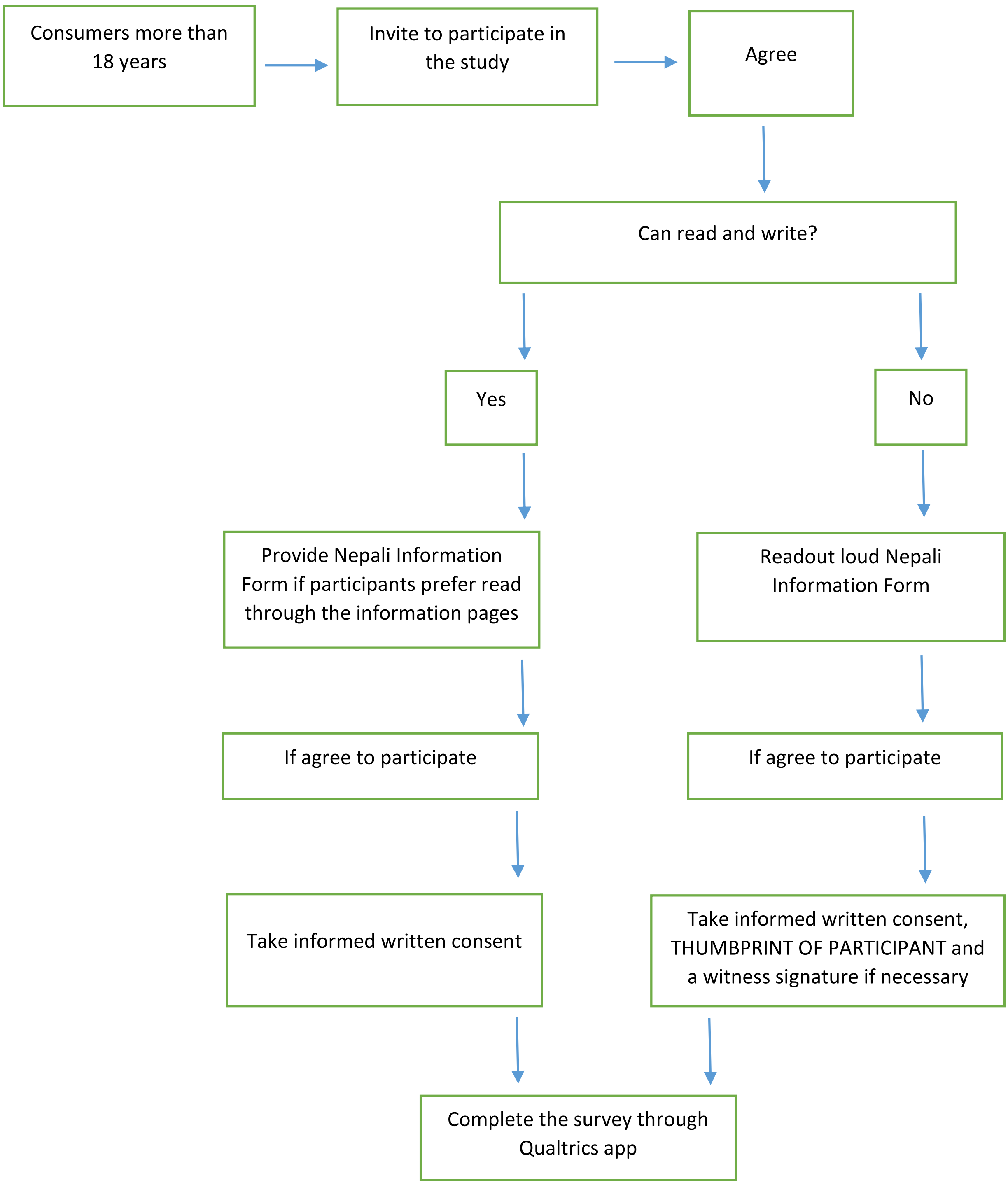
Recommendation for appropriate use of antibiotics

- What is your opinion on antibiotics using behavior in your district?
- What are the main influences on inappropriate use of antibiotics – what do you think drives this? *(e.g. physicians, health workers, nurses, patients, family members, community people, drug companies, government, distributors etc.)*
- What would be the possible intervention strategies for appropriate antibiotic use? *(e.g. possible solutions in controlling antibiotics inappropriate use and the roles of different actors)*

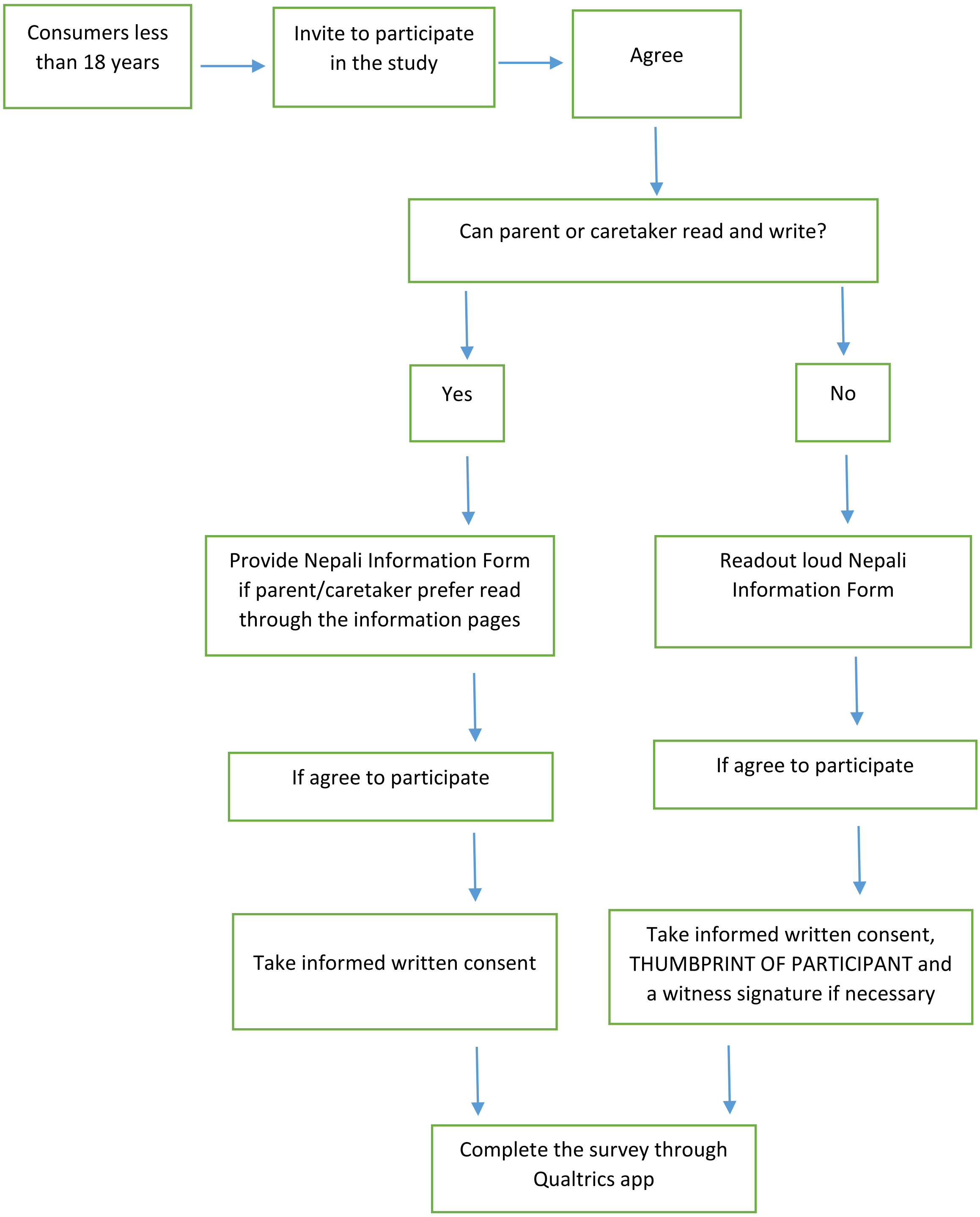
Appendix E Flow chart for recruitment of respondents and consent process



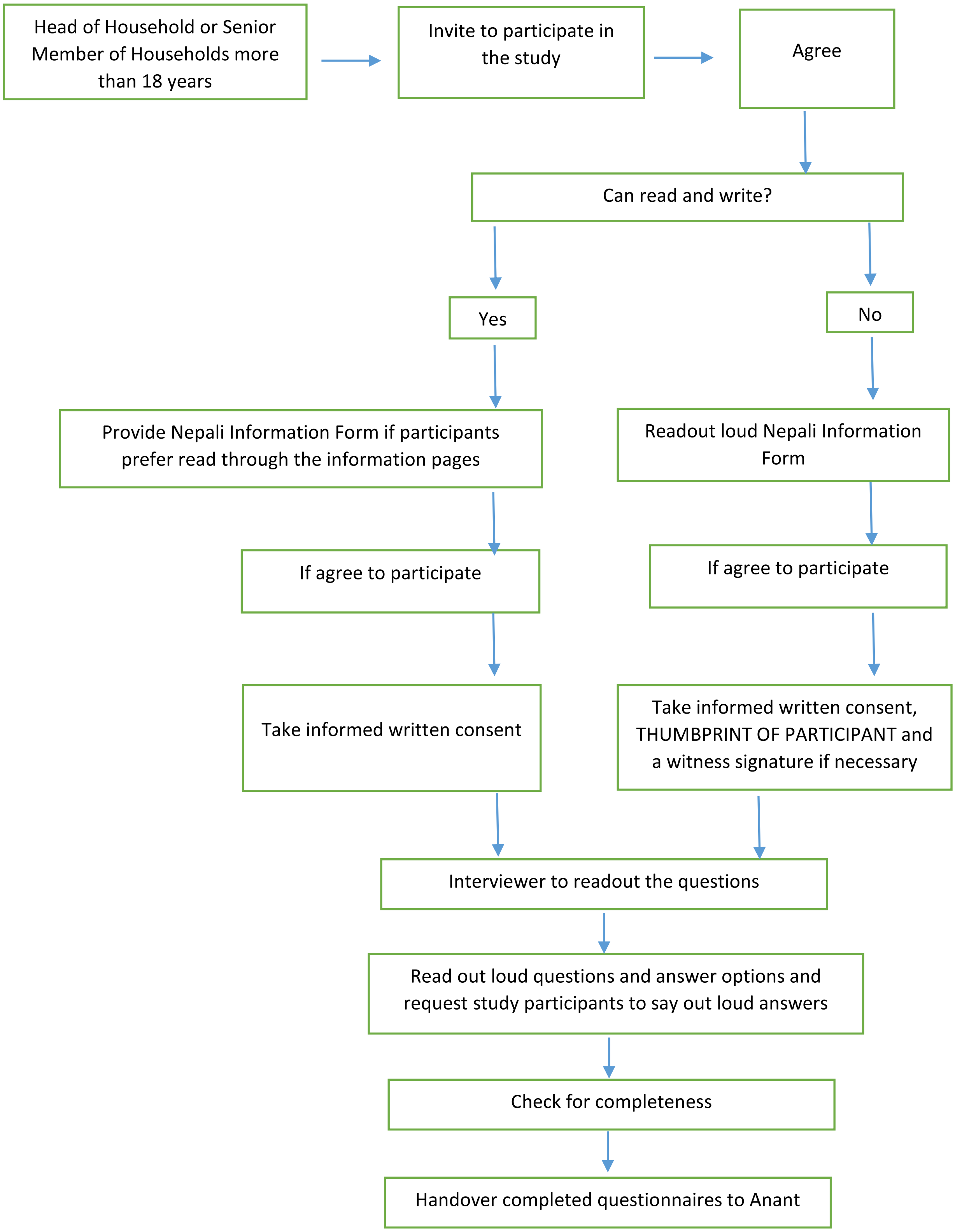
Flow Chart 2: Exit Interview with Consumers



Flow Chart 3: Exit Interview with Consumers



Flow Chart 4: KAP Survey



Appendix F Reliability coefficient of final KAP survey questionnaire

Knowledge

Case Processing Summary

		N	%
Cases	Valid	220	100.0
	Excluded[a]	0	.0
	Total	220	100.0

a. Listwise deletion based on all variables in the procedure.

Reliability Statistics

Cronbach's Alpha	N of Items
.627	12

Item Statistics

	Mean	Std. Deviation	N
amox	3.25	.618	220
R_paracetamol	3.71	.945	220
R_antacid	3.55	.877	220
anti_killgerm	3.98	.581	220
R_anti_coldflu	3.94	.904	220
R_anti_diarrhea	3.38	.965	220
R_anti_killgood	2.13	.628	220
R_anti_secondinf	2.35	.597	220
anti_allergic	3.63	.693	220
resis_anti_diffclt	3.72	.614	220
infect_incres_resist	3.74	.507	220
Misuse_antiresist	3.73	.616	220

Item-Total Statistics

	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted
amox	37.86	12.989	.367	.593
R_paracetamol	37.40	11.374	.430	.570
R_antacid	37.56	10.594	.638	.518
anti_killgerm	37.13	13.585	.253	.611
R_anti_coldflu	37.18	11.708	.401	.578
R_anti_diarrhea	37.73	11.220	.442	.566
R_anti_killgood	38.99	15.813	-.241	.684
R_anti_secondinf	38.76	16.601	-.401	.701
anti_allergic	37.48	13.100	.284	.605
resis_anti_diffclt	37.40	13.016	.364	.593
infect_incres_resist	37.37	13.276	.399	.593
Misuse_antiresist	37.38	13.150	.330	.599

Scale Statistics

Mean	Variance	Std. Deviation	N of Items
41.11	15.005	3.874	12

Attitude

Reliability Statistics

Cronbach's Alpha	N of Items
.647	8

Item Statistics

	Mean	Std. Deviation	N
cold_anti_prevnt	2.40	.938	220
fever_anti_better	2.99	1.029	220
R_anti_devlop_resis	2.34	.681	220
skip_dont_resis	3.38	.626	220
anti_safe_drg	1.95	.987	220
unsatis_not_anti	2.70	1.043	220
take_anit_notneed	2.38	.880	220
change_doc_nopres	3.85	.718	220

Item-Total Statistics

	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted
cold_anti_prevnt	19.58	9.807	.592	.540
fever_anti_better	18.99	10.561	.381	.605
R_anti_devlop_resis	19.64	12.369	.279	.631
skip_dont_resis	18.60	15.501	-.350	.734
anti_safe_drg	20.03	9.848	.540	.554
unsatis_not_anti	19.28	10.046	.459	.579
take_anit_notneed	19.60	10.853	.438	.589
change_doc_nopres	18.13	12.170	.296	.627

Scale Statistics

Mean	Variance	Std. Deviation	N of Items
21.98	14.168	3.764	8

Practice

Reliability Statistics

Cronbach's Alpha	N of Items
.666	6

Item Statistics

	Mean	Std. Deviation	N
feelbetter_stop_anti	1.63	1.105	218
getanti_pharmacy	1.94	.939	218
anti_sorethrt	2.94	.596	218
R_conslt_doc_beforanti	1.61	.678	218
R_chk_exp_anti	1.88	.811	218
use_anti_prophlx	2.10	.903	218

Item-Total Statistics

	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted
feelbetter_stop_anti	19.28	6.656	.593	.227
getanti_pharmacy	18.97	8.861	.271	.408
anti_sorethrt	17.98	11.156	-.063	.502
R_conslt_doc_beforanti	19.30	9.078	.421	.373
R_chk_exp_anti	19.03	9.875	.142	.456
use_anti_prophlx	18.82	11.367	-.152	.559

Scale Statistics

Mean	Variance	Std. Deviation	N of Items
20.91	11.260	3.356	10

Appendix G Ethics approval, Curtin University

Curtin University

Office of Research and Development

GPO Box U1987
Perth Western Australia 6845

Telephone +61 8 9266 7863
Facsimile +61 8 9266 3793
Web research.curtin.edu.au

23-Jun-2017

Name: Delia Hendrie
Department/School: Department of Health Policy and Management
Email: D.V.Hendrie@curtin.edu.au

Dear Delia Hendrie

RE: Ethics Office approval
Approval number: HRE2017-0394

Thank you for submitting your application to the Human Research Ethics Office for the project **Antibiotic use in the general population in Nepal and factors associated with prescribing practices**.

Your application was reviewed through the Curtin University Low risk review process.

The review outcome is: **Approved**.

Your proposal meets the requirements described in the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)*.

Approval is granted for a period of one year from **23-Jun-2017** to **22-Jun-2018**. Continuation of approval will be granted on an annual basis following submission of an annual report.

Personnel authorised to work on this project:

Name	Role
Hendrie, Delia	CI
Nepal, Anant Kumar	Student
Robinson, Suzanne	Supervisor
Selvey, Linda	Supervisor

Approved documents:

Document

Standard conditions of approval

1. Research must be conducted according to the approved proposal
2. Report in a timely manner anything that might warrant review of ethical approval of the project including:
   - proposed changes to the approved proposal or conduct of the study
   - unanticipated problems that might affect continued ethical acceptability of the project
   - major deviations from the approved proposal and/or regulatory guidelines
   - serious adverse events
3. Amendments to the proposal must be approved by the Human Research Ethics Office before they are implemented (except where an amendment is undertaken to eliminate an immediate risk to participants)
4. An annual progress report must be submitted to the Human Research Ethics Office on or before the anniversary of approval and a completion report submitted on completion of the project
5. Personnel working on this project must be adequately qualified by education, training and experience for their role, or supervised
6. Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, that bears on this project
7. Changes to personnel working on this project must be reported to the Human Research Ethics Office
8. Data and primary materials must be retained and stored in accordance with the Western Australian University Sector Disposal Authority (WAUSDA) and the Curtin University Research Data and Primary Materials policy
9. Where practicable, results of the research should be made available to the research participants in a timely and clear manner
10. Unless prohibited by contractual obligations, results of the research should be disseminated in a manner that will allow public scrutiny; the Human Research Ethics Office must be informed of any constraints on publication
11. Approval is dependent upon ongoing compliance of the research with the Australian Code for the Responsible Conduct of Research, the National Statement on Ethical Conduct in Human Research, applicable legal requirements, and with Curtin University policies, procedures and governance requirements
12. The Human Research Ethics Office may conduct audits on a portion of approved projects.

Special Conditions of Approval

None

This letter constitutes low risk/negligible risk approval only. This project may not proceed until you have met all of the Curtin University research governance requirements.

Should you have any queries regarding consideration of your project, please contact the Ethics Support Officer for your faculty or the Ethics Office at hrec@curtin.edu.au or on 9266 2784.

Yours sincerely

[redacted]

Dr Catherine Gangell
Manager, Research Integrity

Appendix H Ethics approval, Nepal Health Research Council

Government of Nepal
Nepal Health Research Council (NHRC)

Ref. No.: 67.
20 July 2017

Mr. Ananta Kumar Nepal
Principal Investigator
Curtin University, Kent St,
Western Australia

Subject: Approval of research proposal entitled **Antibiotic use in the general population in Rupandehi district of Nepal and factors associated with prescribing practices**

Dear Mr. Nepal,

It is my pleasure to inform you that the above-mentioned proposal submitted on **14 June 2017(Reg.no. 189/2017** please use this Reg. No. during further correspondence) has been approved by NHRC Ethical Review Board on **19 July 2017**.

As per NHRC rules and regulations, the investigator has to strictly follow the protocol stipulated in the proposal. Any change in objective(s), problem statement, research question or hypothesis, methodology, implementation procedure, data management and budget that may be necessary in course of the implementation of the research proposal can only be made so and implemented after prior approval from this council. Thus, it is compulsory to submit the detail of such changes intended or desired with justification prior to actual change in the protocol before the expiration date of this approval. Expiration date of this approval is **June 2019.**

If the researcher requires transfer of the bio samples to other countries, the investigator should apply to the NHRC for the permission. The researchers will not be allowed to ship any raw/crude human biomaterial outside the country; only extracted and amplified samples can be taken to labs outside of Nepal for further study, as per the protocol submitted and approved by the NHRC. The remaining samples of the lab should be destroyed as per standard operating procedure, the process documented, and the NHRC informed.

Further, the researchers are directed to strictly abide by the National Ethical Guidelines published by NHRC during the implementation of their research proposal and submit progress report in between and full or summary report upon completion.

As per your research proposal, the research amount is **NRs 2,94,000.00** and accordingly the processing fee amount is **NRs 10,000.** It is acknowledged that the above mentioned processing fee has been received at NHRC.

If you have any queries, please feel free to contact the Ethical Review M & E section of NHRC.

Thanking you,

[redacted]

Dr. Anjani Kumar Jha
Executive Chairma

Appendix I Amended ethics approval, Curtin University

Curtin University

Office of Research and Development

GPO Box U1987
Perth Western Australia 6845

Telephone +61 8 9266 7863
Facsimile +61 8 9266 3793
Web research.curtin.edu.au

03-Aug-2017

Name: Delia Hendrie
Department/School: Department of Health Policy and Management
Email: D.V.Hendrie@curtin.edu.au

Dear Delia Hendrie

RE: Amendment approval
Approval number: HRE2017-0394

Thank you for submitting an amendment request to the Human Research Ethics Office for the project **Antibiotic use in the general population in Rupandehi district of Nepal and factors associated with prescribing practices**.

Your amendment request has been reviewed and the review outcome is: **Approved**

The amendment approval number is HRE2017-0394-01 approved on 03-Aug-2017.

The following amendments were approved:

Inclusion and specification of district name (Rupandehi) in the project title, aims and specific objectives, as recommended by the Nepal Health Research Council.

Any special conditions noted in the original approval letter still apply.

Standard conditions of approval

1. Research must be conducted according to the approved proposal
2. Report in a timely manner anything that might warrant review of ethical approval of the project including:
   - proposed changes to the approved proposal or conduct of the study
   - unanticipated problems that might affect continued ethical acceptability of the project
   - major deviations from the approved proposal and/or regulatory guidelines
   - serious adverse events
3. Amendments to the proposal must be approved by the Human Research Ethics Office before they are implemented (except where an amendment is undertaken to eliminate an immediate risk to participants)
4. An annual progress report must be submitted to the Human Research Ethics Office on or before the anniversary of approval and a completion report submitted on completion of the project
5. Personnel working on this project must be adequately qualified by education, training and experience for their role, or supervised
6. Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, that bears on this project

7. Changes to personnel working on this project must be reported to the Human Research Ethics Office
8. Data and primary materials must be retained and stored in accordance with the Western Australian University Sector Disposal Authority (WAUSDA) and the Curtin University Research Data and Primary Materials policy
9. Where practicable, results of the research should be made available to the research participants in a timely and clear manner
10. Unless prohibited by contractual obligations, results of the research should be disseminated in a manner that will allow public scrutiny; the Human Research Ethics Office must be informed of any constraints on publication
11. Ethics approval is dependent upon ongoing compliance of the research with the Australian Code for the Responsible Conduct of Research, the National Statement on Ethical Conduct in Human Research, applicable legal requirements, and with Curtin University policies, procedures and governance requirements
12. The Human Research Ethics Office may conduct audits on a portion of approved projects.

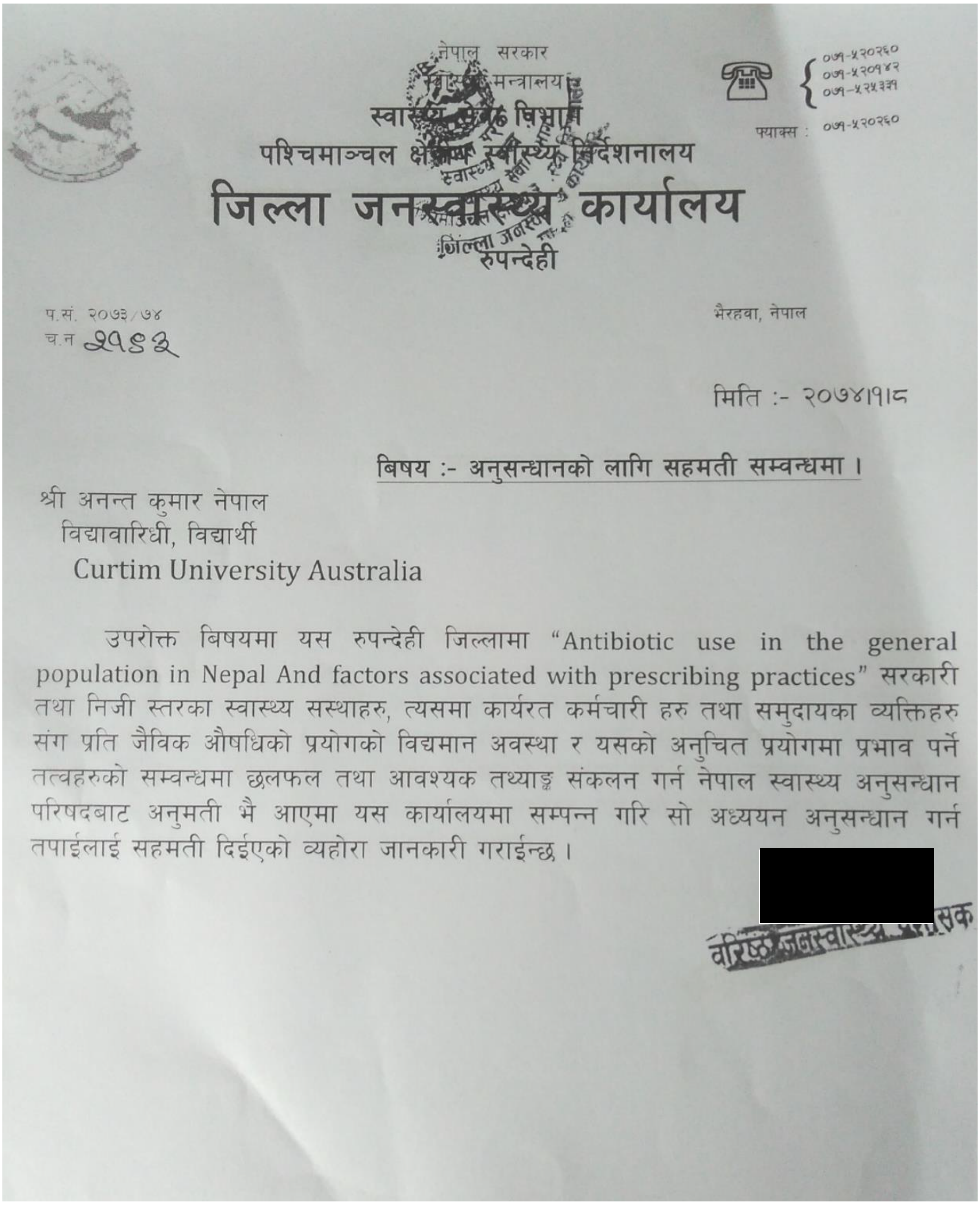
Should you have any queries regarding consideration of your project, please contact the Ethics Support Officer for your faculty or the Ethics Office at hrec@curtin.edu.au or on 9266 2784.

Yours sincerely

[redacted]

Amy Bowater
Acting Manager, Research Integrity

Appendix J Letter of permission, DPHO



नेपाल सरकार
स्वास्थ्य मन्त्रालय
स्वास्थ्य सेवा विभाग
पश्चिमाञ्चल क्षेत्रीय स्वास्थ्य निर्देशनालय
जिल्ला जनस्वास्थ्य कार्यालय
रुपन्देही

☎ ०७१-५२०२६०, ०७१-५२०१४२, ०७१-५२५३३१
फ्याक्स : ०७१-५२०२६०

प.सं. २०७३/७४
च.न २१९३

भैरहवा, नेपाल

मिति :- २०७४।१।८

बिषय :- अनुसन्धानको लागि सहमती सम्वन्धमा ।

श्री अनन्त कुमार नेपाल
विद्यावारिधी, विद्यार्थी
Curtim University Australia

उपरोक्त बिषयमा यस रुपन्देही जिल्लामा "Antibiotic use in the general population in Nepal And factors associated with prescribing practices" सरकारी तथा निजी स्तरका स्वास्थ्य सस्थाहरु, त्यसमा कार्यरत कर्मचारी हरु तथा समुदायका व्यक्तिहरु संग प्रति जैविक औषधिको प्रयोगको विद्यमान अवस्था र यसको अनुचित प्रयोगमा प्रभाव पर्ने तत्वहरुको सम्वन्धमा छलफल तथा आवश्यक तथ्याङ्क संकलन गर्न नेपाल स्वास्थ्य अनुसन्धान परिषदबाट अनुमती भै आएमा यस कार्यालयमा सम्पन्न गरि सो अध्ययन अनुसन्धान गर्न तपाईलाई सहमती दिईएको व्यहोरा जानकारी गराईन्छ ।

[redacted]

वरिष्ठ जनस्वास्थ्य प्रशासक

Appendix K Confidentiality agreement for research assistant

This confidentially agreement is for Research Assistants who will be assisting in data collection for the research entitled "Antibiotic use in the general population in Rupandehi district of Nepal and factors associated with prescribing practices".

Name of Student Researcher: Anant Kumar Nepal
Name of Supervisor: Dr. Delia Hendrie
Name of Organization: Curtin University of Technology, Western Australia
Title of Research: Antibiotic use in the general population in Rupandehi district of Nepal and factors associated with prescribing practices

Introduction:
My name is Anant Kumar Nepal. I am studying PhD in Public Health in Curtin University of Technology, Australia. My supervisor is Dr. Delia Hendrie. We are doing a research on "Antibiotic use in the general population in Rupandehi district of Nepal and factors associated with prescribing practices". In this study, we will be collecting administrative patient data from public health facilities, exit interviews of consumers from private pharmacies, household survey on knowledge, attitudes and practices of the general population related to antibiotic use, and key informant interviews with doctors and allied health professionals working in the public and private sectors. This survey will take place about six months from August 2017.

We want you to be part of this research as a Research Assistant. Your responsibility as a Research Assistant include the following:

☐ Collect administrative patient data from public health facilities

☐ Conduct exit interviews of consumers from private pharmacies

☐ Conduct household survey on knowledge, attitudes and practices of the general population related to antibiotic use of general population

The information collected from health facilities and/or shared with us by the research participants is confidential. This includes excel sheet of administrative patient data collected from health facilities, obtained data including any notes/pictures through Qualtrics survey and data obtained from households survey. In addition, those who share this information with us, as research participants should remain anonymous.

Before we ask you to take this responsibility and your agreement, we must obtain your explicit consent for the following:

☐ I will not reveal any of the content

☐ I will not reveal identities of the participants (women, men or any other)

☐ I will keep any copies of the information nor allow third party to access them

☐ I will delete interviews or any other relevant files from my computers/accessories after handover files to student researcher.

If you agree to these conditions, please provide your signature below:

Research Assistant's Signature: ___________________________

Research Assistant Name and Citizenship No: ________________________________

Date: ________________________________

Signature of Principal Investigator: _________________________________

Name of Principle Investigator: ________________________________

Appendix L Consent form

HREC Project Number:	HRE2017-0394-01
Project Title:	Antibiotic use in the general population in Rupandehi district of Nepal and factors associated with prescribing practices
Chief Investigator:	Dr. Delia Hendrie, Senior Lecturer, School of Public Health Curtin University of Technology, WA
Student researcher:	Mr. Anant Kumar Nepal
Version Number:	2
Version Date:	23/JUL/2017

- I have read/had read to me in my first language, the information statement version listed above and I understand its contents.
- I believe I understand the purpose, extent and possible risks of my involvement in this project.
- I voluntarily consent to take part in this research project.
- I have had an opportunity to ask questions and I am satisfied with the answers I have received.
- I understand that this project has been approved by Curtin University Human Research Ethics Committee and will be carried out in line with the National Statement on Ethical Conduct in Human Research (2007).
- I understand I will receive a copy of this Information Statement and Consent Form.

Participant Name	
Participant Signature	
Date	

Declaration by researcher: I have supplied an Information Letter and Consent Form to the participant who has signed/verbally agreed above, and believe that they understand the purpose, extent and possible risks of their involvement in this project.

Researcher Name	
Researcher Signature	
Date	

CONSENT TICK BOXES

☐ I do	☐ I do not	consent to being audio-recorded

☐ I do	☐ I do not	consent to medicines being photographed

☐ I do	☐ I do not	consent to the storage and use of my information in future ethically-approved research projects related to this project

Appendix M Paper 1

THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Analysis of patterns of antibiotic prescribing in public health facilities in Nepal

Anant Nepal[1], Delia Hendrie[1], Suzanne Robinson[1], Linda A Selvey[2]

[1] *School of Public Health, Faculty of Health Sciences, Curtin University, Bentley, Perth Western Australia, Australia*
[2] *School of Public Health, The University of Queensland, Herston Rd, Queensland, Australia*

Abstract

Introduction: Inappropriate use of antibiotics is recognised as a leading cause of antibiotic resistance. Little is known about antibiotic prescribing practices at public health facilities in low- and middle-income countries. We examined patterns of antibiotic prescribing in public health facilities in Nepal and explored factors influencing these practices.
Methodology: A cross-sectional study of antibiotic prescribing in public health facilities was conducted in the Rupandehi district of Nepal. Six public health facilities were selected based on WHO guidelines, and data were extracted from administrative records for 6,860 patient encounters. Patterns of antibiotic prescribing were investigated using descriptive statistics. Chi-squared tests and logistic regressions were applied to explore factors associated with antibiotic prescribing.
Results: Of patients attending public health facilities, the proportion prescribed at least one antibiotic (44.7%) was approximately twice the WHO recommended value (20.0 to 26.8%). The antibiotic prescribing rate for hospital inpatients (64.6%) was higher than for other facilities, with the prescribing rate also high in primary health care centres (50.4%) and health posts (52.2%). The most frequently (29.9%) prescribed antibiotic classes were third-generation cephalosporins. Females ($p = 0.005$) and younger ($p < 0.001$) patients were more likely to be prescribed antibiotics. High prescribing rates of antibiotics for selected diseases appeared contrary to international recommendations.
Conclusion: Antibiotic prescribing in public health facilities was high compared with WHO guidelines, suggesting the need for strategies to reduce misuse of antibiotics. This study provides useful information to assist in formulating policies and guidelines to promote more appropriate use of antibiotics in Nepal.

Key words: antibiotic use; antibiotic prescribing; antibiotic resistance; public health facility; Nepal.

J Infect Dev Ctries 2020; 14(1):18-27. doi:10.3855/jidc.11817

(Received 04 July 2019 – Accepted 03 October 2019)

Introduction

Increasing bacterial resistance to antibiotics is a serious threat to health care systems globally [1,2]. Antibiotic resistance occurs when bacteria change in some way that reduce the effectiveness of drugs or other agents designed to cure or prevent infections [3]. Inappropriate antibiotic use is an important contributor as it clearly drives the evolution of resistance [4]. Studies conducted worldwide have shown that antibiotics are frequently used inappropriately [5-7]. In the United States and Canada, 30 to 50% of antibiotic prescription is inappropriate [8,9]. Similarly, in some Asian and African nations, 50% of antibiotic use has been identified as inappropriate [7].

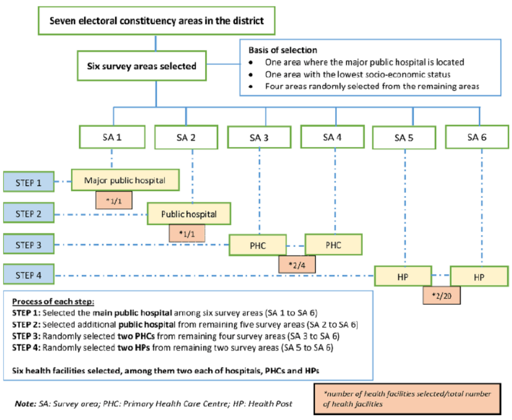
The definition of inappropriate antibiotic prescribing varies between studies [10], making comparisons difficult. A common indicator is the prescription of an antibiotic that is not recommended in prescribing guidelines. As sufficient information about patients' conditions is often unavailable, the World Health Organization (WHO) proposed a standard measure of "*percentage of encounters with an antibiotic prescribed*" in order to assess inappropriate prescribing [11,12]. This measure has been used widely to assess the quality of antibiotic prescribing in health care delivery. However, this proportion is likely to vary according to the mix of presentations to health care. Monitoring the use of antibiotics in countries, assessing factors that promote the inappropriate use of antibiotics and developing effective interventions are important in slowing the pace of resistance development [2,13].

Antibiotics are commonly prescribed and frequently used to treat infections [14]. A substantial amount of antibiotic overuse is likely driven by over diagnosis of certain conditions, particularly when the clinical picture of viral or bacterial aetiology is similar [15]. In developing countries, other factors contributing to the excessive use of antibiotics include inadequate patient education, limited diagnostic facilities, the availability of antimicrobials that can be purchased without a prescription, and lack of appropriate drug regulatory mechanisms [16]. A strong policy together with strict guidelines, access to diagnostic tests and training about diagnosis and appropriate treatment are factors likely to promote more appropriate use of antibiotics [7].

In Nepal, guidelines for the treatment of childhood illnesses, malaria, tuberculosis, leprosy and human immunodeficiency virus (HIV) infection [17] exist. The antibiotics recommended in the guidelines for those conditions are supplied through the government health system. Similarly, the Government of Nepal has also formulated the National Antibiotic Treatment Guidelines 2014 [18], however not all antibiotics listed in the guidelines are currently supplied through the government system. Thus, public health facilities have limited choices of antibiotics for different diseases. Furthermore, strict regulation and enforcement of appropriate antibiotic prescribing is lacking in the Nepalese health system, thus facilitating failure to follow the guidelines by prescribers. Similarly, several reports have suggested high [19-21] and increasing [22] prevalence of antibiotic resistance in Nepal.

Assessments of drug use within public health care facilities in Nepal have been conducted in individual studies [23,24]. However, these surveys have not assessed appropriate antibiotic use across all levels of health care facilities. In the public health system in Nepal, primary health care services are provided at district level through health posts, primary health care centres and district hospitals, and secondary and tertiary care is provided by zonal/regional hospitals and specialized tertiary facilities [25,26]. Prescribing is conducted by physicians and non-physicians such as health assistants (post-secondary training in diagnostics and therapeutics), nurses and other paramedics [27]. The physicians work at hospitals and the non-physicians, who are referred to as health workers, mainly work at primary health care centres and health posts. Authorities for prescribing drugs and training differ among the prescribers [28], thus their prescribing patterns need to be monitored regularly [29]. In addition to differences between prescribers, drug choice may be influenced by patients, health facilities and other factors [30]. The present study examined the patterns of antibiotic prescribing across different types of public health facilities in Nepal and explored factors influencing these practices.

Figure 1. Flow chart of selection of public health facilities.



Methodology

Selection of health facilities

A cross-sectional study was conducted in the Rupandehi district of Nepal. Public health facilities were selected based on WHO guidelines [31,32]. These guidelines provide a systematic method for assessing the pharmaceutical situation, medicine prices and availability at the country, regional and facility levels. Based on these guidelines, six survey areas were selected from the seven electoral areas in the district. As in the guidelines, the district in which the major hospital is located was selected as one survey area and an area with the lowest socio-economic status as another survey area. An additional four survey areas were randomly selected. One public health facility was selected from each survey area using a list obtained from available records of the District Public Health Office. Six public health facilities were selected, two each of hospitals, primary health care centres and health posts, with the major hospital included as one of the hospitals (Figure 1).

Data collection

Administrative records for a single encounter of outpatients (outpatients of general medicine at hospitals and all from other health facilities), inpatients and emergency department patients irrespective of patient age and diagnosis were collected between July 2017 and December 2017 using a standardised data collection tool. Data extracted from the administrative records, which were paper-based, included patient's sex, age, diagnosis and prescribed medicines. To select the administrative records, data for the most recent year (Nepali year 2073) was divided into four main climate seasons [33]. Data for the middle week of each season was extracted for each site. If any public holidays were observed in the sampled week, these days were replaced with records of days following the end of the week.

To ensure confidentially, patients' names were not recorded, but the record indexing system used by the health facilities were adapted in generating codes that allowed only the research team to be able to link the extracted records with the source data. Once information for each patient had been checked twice by the principal researcher (AN), the indexing system was de-coded so that the extracted data could not be re-identified.

The principal researcher coordinated data collection and approached respective authorities and health facilities to obtain approval to collect the data, and research assistants were engaged in data collection. A training session for research assistants was held prior to embarking on data collection and focused on the aim of the study, quality in the data collection and ethical considerations. The research assistants were regularly monitored by the principal researcher to ensure the quality of the data through observation at the study sites and cross-checking of the extracted records.

Table 1. Patient characteristics and prescribing indicators.

Variables	Percentage	n_j/n_k[a,b]
Medicine prescribed		
Yes	81.4	5582/6860
No or uncertain	18.6	1278/6860
Sex		
Male	41.3	2833/6859
Female	58.7	4026/6859
Age group		
Less than 5 years	5.2	360/6860
5 to 14 years	14.5	992/6860
15 to 24 years	20.1	1376/6860
25 to 44 years	29.9	2050/6860
45 to 64 years	18.7	1282/6860
65 and above years	11.7	800/6860
Type and department of health facility		
Inpatient hospital	12.6	865/6860
Ambulatory hospital	28.1	1928/6860
Emergency department hospital	29.9	2052/6860
Primary health centre	13.8	950/6860
Health post	15.5	1065/6860
Disease and conditions		
Fever/pyrexia	9.9	681/6860
Cellulitis/boils/impetigo/dermatitis/wound/skin infection/abscess	6.0	413/6860
Falls/injury	5.9	406/6860
Abdominal pain/nausea/vomiting/dyspepsia	5.7	388/6860
ARI/URTI/LRTI/respiratory infection/chest infection/bronchitis	4.9	337/6860
Diarrhoea/dysentery/AGE/loose motion	4.7	321/6860
Mental problem/anxiety/SOB/depression	4.7	319/6860
APD/gastritis/peptic ulcer	3.1	216/6860
Headache/migraine/TTH	3.0	204/6860
Snake bite	2.9	202/6860
Other	49.2	3373/6860
Prescribing indicator		
Percentage of patients prescribed an antibiotic	44.7	3064/6860
Number of antibiotics prescribed[c]		
Uncertain or none	55.3	3796/6860
One antibiotic	35.7	2452/6860
Two antibiotics	8.4	578/6860
Three antibiotics	0.5	32/6860
Four antibiotics	0.03	2/6860

[a]n_j numerator; [b]n_k denominator; [c]denominator for calculation of percentages is number of patient records collected.
Note: ARI: Acute respiratory tract infection, URTI: Upper respiratory tract Infection, LRTI: Lower respiratory tract infection, AGE: Acute gastroenteritis, SOB: Shortness of breath, APD: Acid peptic disease, TTH: Tension-type headache.

The study was approved by the Human Research Ethics Committee, Curtin University (HRE2017-0394) and the ethics committee of the Nepal Health Research Council (Reg no.189/2017). Permission for collecting the required administrative information of patient from public health facilities was obtained from the District Public Health Office, Rupandehi, Nepal (2193/2016-17).

Data analysis

Data were entered into an Excel spreadsheet for cleaning. Nearly one-fifth of the records (18.6%) had no information about medicines prescribed or administered to patients. These records were classified as having 'uncertain or no prescription (none)'. Analysis was done using Statistical Package for Social Sciences (SPSS) software version 25 (IBM Analytics, Armonk, NY, USA).

The administrative records at public health facilities are populated using text fields. No additional records on provisional or final diagnoses are available, thus the recording of diagnosis in the administrative records was considered as a final diagnosis. Since the disease were often described based on symptoms, similar symptoms or conditions were grouped together.

Antibiotics were defined as antibacterial agents, including metronidazole, irrespective of formulation. A core prescribing indicator, "*the percentage of patients prescribed an antibiotic*" was computed in line with the WHO rational drug use methodology [34]. Antibiotics were grouped into classes based on the antibiotic's chemical structure or chemical class [35]. Frequency distributions of these classes were presented based on type of health facility.

Chi square tests were performed to examine the association between the prescribing of antibiotics for selected disease and conditions and explanatory variables including sex, age group, and type and department of health facility. Logistic regression was also used to examine factors associated with antibiotic prescribing for selected disease and conditions [36]. Selected disease and conditions included common ones for which a high number of antibiotics were prescribed, disease and conditions commonly needing antibiotics, and disease and conditions for which antibiotics are not expected to be prescribed for treatment. The significance level (α) was set at 0.05 for all statistical tests.

Results

Patient characteristics and prescribing indicators

In total 6,860 patient records were collected, with 1,278 (18.6%) records not having any information with regard to medicines, whether a prescribed or other medicine. Of these records, 5,582 (81.4%) had a record of medicines prescribed. Fifty-nine percent of patients were female. The highest number of records was for hospital emergency department presentations (29.9%) and hospital ambulatory visits (28.1%) with similar numbers for health post attendances (15.5%), primary health centre visits (13.8%) and hospital inpatient admissions (12.6%) (Table 1).

The most common presenting condition was pyrexia (9.9%). At least one antibiotic was prescribed in 3064 (44.7%) patient encounters, with more than one-third of patients (35.7%) prescribed one antibiotic and almost one in ten patients (8.9%) prescribed two or more antibiotics.

Antibiotic prescribing practices

Third-generation cephalosporins (29.9%) were the most commonly prescribed class of antibiotic, followed by penicillins (24.9%), quinolones (15.0%) and antiprotozoals (13.0%) (Table 2). Among antibiotics, the most commonly prescribed were ceftriaxone (22.9%), amoxicillin (16.6%), metronidazole (12.5%), ciprofloxacin (11.4%) and cotrimoxazole (7.2%).

Antibiotic prescribing was highest for hospital inpatients (64.6%) and lowest for hospital ambulatory (29.7%), with approximately half of patients visiting health posts (52.2%) and primary health care centres (50.4%) prescribed an antibiotic (Table 3). Conditions for which the antibiotic prescribing rate was highest included pneumonia (85.5%), diarrhoea and related conditions (83.2%), respiratory infections (72.4%), chronic obstructive pulmonary disease (COPD) (68.4%), pyrexia (66.1%), colds, sinusitis and rhinitis (65.3%), snake bites (64.4%) and coughs (63.1%).

The class of antibiotics prescribed varied by health facility and department. Third-generation cephalosporins were the most common antibiotics prescribed for patients presenting at emergency departments and hospital inpatients (56.8% and 49.2%, respectively), whereas penicillins (46.5%) and quinolones (23.1%) were most commonly prescribed in primary health centres. In health posts, prescribing rates of sulfonamides (28.8%), penicillins (26.0%) and quinolones (21.1%) were almost similar.

Third-generation cephalosporins were the most commonly prescribed antibiotic for the treatment of pneumonia (28.6%), COPD (41.0%), fever (40.2%), snake bite (88.6%) and abdominal pain including nausea, vomiting and dyspepsia (62.2%). Penicillins were also often prescribed for the treatment of pneumonia (27.0%) and were the most commonly used antibiotic for respiratory tract infections (43.9%), common colds (41.4%), coughs (48.6%), skin infections (56.2%), and falls and injuries (71.5%). For skin diseases and diarrhoeal cases, sulfoanmides (41.9%) and antiprotozals (57.6%) were the most commonly prescribed antibiotics respectively.

Factors associated with antibiotic prescribing for selected disease and conditions

Across all disease and conditions, antibiotic prescribing was significantly associated with sex, age group and type of facility/department (Table 4). Males were more likely to receive antibiotics than females ($p = 0.005$), patients less than 5 years were more likely than all other age groups to receive antibiotics ($p < 0.001$) and inpatients were more likely to receive antibiotics than other hospital patients and those attending primary health care facilities and health posts ($p < 0.001$).

Factors associated with antibiotic prescribing varied by condition (Supplementary Tables 1-4). The only condition for which the antibiotic prescribing rate differed between males and females was common colds, with males less likely to be prescribed antibiotics than females ($p = 0.023$).

Antibiotic prescribing was significantly associated with age group for several conditions. Older age groups were less likely than children less than 15 years old to receive antibiotics for skin infections ($p < 0.05$), respiratory infections ($p < 0.05$) and skin diseases ($p < 0.01$). Similarly, younger patients were less likely to receive antibiotics for diarrhoea ($p = 0.015$) and COPD ($p = 0.001$). In contrast, patients aged 45 years and above age were less likely to receive antibiotics for snake bite than those less than 25 years old ($p < 0.05$).

Table 2. Commonly prescribed antibiotics by class and name.

SN	Prescribed antibiotic's name and classes	Total no	Total share (%)	Total share within class (%)	Total share (%)
1	**Penicillins**	**926**	**24.9**		
	Amoxicillin	618		66.7	16.6
	Ampicillin	112		12.1	3.0
	Cloxacillin	65		7.0	1.8
	Amoxicillin Clavulanate	35		3.8	0.9
	Other	96		10.4	2.6
2	**Tetracyclines**	**58**	**1.6**		
	Doxycycline	47		81.0	1.3
	Other	11		19.0	0.3
3	**Cephalosporins**	**1111**	**29.9**		
	Ceftriaxone	851		76.6	22.9
	Cefixime	143		12.9	3.9
	Cefpodoxime	60		5.4	1.6
	Other	57		5.1	1.5
4	**Quinolones**	**557**	**15.0**		
	Ciprofloxacin	424		76.1	11.4
	Levofloxacin	120		21.5	3.2
	Other	13		2.3	0.4
5	**Macrolides**	**171**	**4.6**		
	Azithromycin	163		95.3	4.4
	Other	8		4.7	0.2
6	**Sulfonamides**	**267**	**7.2**		
	Cotrimoxazole	267		100.0	7.2
	Other	0		0.0	0.0
7	**Antiprotozoal**	**484**	**13.0**		
	Metronidazole	465		96.1	12.5
	Other	19		3.9	0.5
8	**Others**	**138**	**3.7**		
	Amikacin	62		45.3	1.7
	Fluconazole	49		35.8	1.3
	Other	27		19.0	0.7
	Total	**3712**	100.0		100.0

Table 3. Descriptive analysis of prescriptions and prescribed classes of antibiotic by types and department of health facility and selected diseases and conditions.

Variables	Antibiotic prescribed (n=6860)		Classes of antibiotic prescribed (%) (n = 3712)							
	Yes, n (%)	Uncertain or none, n (%)	Penicillins	Tetracyclines	Cephalosporins	Quinolones	Macrolides	Sulfonamides	Antiprotozoal	Others
Types and department of health facility										
All	3064 (44.7)	3796 (52.2)	24.9	1.6	29.9	15.0	4.6	7.2	13.0	3.7
Inpatient hospital	559 (64.6)	306 (35.4)	14.0	1.1	49.2	13.4	1.9	0.0	12.8	7.6
Ambulatory hospital	572 (29.7)	1365 (70.3)	46.5	0.8	10.0	14.2	8.9	5.2	11.4	3.2
Emergency hospital	898 (43.8)	1154 (56.2)	15.9	0.0	56.8	9.5	2.2	0.0	13.7	2.0
Primary Health Centre	479 (50.4)	471 (49.6)	33.8	1.3	1.1	23.1	10.2	12.0	15.5	3.1
Health Post	556 (52.2)	509 (47.8)	26.0	6.3	0.2	21.1	3.3	28.8	11.6	2.7
Selected disease and conditions										
Pneumonia	46 (85.5)	6 (11.5)	27.0	0.0	28.6	14.3	6.3	15.9	1.6	6.3
Diarrhoea/dysentery/AGE/loose motion	267 (83.2)	54 (16.8)	1.7	1.2	20.0	16.5	0.5	2.2	57.6	0.2
ARI/URTI/LRTI/respiratory infection/ chest infection/bronchitis	244 (72.4)	93 (27.6)	43.9	2.7	9.8	8.2	14.5	19.2	0.8	0.8
COPD	128 (68.4)	59 (31.6)	19.7	1.1	41.0	24.2	9.0	2.2	2.2	0.6
Fever/pyrexia/PUO/FUO	450 (66.1)	231 (33.9)	23.7	1.1	40.2	19.4	4.3	2.4	3.7	5.0
Common cold/sinusitis/rhinitis	66 (65.3)	35 (34.7)	41.4	5.7	1.4	7.1	8.6	31.4	4.3	0.0
Snake bite	130 (64.4)	72 (35.6)	11.4	0.0	88.6	0.0	0.0	0.0	0.0	0.0
Cough/dry cough/allergic cough	99 (63.1)	58 (36.9)	48.6	1.8	5.5	9.2	21.1	11.9	0.0	1.8
Cellulitis/boils/impetigo/dermatitis/wound/skin infection/abscess	201 (48.7)	212 (51.3)	56.2	0.5	2.4	7.1	3.3	25.2	2.4	2.9
Falls and injury/injury/cut injury	157 (38.7)	249 (61.3)	71.5	0.0	16.3	4.7	1.2	4.7	1.7	0.0
Abdominal pain/nausea/ vomiting/dyspepsia	143 (36.9)	245 (63.1)	1.6	0.5	62.2	5.9	1.6	0.0	28.1	0.0
Skin diseases/skin allergy/sunburn/allergy/itching	59 (30.7)	133 (69.3)	37.1	3.2	3.2	4.8	6.5	41.9	3.2	0.0
Other	1074 (31.4)	2349 (68.6)	19.7	2.1	31.8	19.6	3.3	4.5	12.0	7.1

AGE: Acute Gastroenteritis, ARI: Acute Respiratory Tract Infection, URTI: Upper Respiratory Tract Infection, LRTI: Lower Respiratory Tract Infection, COPD: Chronic Obstructive Pulmonary Disease, PUO: Pyrexia of Unknown Origin, FUO: Fever of Unknown Origin.

Antibiotic prescribing was also significantly associated with type of health facilities. Patients attending health posts and health centre were more likely to receive antibiotics for respiratory infections (p = 0.007) and coughs (p = 0.002) than those attending hospitals. On the other hand, patient attending health posts and health centre were less likely to receive antibiotics for fever (p = 0.025) and COPD (p = 0.024). Patients presenting at emergency department with snake bites were more likely to receive antibiotics than patients admitted to the hospitals (p < 0.001).

Discussion

Antibiotic prescribing and associated factors

The percentage of patients prescribed at least one antibiotic (44.7%) was approximately twice the WHO recommended value of 20.0 to 26.8% [11,12]. The antibiotic prescribing rate for inpatients (64.6%) was higher than for patients in other facilities. This would be expected given the relative severity of illness of inpatients. In primary health care centres and health posts approximately half of medicines prescribed were antibiotics, possibly indicating excessive and inappropriate prescribing of antibiotics. These facilities often lack laboratory services and can be run single-handedly by a health worker who, although untrained, is expected to provide the full spectrum of services [26]. While other studies have tended not to cover all types of public health facilities, our findings on antibiotic prescribing rates in specific health care settings are consistent with several other studies in low- and middle-income countries [36-39].

Despite female attendance in public health facilities being higher than male attendance, consistent with reports of Nepal's Ministry of Health and Population [40], females were less likely to be prescribed antibiotics than males. This contrasts with the findings of a systematic review conducted in 10 high-income countries, which found females to be more likely to receive antibiotics [41]. Being a younger age increased the possibility of an antibiotic being prescribed in our study, although this varied by disease and conditions. Younger patients visiting a public health facility for skin infection, respiratory infection, skin disease and snakebite were more likely to be prescribed an antibiotic than older patients. A reason for higher antibiotic prescribing for children may be because children tend to get more infections [42]. Also infectious diseases are the leading cause of child mortality in many developing countries [43], and this may influence prescribing decisions to err on the side of caution when unsure of the underlining cause of symptoms.

Findings in our study of high prescribing rates of antibiotics for selected diseases such as diarrhoeal cases and respiratory infections suggested possible overprescribing and appear contrary to international recommendations. The WHO guidelines recommend oral rehydration solution with other supplements for

Table 4. Factors associated with antibiotic prescribing (n=6860).

Variables	Antibiotic prescribing			Univariable analysis			Multiple logistic regression	
	Yes, n (%)	Uncertain or none, n (%)	χ^2 (p value)	n	OR (95% CI)	p value	OR (95% CI)	p value
Gender								
Male	1346 (47.5)	1487 (52.5)	15.753 (**< 0.001**)	2833	1	**< 0.001**	1	**0.005**
Female	1718 (42.7)	2308 (57.3)		4026	0.822 (0.747, 0.906)		0.863 (0.779, 0.956)	
Age group								
Less than 5 years	251 (69.7)	109 (30.3)	183.883 (**< 0.001**)	360	1		1	
5 to 14 years	538 (54.2)	454 (45.8)		992	0.515 (0.398, 0.666)	**< 0.001**	0.568 (0.435, 0.740)	**< 0.001**
15 to 24 years	549 (39.9)	827 (60.1)		1376	0.288 (0.225, 0.370)	**< 0.001**	0.293 (0.227, 0.379)	**< 0.001**
25 to 44 years	791 (38.6)	1259 (61.4)		2050	0.273 (0.214, 0.347)	**< 0.001**	0.298 (0.232, 0.382)	**< 0.001**
45 to 64 years	537 (41.9)	745 (58.1)		1282	0.313 (0.244, 0.402)	**< 0.001**	0.328 (0.253, 0.425)	**< 0.001**
65 and above	398 (49.8)	402 (50.3)		800	0.430 (0.330, 0.560)	**< 0.001**	0.481 (0.366, 0.631)	**< 0.001**
Type and department of health facility								
Inpatient hospital	559 (64.4)	306 (35.4)	352.791 (**< 0.001**)	865	1		1	
Ambulatory hospital	572 (29.7)	1356 (70.3)		1928	0.231 (0.195, 0.274)	**< 0.001**	0.218 (0.183, 0.259)	**< 0.001**
Emergency hospital	898 (43.8)	1154 (56.2)		2052	0.426 (0.361, 0.502)	**< 0.001**	0.416 (0.352, 0.492)	**< 0.001**
Primary Health Centre	479 (50.4)	471 (49.6)		950	0.557 (0.461, 0.672)	**< 0.001**	0.507 (0.417, 0.615)	**< 0.001**
Health Post	556 (52.2)	509 (47.8)		1065	0.598 (0.497, 0.719)	**< 0.001**	0.582 (0.482, 0.703)	**< 0.001**

OR: Odds ratio; CI: Confident intervals.

non-bloody diarrhoea [44] and home care without antibiotics for children with respiratory symptoms [45].

Antibiotics usage patterns

Third-generation cephalosporins, penicillins and quinolones were the most frequently prescribed antibiotic classes, similar to findings of studies conducted in Pakistan [12], Saudi Arabia [46], Turkey [47] and Jordan [48]. Many hospitals in high-income countries also use large amounts of the cephalosporin class of antibiotics across a wide variety of infections. Their undoubted popularity relies upon lesser allergenic and toxicity risks as well as a broad spectrum of activity [49], although guidelines including in Nepal do not recommend cephalosporins as a first-line treatment for some indications [18]. Guidelines advise that cephalosporins should be avoided as a first-line treatment, when a narrower spectrum antibiotic would be effective because they increase the risk of *Clostridioides difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA) and other resistant infections [49,50]. Countries, and even individual hospitals, where cephalasporins are used more often have been shown to experience higher rates of multidrug resistant organisms, although determining if these rates result from the higher use specifically of cephalosporin antibiotics rather than all antibiotic classes is difficult [49].

Policy implications

Levels of antibiotic prescribing above the WHO recommended rate suggest the need to implement measures to reduce potential overprescribing. Diagnostic uncertainty is a likely factor contributing to the high prescribing rate of antibiotics, particularly at primary health care centres and health posts. Almost half of primary health care centres in Nepal do not have physicians or laboratory technicians [26], and initiatives to fill these positions could improve prescribing practices. The patient-provider relationship may also impact on prescribing [51]. The expectation of patient is also a crucial factor for antibiotic prescribing and providers often prescribe antibiotics to meet their expectation [52]. With primary health care centres mostly located in the villages and these populations geographically isolated [53], few other options for treatment are available. Providers and community members are known to each other and providers may be under pressure to prescribe antibiotics [39,51,54]. A targeted intervention to provide education and training to physicians and health workers about antimicrobial resistance and prescribing antibiotics only when they are necessary, together with initiatives to monitor antimicrobial prescribing, could promote more appropriate prescribing behaviours.

Additionally, the relatively high prescribing rate of third-generation cephalosporins and quinolones in public facilities in Nepal is of concern, given that third-generation cephalosporins and quinolones are considered second-line antibiotics in most guidelines. When antibiotic therapy is necessary, the use of narrow-spectrum antibiotics should be used as first-line treatment whenever possible [55] to avoid drug-resistant bacteria developing. Therefore, any educational interventions to reduce inappropriate prescribing of antibiotics in unwarranted situations should also include education and training on the proper selection of antibiotics.

Strength and limitations

A strength of this study was the collection of data relating to antibiotic use across all levels of public health facilities, including hospitals, primary health care centres and health posts. At hospitals, data were separately collected for inpatients, patients attending ambulatory care clinics and those presenting at emergency departments. This enabled comparisons to be made across different levels of the public health system, and provides baseline evidence against which initiatives to improve antibiotic prescribing practices can be monitored. However, the study has several limitations. Almost one-fifth of records had no prescription information, and a medicine may have been prescribed but not recoded or a medicine may not have been prescribed at all. These cases were recorded as ‘uncertain or no prescription’. Also many recorded diagnoses were non-specific, and coded as symptoms. These cases were grouped into broad categories together with related conditions. Having such broad categories made it difficult to assess appropriate use of antibiotics. It also prevented any investigation of whether antibiotic prescribing followed the standard guidelines.

Conclusion

Current patterns of antibiotic use in public health facilities in Nepal, especially in primary health care facilities, were found to be high compared with WHO guidelines. To prevent overuse and misuse of antibiotics, antimicrobial stewardship programmes should be adopted in public health facilities in Nepal. Given the lack of data on antibiotic use in public health facilities in Nepal, the information gained from this study will help in formulating policies and guidelines to improve antibiotic use in public health facilities and limit the spread of antibiotic resistance. The findings may also be applicable to other low- and middle-income countries where the health system is similar to Nepal.

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Author contributions
Anant Nepal (AN) designed the study with input from Delia Hendrie (DH), Suzanne Robinson (SR) and Linda Selvey (LS). AN conducted the research including the analysis. DH conducted the coding check. AN drafted the manuscript and DH edited the manuscripts. All authors contributed to revisions and approved the final manuscript.

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Supplementary Table 1. Factors associated with antibiotic prescribing for selected diseases and conditions.

Variables	Diarrhoea (n = 321)						Falls and injuries (n = 406)						Abdominal pain (n = 388)					
	Univariable analysis			Multiple logistic regression			Univariable analysis			Multiple logistic regression			Univariable analysis			Multiple logistic regression		
	Yes, n (%)	Uncertain or none, n (%)	χ^2 (p value)	n	OR (95% CI)	p value	Yes, n (%)	Uncertain or none, n (%)	χ^2 (p value)	n	OR (95% CI)	p value	Yes, n (%)	Uncertain or none, n (%)	χ^2 (p value)	n	OR (95% CI)	p value
Gender																		
Male	103 (78.6)	28 (21.4)	3.277 (0.070)	131	0.700 (0.379, 1.292)	0.254	101 (40.9)	146 (59.1)	1.312 (0.252)	247	1	0.223	67 (38.7)	106 (61.3)	0.470 (0.493)	173	1	0.372
Female	164 (86.3)	26 (13.7)		190	1		56 (35.2)	103 (64.8)		159	0.772 (0.509, 1.170)		76 (35.3)	139 (64.7)		215	0.823 (0.536, 1.263)	
Age group																		
Less than 15 years	50 (68.5)	23 (31.5)		73	0.398 (0.189, 0.837)	**0.015**	42 (36.5)	73 (63.5)		115	0.699 (0.403, 1.212)	0.202	20 (32.3)	42 (67.7)		62	1	
15 to 44 years	134 (89.9)	15 (10.1)	16.140 (**< 0.001**)	149	1.573 (0.730, 3.390)	0.247	70 (37.2)	118 (62.8)	1.481 (0.477)	188	0.739 (0.451, 1.210)	0.229	93 (40.1)	139 (59.9)	2.590 (0.274)	232	1.407 (0.761, 2.601)	0.276
45 and above	83 (83.8)	16 (16.2)		99	1		45 (43.7)	58 (56.3)		103	1		30 (31.9)	64 (68.1)		94	0.910 (0.451, 1.836)	0.792
Type of health facilities																		
All hospital	170 (82.5)	36 (17.5)	0.175 (0.675)	206	0.754 (0.395, 1.440)	0.392	133 (37.6)	221 (62.4)	1.408 (0.235)	354	0.689 (0.381, 1.246)	0.218	134 (38.3)	216 (61.7)	3.140 (0.076)	350	1	0.077
Health post and health centre	97 (82.1)	18 (17.9)		115	1		24 (46.2)	28 (53.8)		52	1		9 (23.7)	29 (76.3)		38	0.490 (0.222, 1.081)	

OR: Odds ratio; CI: Confident intervals. Note: The following different conditions had included in the group for analysis: **Diarrhoea**: Diarrhoea/dysentery/AGE/loose motion; **Fall and Injuries**: Falls and injury/injury/cut injury; **Abdominal pain**: Abdominal pain/nausea/vomiting/dyspepsia.

Supplementary Table 2. Factors associated with antibiotic prescribing for selected diseases and conditions.

Variables	Skin Infection (n = 413)						Fever (n = 681)						ARI (n = 337)					
	Univariable analysis			Multiple logistic regression			Univariable analysis			Multiple logistic regression			Univariable analysis			Multiple logistic regression		
	Yes, n (%)	Uncertain or none, n (%)	χ^2 (p value)	n	OR (95% CI)	p value	Yes, n (%)	Uncertain or none, n (%)	χ^2 (p value)	n	OR (95% CI)	p value	Yes, n (%)	Uncertain or none, n (%)	χ^2 (p value)	n	OR (95% CI)	p value
Gender																		
Male	107 (50.7)	104 (49.3)	0.720 (0.396)	211	1	0.530	212 (66.5)	107 (33.5)	0.038 (0.845)	319	0.992 (0.718, 1.369)	0.959	121 (74.2)	42 (25.8)	0.529 (0.467)	163	1	0.494
Female	94 (46.5)	108 (53.5)		202	0.881 (0.593, 1.308)		238 (65.7)	124 (34.3)		362	1		123 (70.7)	51 (29.3)		174	0.841 (0.512, 1.381)	
Age group																		
Less than 15 years	111 (58.7)	78 (41.3)		189	1		176 (69.3)	78 (30.7)		254	1		83 (82.2)	18 (17.8)		101	1	
15 to 44 years	56 (37.6)	93 (62.4)	15.321 (**< 0.001**)	149	0.428 (0.275, 0.665)	**< 0.001**	163 (63.2)	95 (36.8)	2.150 (0.341)	258	0.753 (0.519, 1.092)	0.135	95 (66.4)	48 (33.6)	7.476 (**0.024**)	143	0.437 (0.233, 0.817)	**0.009**
45 and above	34 (45.3)	41 (54.7)		75	0.586 (0.342, 1.005)	0.052	111 (65.7)	58 (34.3)		169	0.828 (0.546, 1.258)	0.377	66 (71.0)	27 (29.0)		93	0.464 (0.231, 0.930)	**0.030**
Type of health facilities																		
All hospital	100 (50.3)	99 (49.7)	0.385 (0.535)	199	1	0.766	338 (68.6)	155 (31.4)	4.902 (**0.027**)	493	1	**0.025**	91 (65.0)	49 (35.0)	6.570 (**0.010**)	140	0.503 (0.304, 0.830)	**0.007**
Health post and health centre	101 (47.2)	113 (52.8)		214	0.942 (0.634, 1.399)		112 (59.6)	76 (40.4)		188	0.671 (0.473, 0.951)		153 (77.7)	44 (22.3)		197	1	

OR: Odds ratio; CI: Confident intervals. Note: The following different conditions had included in the group for analysis: **Skin infection:** Cellulitis/boils/impetigo/dermatitis/wound/skin infection/abscess; **Fever:** Fever/pyrexia/PUO/FUO; **ARI**: ARI/URTI/LRTI/respiratory infection/chest infection/bronchitis.

Supplementary Table 3. Factors associated with antibiotic prescribing for selected diseases and conditions.

Variables	Cough (n = 157)						Skin diseases (n=192)						Common cold (n=101)					
	Univariable analysis			Multiple logistic regression			Univariable analysis			Multiple logistic regression			Univariable analysis			Multiple logistic regression		
	Yes, n (%)	Uncertain or none, n (%)	χ^2 (p value)	n	OR (95% CI)	p value	Yes, n (%)	Uncertain or none, n (%)	χ^2 (p value)	n	OR (95% CI)	p value	Yes, n (%)	Uncertain or none, n (%)	χ^2 (p value)	n	OR (95% CI)	p value
Gender																		
Male	39 (57.4)	29 (42.6)	1.676 (0.196)	68	0.592 (0.295, 1.189)	0.141	23 (29.5)	55 (70.5)	0.095 (0.758)	78	1	0.895	16 (50.0)	16 (50.0)	4.872 **(0.027)**	32	0.332 (0.128, 0.860)	**0.023**
Female	60 (67.4)	29 (32.6)		89	1		36 (31.6)	78 (68.4)		114	0.955 (0.482, 1.893)		50 (72.5)	19 (27.5)		69	1	
Age group																		
Less than 5 years 5 to 14 years 15 to 24 years	22 (71.0)	9 (29.0)	1.038 (0.595)	31	1		32 (56.1)	25 (43.9)	24.647 **(< 0.001)**	57	1		28 (73.7)	10 (26.3)	1.893 (0.388)	38	1	
25 to 44 years	41 (61.2)	26 (38.8)		67	0.507 (0.190, 1.351)	0.174	17 (19.3)	71 (80.7)		88	0.182 (0.086, 0.386)	**< 0.001**	25 (61.0)	16 (39.0)		41	0.415 (0.145, 1.182)	0.100
45 to 64 years 65 and above	36 (61.0)	23 (39.0)		59	0.536 (0.200, 1.435)	0.215	10 (21.3)	37 (78.7)		47	0.203 (0.083, 0.498)	**< 0.001**	13 (59.1)	9 (40.9)		22	0.491 (0.151, 1.594)	0.237
Type of health facilities																		
All hospital	41 (51.2)	39 (48.8)	9.762 (0.002)	80	0.335 (0.168, 0.667)	**0.002**	18 (30.5)	41 (69.5)	0.002 (0.965)	59	1	0.581	9 (50.0)	9 (50.0)	2.278 (0.131)	18	0.600 (0.199, 1.803)	0.363
Health post and health centre	58 (75.3)	19 (24.7)		77	1		41 (30.8)	92 (69.2)		133	0.817 (0.398, 1.676)		57 (68.7)	26 (31.3)		83	1	

OR: Odds ratio; CI: Confident intervals. Note: The following different conditions had included in the group for analysis: **Cough:** Cough/dry cough/allergic cough; **Skin diseases:** Skin diseases/skin allergy/sunburn/allergy/itching; **Common cold:** Common cold/sinusitis/rhinitis.

Supplementary Table 4. Factors associated with antibiotic prescribing for selected diseases and conditions.

Variables	COPD (n = 187)					
	Univariable analysis			Multiple logistic regression		
	Yes, n (%)	Uncertain or none, n (%)	χ^2 (p value)	n	OR (95% CI)	p value
Gender						
Male	58 (73.4)	21 (26.6)	1.564 (0.211)	79	1	0.209
Female	70 (64.8)	38 (35.2)		108	0.646 (0.327, 1.276)	
Age group						
Less than 65 years	39 (51.3)	37 (48.7)	17.404 **(< 0.001)**	76	0.287 (0.147, 0.559)	**< 0.001**
65 and above	89 (80.2)	22 (19.8)		111	1	
Type of health facilities						
All hospital	116 (73.0)	43 (27.0)	9.987 **(0.002)**	159	1	**0.024**
Health post and health centre	12 (42.9)	16 (57.1)		28	0.366 (0.153, 0.877)	

Variables	Snakebite (n = 202)					
	Univariable analysis			Multiple logistic regression		
	Yes, n (%)	Uncertain or none, n (%)	χ^2 (p value)	n	OR (95% CI)	p value
Gender						
Male	53 (68.8)	24 (31.2)	1.086 (0.297)	77	1	0.193
Female	77 (61.6)	48 (38.4)		125	0.644 (0.331, 1.250)	
Age group						
Less than 25 years	62 (68.9)	28 (31.1)	4.109 (0.128)	90	1	
25 to 44 years	50 (65.8)	26 (34.2)		76	0.848 (0.419, 1.718)	0.647
45 and above	18 (50.0)	18 (50.0)		36	0.399 (0.170, 0.935)	**0.035**
Type and department						
Hospital Inpatient	25 (39.1)	39 (60.9)	26.128 **(< 0.001)**	64	0.191 (0.100, 0.367)	**< 0.001**
Hospital Emergency	105 (76.1)	33 (23.9)		138	1	

OR: Odds ratio; CI: Confident intervals.

Appendix N Paper 2

Open access Original research

BMJ Open

Survey of the pattern of antibiotic dispensing in private pharmacies in Nepal

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ABSTRACT

Objectives Private pharmacies are widely established in most low/middle-income countries (LMICs) including Nepal, and are often considered as a patient's first point of contact for seeking healthcare. The aim of this study was to investigate the pattern of antibiotic dispensing in private pharmacies through exit interviews with patients to review their medication information.

Design and setting Cross-sectional study. Data collection was carried out in 60 days at 33 randomly selected private pharmacies in the Rupandehi district of Nepal.

Participants Patients attending private pharmacies (n=1537).

Main outcome measure The pattern of antibiotic prescribing and dispensing was investigated using WHO's core prescribing indicator, '*the percentage of patients prescribed an antibiotic*'. Frequency distributions were presented based on patients' characteristics, sources of antibiotic, registration status of pharmacies and education of the pharmacist or drug retailer, and disease or condition. χ^2 tests and regression analysis were applied to explore factors associated with the pattern of antibiotic dispensing.

Results Of patients attending private pharmacies, the proportion receiving at least one antibiotic (38.4%) was above the WHO recommended value (20.0%–26.8%). The most commonly dispensed antibiotics were cefixime (16.9%) and the third-generation cephalosporins (38.0%) class. High dispensing rates of antibiotics for selected conditions (eg, respiratory infections, diarrhoeal cases) appeared contrary to international recommendations. The percentage of antibiotic dispensed was highest for patients who obtained their medicines from unlicensed pharmacies (59.1%). Young people were more likely to receive antibiotics than other age groups.

Conclusions The antibiotic dispensing pattern from private pharmacies in Nepal was high compared with WHO guidelines, suggesting initiatives to reduce inappropriate use of antibiotics should be implemented. The findings of this study may be generalisable to other LMICs in order to assist in developing policies and guidelines to promote more appropriate dispensing and prescribing practices of antibiotics and limit the spread of antibiotic resistance.

Strengths and limitations of this study

- ► This is the first study to investigate the pattern of antibiotic dispensing in private pharmacies in Nepal.
- ► Data on dispensing of medications including antibiotics were sourced directly from patients and validated from the dispensed medicines.
- ► Data were collected from a wide range of private pharmacies including high-end outlets staffed by pharmacists and small outlets staffed by drug retailers without formal health qualifications.
- ► Exit interviews were based on convenience sampling with interviews conducted between 09:00 and 17:00, thus may not be representative of all patients attending private pharmacies.
- ► Description of diagnoses or conditions by patients were symptom-based rather than disease-specific, which made it difficult to assess appropriate use of antibiotics and whether antibiotic dispensing and prescribing followed the standard guidelines.

INTRODUCTION

The role of the private sector in healthcare in low/middle-income countries (LMICs) has often been neglected by governments and international public health communities.[1] However, private pharmacies are widely established in most LMICs, and usually considered as a patient's first point of contact for healthcare and the preferred channel through which to get health services and medicines.[2] These pharmacies range from high-end outlets to small, rural, road side stalls and can be staffed by fully trained pharmacists or a drug retailer or seller without formal health qualifications. Because of ease of access, more flexible opening hours, availability of cheaper medicines and credit[3] and personal intimacy,[4] consumers often tend to use private rather than public facilities.[5] Further, many patients have neither the time nor money to consult a physician[6] preferring over-the-counter medicines and healthcare advice. About three in four antibiotic requests and three in five consultations in community pharmacies around the world result in the sale of antibiotics without a prescription.[7]

Non-prescription use of antibiotics is associated with the risk of inappropriate drug use, defined as patients not receiving the appropriate medicines in doses that meet their individual requirements, for an adequate duration, and at the lowest cost.[8] Inappropriate use of medicines is a serious global problem occurring in both developed and developing countries,[9] with the WHO estimating more than half of all medicines are inappropriately prescribed, dispensed or sold.[8] This overuse and misuse of antibiotics is one of the main causes of antibiotics becoming ineffective,[10] thus posing problems relating to treatment failure and other costs to the individual and society.[11–13]

In Nepal, dispensing of medicines is undertaken by pharmacists and drug retailers or sellers and many dispensers have admitted treating patients too by also prescribing medicines.[14] Pharmacists have 3–5 years of pharmacy education[14]; however, drug retailers and sellers include individuals who are only associated with private pharmacies, do not necessarily have formal education in dispensing medicines, but can undertake training and obtain a licence to own and operate a pharmacy from the Department of Drug Administration (DDA), the government body dealing with medicines and their related affairs.[15 16] Practising healthcare without a license is illegal in Nepal[17]; however, many unlicensed pharmacies are also operating in remote areas of Nepal.[18] Little is known about the antibiotic dispensing practices from licensed or unlicensed private pharmacies in Nepal. Previous studies conducted in Nepal that have examined antibiotic dispensing practices from private pharmacies have collected data directly from pharmacists or drug sellers themselves,[18 19] which may result in inaccurate reporting of dispensing practices. This study has investigated patterns of antibiotic dispensing through exit interviews with patients by reviewing their medication information, thus ensuring collection of reliable information. The findings of this study reveal issues about inappropriate use of antibiotics and can be used as a baseline against which to evaluate initiatives to improve antibiotic dispensing and prescribing practices in the private pharmacy sector in Nepal.

METHODS

The study was a cross-sectional study conducted in the Rupandehi district of Nepal. This district was selected because it has an almost equal mix of urban and rural residents[20 21] and a well-represented population of different castes and ethnicities with >63 castes/ethnicities residing in the district[22] out of 126 castes/ethnicities in the country.[23] Within the district, there is varying access to transport, with good transport only available in urban areas, which is similar to other districts of Nepal.

Private pharmacies were selected based on WHO guidelines.[24 25] Before deciding on the private pharmacies, six survey areas were selected from the seven electoral areas in the district. The district in which the major hospital is located was selected as one survey area and an area with the lowest socioeconomic status as another survey area. An additional four survey areas were randomly selected. One public health facility was selected from each survey area using a list obtained from available records of the District Public Health Office. Altogether, six public health facilities were selected, two each from hospitals, primary healthcare centres and health posts, with the major hospital included as one of the hospitals (as per WHO guidelines). These health facilities were used as the basis for selecting the private pharmacies.

Private pharmacies to include in the study were selected from a list made available by the Nepal Chemists and Druggists Association (NCDA), Lumbini, Nepal. Separate pharmacies and pharmacies attached to private hospitals were included to represent both types. The NCDA list was verified after visiting each selected survey area and updated by deleting any duplicates in the list of pharmacies and adding any missing from the records. In total, 441 private pharmacies were in the NCDA list. Among them, 49 did not exist in the field while 31 were missing on the list. After adjusting the list for these pharmacies, 423 private pharmacies were included in the final list.

As outlined in the WHO guidelines, within each survey area, pharmacies on the final list were grouped according to whether they were located within or beyond 5 km from each selected public health facility. Within each group in every survey area, pharmacies were assigned a number and then selected for inclusion in the study using a random number generator, with three private facilities selected from the within the 5 km group and two selected from the >5 km group. Three private pharmacies were added to the original sample due to refusal of the initially selected pharmacies to allow data collection on the second day. Each pharmacy was surveyed for 2 days, other than the three that refused data to be collected on the second day and the three replacement pharmacies, which were surveyed for 1 day. Thus, data collection covered 60 days with 33 private pharmacies (2 days per pharmacy for 27 pharmacies and 1 day per pharmacy for 6 pharmacies).

Data collection

Private pharmacies in Nepal do not follow the practice of keeping patients' records, so exit interviews were conducted with patients who had attended the selected pharmacies. Interviews were conducted from July 2017 to December 2017 from 09:00 to 17:00. The days allocated for data collection were based on the advice of pharmacists to obtain as representative a sample of days as possible. Patients were invited to participate based on convenience sampling, with as many patients as possible who attended the selected pharmacies approached to participate. In total, 1554 patients were approached, with 15 (1%) patients refusing to participate and 1537 patients included in the study. Individuals obtaining medicines on behalf of another person were excluded from the exit interviews as they may not have been able to provide the relevant details about the patient or their condition. In contrast, parents have these details for their children so children attending the pharmacies with their parents were included in the survey.

Data were collected using the Qualtrics Offline Surveys Application.[26] Demographic characteristics of the patients for whom the medicines had been bought (age, sex), the disease or condition and sources of antibiotic[27] (self-medicated, recommended and supplied by a pharmacist or drug retailer without a prescription, prescribed by a doctor and dispensed by a pharmacist or drug retailer, other) were collected. Photographs were taken of the medicines, with no patient identifiers included, and attached to the application. The maximum time taken for the exit interview was 3 min. Prior to the interview, all consumers were informed of the nature of the study and written consent was sought to interviews being conducted. Consent for patients younger than 18 years was sought from the accompanying parent or caretaker.

The principal researcher coordinated data collection and approached respective authorities and health facilities to obtain approval to collect the data, and four Nepali research assistants were engaged in data collection. A training session for research assistants was held prior to embarking on data collection and focused on the aim of the study, the importance of ensuring quality in the data collection and ethical considerations. The research assistants were regularly monitored by the principal researcher to ensure the quality of the data through observation at the study sites and cross-checking of the entered records in the Qualtrics Application.

Data analysis

The data were imported from the Qualtrics Application to a MS-Excel spreadsheet for cleaning. The cleaned data were transferred to the SPSS statistical software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows V.25.0). Diseases or conditions collected from the interviews were generally described based on symptoms, thus similar symptoms were grouped together. For some analyses, the most commonly occurring groups (such as fever, respiratory symptoms and skin conditions) were separately analysed, with remaining groups combined into those likely to have an infectious cause ('other: infectious'), and those not likely to have an infectious cause ('other: non-infectious'). Antibiotics were also grouped into classes for analysis.[28] A core prescribing indicator, '*the percentage of patients prescribed an antibiotic*' was computed in line with the WHO's standard values.[29] Descriptive analysis was conducted to show commonly dispensed antibiotics, sources of antibiotic, registration status of pharmacies and education of the pharmacist or drug retailer, and disease or condition. χ^2 tests were performed to examine the association between antibiotic dispensing and explanatory variables including sex, age group of patient, sources of antibiotic and registration status of pharmacies and education status of the pharmacist or drug retailer. Logistic regression was also used to examine factors associated with antibiotic dispensing. An interaction term of sources of antibiotic with registration status and education was also examined. The significance level (α) was set at 0.05 for all statistical tests.

Patient and public involvement

No patients or public were involved in the design and conduct of the study.

RESULTS

Characteristics of patients and prescription information

The sample comprised a similar number of male and female respondents, with all age groups relatively well represented (table 1). Just over half of patients (55.2%) had a prescription from a doctor or health worker, with about one-quarter not having a prescription but purchasing a medicine recommended and supplied by the pharmacist. Almost equal numbers of patients received their medicine from a pharmacist who had a diploma or bachelor's degree in pharmacy (49.6%) and drug retailers who had completed training from DDA (46.1%). The most commonly occurring diseases or conditions were fevers (18.1%), coughs (5.3%) and respiratory infection (4.9%). At least one antibiotic was dispensed in 947 (38.4%) patient encounters.

Commonly dispensed antibiotics

Among antibiotics, the most commonly dispensed were cefixime (16.9%), amoxicillin (12.2%), cefpodoxime (10.3%), ampicillin + cloxacillin (8.7%) and ciprofloxacin (8.7%). Cephalosporins (38.0%) were the most commonly dispensed class of antibiotics, followed by penicillins (29.3%), quinolones (13.7%) and marcolides (8.1%) (table 2).

The percentage of antibiotics dispensed was highest for those patients for whom the medicine had been prescribed by a doctor or health worker (58%). It was also highest for patients who obtained their medicines from an unlicensed pharmacy (59.1%). For several conditions, antibiotics were the most commonly dispensed medicine, including for respiratory infection (93.3%), diarrhoea and dysentery (91.3%), skin infection (87.1%), fever (70.5%) and urinary tract infection (57.9%).

The class of antibiotics dispensed was relatively similar by sources of antibiotic and registration status and education. Third-generation cephalosporins were the most common class of antibiotics recommended and supplied by a pharmacist or drug retailer without a prescription (40.7%) and prescribed by a doctor or health worker (38.1%), with antiprotozoals the most common among patients who self-medicated (38.5%). Cephalosporins were also most commonly dispensed by both drug retailers who had training from DDA (41.3%) and those with a diploma or bachelors in pharmacy (36.1%). The highest dispensing rate of cephalosporins was for the treatment of fever (69.5%), whereas penicillins were common for respiratory infection (60.8%), injuries (78.8%) and skin infection (67.2%) (table 3).

Factors associated with antibiotic dispensing

Across all diseases and conditions, antibiotic dispensing was significantly associated with age group, sources of

Table 1 Patient characteristics and information related to dispensing of medicines

Variables	Percentage	n_i/n_k*†
Sex		
Male	50.5	776/1537
Female	49.5	761/1537
Age group of patient		
Less than 14 years	19.4	298/1537
15–24 years	20.2	310/1537
25–44 years	35.0	538/1537
45 and above years	25.4	391/1537
Sources of antibiotic		
Prescribed by a doctor or health worker and dispensed by a pharmacist or drug retailer	55.2	848/1537
Recommended and supplied by a pharmacist or drug retailer without a prescription	26.1	401/1537
Self-medicated	13.3	205/1537
Other (invalid prescription)	5.4	83/1537
Registration status/education		
Licensed/diploma or bachelors in pharmacy	49.6	762/1537
Licensed/training from DDA	46.1	709/1537
Unlicensed/education unknown	4.3	66/1537
Disease or condition‡		
Fever	18.1	278/1537
Cough	5.3	82/1537
Respiratory infection	4.9	75/1537
Headache	4.8	74/1537
Loss of appetite	4.7	72/1537
Skin infection	4.6	70/1537
Common cold	4.4	68/1537
Injury	4.4	67/1537
Acid peptic disease	4.3	66/1537
Body ache	4.2	65/1537
Heart disease	4.2	64/1537
Fungal infection	3.8	59/1537
Skin disease	3.7	57/1537
Abdominal discomfort	3.6	55/1537
Arthritis and bone pain	3.3	50/1537
Others	21.8	335/1537
Prescribing indicator		
Percentage of patients dispensed an antibiotic	38.4	590/1537
No of antibiotics dispensed		
No antibiotic	61.6	947/1537
One antibiotic	35.8	551/1537
Two antibiotics	2.5	39/1537

Continued

Table 1 Continued

Variables	Percentage	n_i/n_k*†

*n_i numerator.
†n_k denominator.
‡Diseases or conditions included: fever: fever and pyrexia. Cough: cough, dry cough and allergic cough. Respiratory infections: acute respiratory infection, respiratory infection, chest infection and bronchitis. Loss of appetite: weakness, anorexia and loss of appetite. Skin infections: boils, dermatitis, wound and skin infection. Common cold: common cold and sinusitis. Injury: injuries. Acid peptic disease: acid peptic diseases, gastritis, peptic ulcer and upper gastrointestinal bleeding. Body ache: body ache and backache. Heart disease: heart disease and hypertension. Fungal infection: fungal infection and ring worm. Skin disease: skin diseases and skin allergy. Abdominal discomfort: abdominal pain, nausea, vomiting and dyspepsia. Arthritis and bone pain: arthritis, joint pain, leg pain and shoulder pain.
DDA, Department of Drug Administration;

antibiotic, and registration status and education of pharmacists (table 4). Patients <15 years were more likely than all other age groups to receive antibiotics (p≤0.001). Those patients who attended a pharmacy without a prescription from a doctor or health worker were less likely to receive antibiotics than patients with a prescription (p≤0.001). In addition, patients were less likely to receive antibiotics from pharmacists who had a diploma or bachelors in pharmacy (p=0.001) compared with unlicensed drug retailers or licensed retailers with training from DDA only. The interaction term shows that patients who presented with no prescription were more likely to receive an antibiotic if they presented with no prescription to a pharmacy attended by a trained pharmacist.

DISCUSSION

In most developing countries, private pharmacies or drug stores are the first point of contact for people seeking healthcare.[2] Antibiotics (and other prescription medicines) are readily available with or without prescription, and self-medication by patients is common. Non-prescription use of antibiotics is associated with a risk of inappropriate use due both to failure in dispensing in accordance with clinical guidelines and patients not using the drug appropriately.[30] It is also one of the drivers of the emergence of antimicrobial resistance.[31]

Findings of this study show the overuse of antibiotics dispensed from private pharmacies, with the percentage of patients dispensed an antibiotic (38%) being considerably higher than the level recommended by the WHO (20%–26.8%).[29] This finding of overuse is consistent with studies conducted in private facilities in other LMICs including 43% in both India[32] and Uganda[33] and 53% in Bangladesh.[34]

Unlicensed pharmacies, especially outside of cities, often exist in LMICs.[35] These pharmacies sell medicines informally and are not legally recognised by the health system of the countries in which they operate.[36]

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Table 2 Commonly dispensed antibiotics

	Dispensed antibiotics	No	%		Dispensed antibiotic classes	No	%
1	Cefixime	106	16.9	1	Cephalosporins	239	38.0
2	Amoxicillin	77	12.2	2	Penicillins	184	29.3
3	Cefpodoxime	65	10.3	3	Quinolones	86	13.7
4	Ampicillin+cloxacillin	55	8.7	4	Marcolides	51	8.1
5	Ciprofloxacin	55	8.7	5	Antiprotozoal	50	7.9
6	Azithromycin	49	7.8	6	Others	19	3.0
7	Metronidazole	48	7.6		**Total**	**629**	**100**
8	Amoxicillin+clavulanate	31	4.9				
9	Cefadroxil	16	2.5				
10	Cephalexin	16	2.5				
11	Levofloxacin	14	2.2				
12	Ofloxacin	14	2.2				
13	Amoxicillin+cloxacillin	11	1.7				
14	Cefixime+clavulanic acid	11	1.7				
15	Other	61	9.7				
Total		**629**	**99.6**				

While, practicing healthcare without a license is illegal in Nepal,[17] weak regulatory oversight of the Nepalese health system encourages pharmacies to operate without licences. This study found the level of dispensing of antibiotics was higher by unlicensed drug retailers and drug retailers with limited training. Interestingly, the interaction term in the multivariable model suggests that, while this is the case, if patients presented to a pharmacy with a trained pharmacist without a prescription, they were more likely to receive antibiotics. It has been suggested that drug retailers may approach dispensing of medicines as any other sales job, not wanting a customer to leave without making a purchase.[35] More generally, inappropriate dispensing of antibiotics may occur due to the business motive of private pharmacies with profits from antibiotics contributing to total profit.[37]

Third-generation cephalosporins were the most common antibiotic type recommended and dispensed with or without prescription. The finding is consistent with the studies conducted in India showing cephalosporins were the most commonly supplied class of antibiotic in private pharmacies or clinics[32] and often used by urban private health facilities.[38] Guidelines often advise that cephalosporins should be avoided as a first-line treatment when a narrower spectrum antibiotic would be effective because they increase the risk of *Clostridium difficile, methicillin-resistant Staphylococcus aureus* and other resistant infections.[39 40] Noticeably, third-generation cephalosporins were dispensed to patients with minor symptoms, such as fever, which is self-limiting in most cases and could be a common symptom of several infections. The popularity of third-generation cephalosporins lies in their lesser allergenic and toxicity risks as well as having a broad spectrum of activity.[39] In Nepal, treatment guidelines do not recommend cephalosporins as a first-line treatment for several infections such as respiratory tract infections, enteric fever, pneumonia and urinary tract infections.[41]

Overprescribing and overuse of antibiotics in the treatment of respiratory infections and diarrhoea is a worldwide problem, potentially leading to widespread antimicrobial resistance.[42] Contrary to international recommendations, this study found high prescribing rates of antibiotics for both conditions, suggesting possible overprescribing. The WHO guidelines recommend oral rehydration solution with other supplements for non-bloody diarrhoea[43] and home care without antibiotics for children with respiratory symptoms.[44]

Across all conditions collectively, antibiotics were more likely to be dispensed to younger age groups especially <15 years of age compared with older groups. Respiratory diseases and diarrhoea impose a considerable health burden especially to children in LMICs,[45 46] and may lead to antibiotics being used more widely for the treatment of these diseases.[47 48] Higher self-medication practices among younger age groups could also be a factor contributing to higher antibiotic dispensing for younger age groups, with a study in Albania finding an association between self-medication and a higher use of antibiotics among younger age groups.[49] Additionally, increased education has been found to increase the risk of self-medication with antibiotics,[50] and globally the literacy rates of young adults is higher than the elderly, with the differences even wider in developing countries.[51]

Table 3 Descriptive analysis of dispensed classes of antibiotics by sources of antibiotic, registration status and education, and selected diseases and conditions

Variables	Antibiotics dispensed		Classes of antibiotics dispensed (%)					
	Yes=n (%)	No=n (%)	Cephalosporins=n (%)	Penicillins=n (%)	Quinolones=n (%)	Marcolides=n (%)	Antiprotozoal=n (%)	Others=n (%)
Sources of antibiotic								
Self-medicated	12 (4.2)	276 (95.8)	2 (15.4)	2 (15.4)	2 (15.4)	1 (7.7)	5 (38.5)	1 (7.7)
Recommended and supplied by a pharmacist or drug retailer without a prescription	86 (21.4)	315 (78.6)	35 (40.7)	14 (16.3)	12 (14.0)	8 (9.3)	14 (16.3)	3 (3.5)
Prescribed by a doctor or health worker and dispensed by a pharmacist or drug retailer	492 (58.0)	356 (42.0)	202 (38.1)	168 (31.7)	72 (13.6)	42 (7.9)	31 (5.8)	15 (2.8)
Registration status/education								
Licensed/diploma and bachelors in pharmacy	260 (34.1)	502 (65.9)	101 (36.1)	81 (28.9)	35 (12.5)	33 (11.8)	24 (8.6)	6 (2.1)
Licenced/training from DDA	291 (41.0)	418 (59.0)	128 (41.3)	90 (29.0)	39 (12.6)	16 (5.2)	26 (8.4)	11 (3.5)
Unlicensed/education unknown	39 (59.1)	27 (40.0)	10 (25.6)	13 (33.3)	12 (30.8)	2 (5.1)	0 (0.0)	2 (5.1)
Disease or condition*								
Respiratory infection	70 (93.3)	5 (6.7)	12 (16.2)	45 (60.8)	3 (4.1)	13 (17.6)	0 (0.0)	1 (1.4)
Diarrhoea and dysentery	42 (91.3)	4 (8.7)	4 (7.8)	0 (0.0)	10 (19.6)	0 (0.0)	37 (72.5)	0 (0.0)
Skin Infection	61 (87.1)	9 (12.9)	12 (19.7)	41 (67.2)	1 (1.6)	2 (3.3)	0 (0.0)	5 (8.2)
Fever	196 (70.5)	82 (29.5)	141 (69.5)	29 (14.3)	21 (10.3)	11 (5.4)	1 (0.5)	0 (0.0)
Urinary tract infection	22 (57.9)	16 (42.1)	1 (4.5)	0 (0.0)	18 (81.8)	0 (0.0)	0 (0.0)	3 (13.6)
Injury	33 (49.3)	34 (50.7)	4 (12.1)	26 (78.8)	2 (6.1)	1 (3.0)	0 (0.0)	0 (0.0)
Common cold	16 (23.5)	52 (76.5)	6 (37.5)	5 (31.3)	1 (6.3)	4 (25.0)	0 (0.0)	0 (0.0)
Abdominal discomfort	10 (18.2)	45 (81.8)	3 (27.3)	0 (0.0)	4 (36.4)	0 (0.0)	4 (36.4)	0 (0.0)
Skin disease	7 (12.3)	50 (87.7)	4 (57.1)	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)
Cough	7 (8.5)	75 (91.5)	4 (40.0)	1 (10.0)	0 (0.0)	5 (50.0)	0 (0.0)	0 (0.0)
Other: infectious	104 (49.5)	106 (50.5)	38 (32.2)	29 (24.6)	23 (19.5)	14 (11.9)	6 (5.1)	8 (6.8)
Other: non-infectious	22 (4.5)	469 (95.5)	10 (43.5)	6 (26.1)	3 (13.0)	1 (4.3)	2 (8.7)	1 (4.3)

*Diseases or conditions included: respiratory infection: acute respiratory infection, respiratory infection, chest infection and bronchitis. Diarrhoea and dysentery: diarrhoea, dysentery and loose motion. Skin infection: boils, dermatitis, wound and skin infection. Fever: fever and pyrexia. Injury: injuries. Common cold: common cold and sinusitis. Abdominal discomfort: abdominal pain, nausea, vomiting and dyspepsia. Skin disease: skin diseases and skin allergy. Cough: cough, dry cough and allergic cough. Other: infectious: likely to have an infectious cause. Other: non-infectious: not likely to have an infectious cause.
.DDA, Department of Drug Administration.

Table 4 Factors associated with antibiotic dispensing

Variables	Antibiotics dispensing: Yes=n (%)	Antibiotics dispensing: No=n (%)	Antibiotics dispensing: X^2 (p value)	Bivariable analysis: n	Bivariable analysis: OR (95% CI)	Bivariable analysis: P value	Multivariable analysis: OR (95% CI)	Multivariable analysis: P value
Sex								
Male	302 (38.9)	474 (61.1)	0.187 (0.666)	776	1	0.666	1	0.576
Female	288 (37.8)	473 (62.2)		761	0.956 (0.778 to 1.174)		0.934 (0.734 to 1.188)	
Age group of patient								
Less than 15 years	177 (59.4)	121 (40.6)	98.876 (<0.001)	298	1		1	
15–24 years	116 (37.4)	194 (62.6)		310	0.409 (0.295 to 0.566)	<0.001	0.464 (0.320 to 0.672)	<0.001
25–44 years	210 (39.0)	328 (61.0)		538	0.438 (0.328 to 0.584)	<0.001	0.432 (0.311 to 0.602)	<0.001
45 and above years	87 (22.3)	304 (77.7)		391	0.196 (0.140 to 0.273)	0.001	0.206 (0.142 to 0.299)	<0.001
Sources of antibiotic								
Recommended and supplied by a pharmacist or drug retailer without a prescription (includes self-medication)	98 (14.2)	591 (85.8)	308.278 (<0.001)	689	0.120 (0.093 to 0.155)	<0.001	0.087 (0.059 to 0.128)	<0.001
Prescribed by a doctor or health worker and dispensed by a pharmacist or drug retailer	492 (58.0)	356 (42.0)		848	1		1	
Registration status and education								
Licensed/diploma and bachelors in pharmacy	260 (34.1)	502 (65.9)	11.627 (0.001)	762	0.698 (0.568 to 0.859)	0.001	0.617 (0.465 to 0.819)	0.001
Licensed/training from DDA (Includes unlicensed)	330 (42.6)	445 (57.4)		775	1		1	
Interaction term with sources of antibiotic, and registration status and education							1.987 (1.177 to 3.354)	0.010

DDA, Department of Drug Administration.

Policy implications

Levels of antibiotic prescribing above the WHO recommended rate suggests the need to implement measures to reduce potential inappropriate use in Nepal. Almost half of patients were dispensed antibiotics by drug retailers who, unlike pharmacists are professionally trained and do not have formal education in dispensing medicines. While this study did not examine their technical competencies, drug retailers should be encouraged to increase their skills through continued professional education.

In Nepal, prescribing is conducted by physicians and non-physicians such as auxiliary health workers and health assistants, who have 18 months to 3years post-secondary training in diagnostics and therapeutics, and nurses.[52] The physicians work at hospitals and non-physicians, who are referred to as health workers, mostly work in public health facilities at the community level and have their own private pharmacies. Health workers are less qualified than physicians but are authorised to prescribe medicines as outlined in the antibiotic treatment guidelines.[41] However, such guidelines are barely in practice or monitored.[53] WHO's guideline of good pharmacy practices confines the role of pharmacists to dispensing only.[54] A general lack of enforcement of the legislation covering registration of pharmacies and the distribution of antibiotics facilitates the inappropriate use of antibiotics in Nepal. Stronger enforcement mechanisms of pharmacy registration and restricting pharmacists and drug retailers supplying antibiotics without prescription should be established.

Private pharmacies are widely established in most LMICs including Nepal. They are usually considered as a patient's first point of contact and preferred channel to receive health services[2] particularly given issues relating to the unavailability and inaccessibility of quality of care from public health facilities.[55] Private pharmacists and community members are often known to each other and pharmacists can be under pressure to supply antibiotics.[56] Pharmacists and drug retailers generally do not charge consultation fees and profits from selling drugs is a main source of their income,[57] which could encourage the selling of antibiotics since it is one of the more profitable medicines.[37] A targeted intervention to provide education and training relating to antimicrobial resistance and supplying antibiotics only with prescriptions will lead to greater consideration of antibiotic dispensing practices based on the standards of good pharmacy practices, thus contributing to a reduction in the risk of development of antibiotic resistance bacteria.

Additionally, the relatively high prescribing rate of third-generation cephalosporins in private health facilities in Nepal is of concern, given that these classes are considered second-line antibiotics in most guidelines. When antibiotic therapy is necessary, the use of narrow-spectrum antibiotics should be used as first-line treatment whenever possible[58] to prevent drug-resistant bacteria developing. Educational interventions to reduce inappropriate dispensing or prescribing of antibiotics in unwarranted situations should include guidance on the proper selection of antibiotics.

Strengths and limitations

Limited evidence is available in regard to the pattern of antibiotic dispensing in LMICs. This study has provided an evidence base about the current pattern of antibiotic dispensing from private pharmacies in Nepal, with data on dispensing of medications including antibiotics sourced directly from patients and validated from the dispensed medicines. Data on dispensed medicines were collected from a wide range of private pharmacies including high-end outlets staffed by pharmacists and small outlets staffed by someone without formal health qualifications. The information on dispensed medicines provides a useful baseline against which to measure the effectiveness of future policies and programmes to reduce the level of inappropriate dispensing of antibiotics. The findings of the study also reinforce calls to build a strong regulatory environment in advancing prudent antibiotic use. The findings may also be applicable to other LMICs, where the health system is similar to Nepal.

However, the study has several limitations. The study covered about 8% (33/423) of private pharmacies in the Rupandehi district. While the selection process followed WHO guidelines, these guidelines do not account for the number of facilities in the district, thus the sample of pharmacies selected may not be representative. Interviews were conducted between 09:00 and 17:00 at the selected pharmacies, which excludes patients attending the pharmacies at other times, and exit interviews were based on convenience sampling. Diagnoses or conditions of patients were non-specific and recorded based on the understanding of the patients. Description of diagnoses or conditions were more symptom-based and were grouped into broad categories together with related conditions. Having such broad categories made it difficult to assess appropriate use of antibiotics. It also prevented any investigation of whether antibiotic dispensing and prescribing followed the standard guidelines. Another limitation is that the Rupandehi district lies in a low-land region of Nepal, which has a greater availability of health services than in hill and high-hill regions. Results of the study are thus more generalisable to districts falling in low-land regions than hill and high-hill regions, a factor which needs to be considered in using findings from the study in developing and implementing policy to improve pharmacy practice in Nepal and similar countries.

CONCLUSION

This study documents antibiotic dispensing practices in private pharmacies in Nepal that were high compared with WHO guidelines. The overuse of antibiotics has been associated with a higher prevalence of antimicrobial resistance. Given global concerns about antimicrobial resistance, evidence relating to overuse and misuse in Nepal provides a rationale to consider introducing initiatives to reduce inappropriate use of antibiotics. Additionally, this evidence may be more widely generalisable to other countries with similar health system financing arrangements.

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Appendix O Paper 3

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Knowledge, attitudes and practices relating to antibiotic use among community members of the Rupandehi District in Nepal

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Abstract

Background: The development of antibiotic resistance is one of the biggest threats to global public health. Inappropriate use of antibiotics is recognised as a leading cause of antibiotic resistance. The aim of this study was to explore the knowledge, attitudes and practices (KAP) towards antibiotic use among adults in Nepal.

Methods: A quantitative survey was conducted with 220 community members of the Rupandehi district of Nepal, with cluster sampling techniques applied to select households. Interviews were carried out face-to-face using a structured questionnaire. Responses were presented using descriptive analysis, with chi-squared tests and regression analysis applied to identify factors associated with KAP about antibiotic use and the Spearman's rank order correlation coefficient calculated to examine the relationship between responses to the KAP questions.

Results: The sample comprised more females (54%) than males, the average age of respondents was 38.5 years and almost 60% of respondents lived in rural areas. Respondents had relatively good knowledge about aspects of antibiotic use other than identifying antibiotics. The concept of antibiotic resistance was well known but imperfectly understood. Half of respondents (50.9%) were unsure whether skipping doses would contribute to the development of antibiotic resistance, 88.2% indicated they would go to another doctor if not prescribed an antibiotic when they thought one was needed and nearly half (47.7%) believed antibiotics helped them get better more quickly if they had a fever. Most respondents reported correct practices accessing and using antibiotics, however, 84.6% at least sometimes preferred an antibiotic when they have a cough and sore throat.
Logistic regression showed respondents with higher levels of education tended to have better knowledge, more appropriate attitudes and better practices about antibiotic use. Rural respondents were less likely to have better knowledge about antibiotic use, while females were more likely to report better practices.

Conclusion: The study provides baseline evidence about the knowledge, attitudes and practices regarding antibiotic use among the population of the Rupandehl district. Its findings will be useful in designing effective and targeted interventions to decrease misconceptions about antibiotic use and to increase awareness about the risks of inappropriate use of antibiotics in the community.

Keywords: Antibiotic use, Antibiotic resistance, Knowledge, Attitudes, Practices, Nepal

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Background

Inappropriate use of antimicrobial agents and the consequences of spread of antimicrobial resistance is an increasing public health problem [1]. In recent years, resistance to antimicrobial agents that were previously effective has emerged or re-emerged in many regions causing a global health threat and economic consequences. Among many other factors, behaviours of community members and their limited knowledge associated with inappropriate antibiotics use [2, 3] is contributing to antibiotic resistance. A recent review found one-third (33.7%) of the population of low and middle income countries lack knowledge about antibiotics and their role [4]. A study conducted in Bhutan found unsatisfactory knowledge (52.8%) and practices (47%) on antibiotic use [5]. Similarly, more than one-third (36%) of people in Kuwait reported not completing the prescribed course of antibiotics and around 28% had self-medicated with antibiotics [6].

A number of studies relating to antibiotic use in a range of different countries have investigated the knowledge, attitudes and practices of the general population [4, 7–16], secondary school teachers and university faculty members [17], students [18–21], primary care center attendants [22] and parents [23, 24]. These studies have shown patients' or parents' expectations of antibiotic therapy, or expectations as perceived by the doctor, to be a determining factor for antibiotic prescribing [6, 25, 26]. The rationale for educating the public is that knowledge about antibiotic treatment and awareness of antibiotic resistance are thought to influence patient and parent demand for antibiotic prescribing [27]. Because of wide cross-national differences in antibiotic use [28] tailoring of educational interventions requires determination of the needs of the audience in each country.

This paper reports on research that explores the knowledge, attitudes and practices of community members in relation to antibiotic use in the Rupandehi district in Nepal. Previous studies in Nepal have investigated surgical site infection and antibiotic use [29], antibiotic resistance [30–33], antibiotic prescribing and sensitivity [34], antibiotic prescribing patterns [35, 36], antibiotic dispensing practices [37], knowledge, attitudes and practices of medical students in relation to antibiotics use [38], and dispensing practices and patients' knowledge about drug use [39]. However, to our knowledge no population based studies have been conducted on knowledge, attitudes and practices relating to antibiotics use. Moreover, some studies conducted in Nepal have found that antibiotics are among the most commonly sold drug classes [30, 37, 38]. Thus, it is important to measure this phenomenon, exploring the knowledge, attitudes and practices towards antibiotic usage, and awareness about anti-microbial resistance among adults of Nepal. The findings will aid in planning strategies for local health education purposes and developing intervention tools aimed at changing the practices of patients and the public.

Methods

Study area and sampling

A cross sectional quantitative survey of community members was conducted in the Rupandehi district of Nepal. At the time of developing the study design for this research, the administrative re-structure of Nepal had not been fully implemented. As per the earlier structure, Nepal was divided into five developmental regions and subdivided into 75 districts [40]. The districts were further divided into village development committees (VDCs) and municipalities, which were divided into wards as the basic administrative units. Districts are spread across three geographic regions, high-hill, hill and low-land, with approximately half of the population living in low-land regions [41].

According to the 2011 census, the total population of Nepal was 26,494,504 with 3.3% (880,196) of the population living in the Rupandehi district [41]. Almost two-thirds (66.0%, 580,688) were adults. The district is situated towards the central southern part of the country. As per the earlier structure, the district was divided into six municipalities and 42 VDCs. Municipalities and VDCs were aggregated in seven electoral areas [42].

We used guidelines developed by the World Health Organization (WHO) [43, 44] for the selection of households. Following these guidelines, public health facilities were selected as the basis of household selection. We chose six of the seven electoral areas to survey. Two were purposively selected: one that includes the largest hospital in the district and the other was the area with the lowest socio-economic status. An additional four areas were selected randomly from the remaining five electoral areas as recommended by the guidelines. One public health facility was selected from each survey area, consisting of all types of health facilities i.e. two each of hospitals (the largest as discussed above plus another), primary health care centres and health posts. The additional hospital plus other facilities were randomly selected. The VDCs and municipalities in which the public health facilities were located were used as the sampling area for selection of households. Of the total of six areas selected, four consisted of VDCs and two were municipalities.

A cluster sampling technique was applied to identify households to survey within the selected survey areas. Based on the WHO manual [45], we identified 20 clusters from the selected municipalities and VDCs. The smallest administrative unit, the "ward", was considered as a cluster. Four clusters per municipality and three clusters per VDC were selected randomly. The sample size of 220 was based on an estimated prevalence of 33.7% of the population lacking knowledge on antibiotics and their role [4], a 95% confidence interval, a precision effect of 10%, a design effect of two to account for heterogeneity between clusters and an adjustment of 25% to allow for non-response [12, 46].

A list of households in each cluster was obtained from the records of respective municipalities and VDC offices. This list was verified after visiting each cluster and updated by deleting any duplicate households and adding any households missing from the records. Using the updated list of households in each cluster, an equal number of subjects (eleven) was selected from each cluster applying simple random sampling techniques.

The head of household was the preferred respondents for the study. However, if the head of household was absent at the time of interview, the most senior member of the household, who was 18 years and older, was interviewed.

Data instrument and collection

A structured questionnaire was developed by adapting related questionnaires including one from the United States Agency for International Development (USAID) module "Antimicrobial resistance module for population-based surveys" [47] and those used in previous studies [48, 49] (Additional file 1).

A set of questionnaires was pre-tested with 30 respondents in urban and rural areas of the Nawalparasi district, Nepal (a neighboring district of Rupandehi), to ensure the cultural appropriateness, any problems with question wording, layout and understanding or a respondent's reaction. As a result, minor adjustments were made to the final questionnaire based on the pre-test results. With a few people not knowing what the word "antibiotics" was, the questionnaire was amended to ask if they had heard of widely used antibiotics such as penicillin or metronidazole before being asked the main questions. Similarly a few respondents were unsure of the difference between "good" and "bad" bacteria present in our bodies so this difference was explained before they answered the question. Following explanation, issues with language did not appear to cause ambiguity that might impact on interpretation of the survey and the ensuing results. The final questionnaire included twelve questions relating to knowledge, eight questions to attitudes and six questions to practices. The reliability coefficient of responses to the final questionnaire was calculated using the Cronbach's alpha score with the following results recorded: knowledge (0.63), attitudes (0.65) and practices (0.67).

The questionnaire comprised four sections: socio-demographic characteristics of respondents and a section on each of knowledge, attitudes and practices relating to antibiotics and their use. Questions about knowledge were divided into four domains, namely "identification of antibiotics" (Q1-Q3), "knowledge on the role of antibiotics" (Q4-Q6), "side-effects of antibiotics" (Q7-Q9) and "antibiotic resistance" (Q10-Q12). The questions on attitudes were divided into three domains: "preference for use of antibiotics" (Q13-Q15), "antibiotic resistance and safety" (Q16-Q18), and "attitudes to doctor's prescribing of antibiotics" (Q19-Q20). The six questions relating to practices (Q21-Q26) were not divided into domains. The English version of the questionnaire was translated into Nepali and back translated into English to ensure the accuracy of the translated text.

Interviews were conducted in the Nepali language by two trained research assistants from September 2017 to December 2017. The training of research assistants covered the objectives of the study and familiarising them with the data collection techniques. A flow chart for the recruitment of respondents and consent process was provided to the research assistants and used in the data collection process. The average duration per interview was 20 min. Ten households were replaced in the original sample due to refusal to participate ($n = 7$) and no one at home at the time of interview ($n = 3$).

All respondents were informed of the nature of the study and written consent was sought to interviews being conducted. The study was approved by the Human Research Ethics Committee, Curtin University (HRE2017–0394) and the ethics committee of the Nepal Health Research Council (Reg. no.189/2017).

Data management and analysis

Data were collected via paper-based questionnaires and the data were entered and analysed using the Statistical Package for the Social Sciences (SPSS) version 25.0 for Windows (IBM Corp., Armonk, NY, USA).

Demographic variables and responses to the knowledge, attitudes and practices questions were analysed using descriptive statistics. Responses to the five-point Likert scale for the knowledge and attitudes questions were combined into three groups: 'strongly agree' and 'agree', 'strongly disagree' and 'disagree', and 'uncertain'. The three groups are referred to as "Yes", "No" and "Don't know", respectively [50]. Questions relating to practices were assessed using the five-point Likert scales scoring scheme of 'never', 'seldom', 'sometimes', 'often' and 'always'.

Regression analysis was conducted to identify demographic factors associated with knowledge, attitudes and practices. Responses to the knowledge and attitudes questions were given a score of "1" for a correct response and "0" for an incorrect or uncertain response, and scores summed for respondents across each of the domains. For the practices questions, responses were given a score based on the five-point Likert scale, ranging from "5" for the most appropriate answer to "1" for the least appropriate answer, and summed. The median score based on responses to questions in each of the knowledge, attitudes and practices sections was used as the cut-off to dichotomize the continuous variable for use as the dependent variable in multiple logistic regression analysis. Respondents scoring higher than the median were assessed as having "better knowledge", "more appropriate attitudes" and "better practices" relating to antibiotic use [51]. The significance level (α) was set at 0.05 for all statistical tests. Spearman's rank order correlation coefficient was used to describe the strength and direction of the relationship between responses to the knowledge, attitudes and practices questions.

Results

Characteristics of respondents

The sample consisted of 220 households (Table 1), with a response rate of 97% (n = 210). Compared to the adult population of the Rupandehi district, the sample included slightly more females (54% vs 52%) and respondents from rural areas (60% vs 51%). The mean age was 38.5 years (SD 11.5). Most respondents had achieved a level of education of primary/secondary school level (31.4%) or high school/intermediate level (30.0%). The mean monthly income of respondents was Nepalese Rupees (NPR) 42,491 (SD 16,835), compared with an estimated average monthly household income for Nepal of NPR 30,121 in 2015 [52].

Knowledge, attitudes and practice relating to antibiotic use

Respondents had relatively good knowledge about three of the four knowledge domains: "knowledge about the role of antibiotics (Q4-Q6)", "side-effects of antibiotics (Q7-Q9)", and "antibiotic resistance (Q10-Q12)" (Fig. 1). While the majority of responses to questions in the three domains were correct, for questions on "side-effects of antibiotics" and "antibiotic resistance" a relatively high percentage of responses to five of the six questions fell in the "don't know" category (16–27%). Statements for

Table 1 Socio-demographic characteristics of respondents

Variables	Study, n (% distribution)	Rupandehi, n (% distribution)[a]
Gender		
Male	101 (45.9)	277,714 (47.8)[b]
Female	119 (54.1)	302,974 (52.2)[b]
Area of residence		
Urban	88 (40.0)	(49.0)[b]
Rural	132 (60.0)	(51.0)[b]
Age (Years)		
15–24	25 (11.4)	185,430 (31.9)[b]
25–34	50 (22.7)	134,798 (23.2)[b]
35–44	81 (36.8)	99,013 (17.1)[b]
45–54	38 (17.3)	69,363 (11.9)[b]
55+	26 (11.8)	92,084 (15.9)[b]
	Min = 18, Max = 69, Mean = 38.5, SD = 11.511	
Level of education		
General literate	38 (17.3)	
Primary/Secondary school	69 (31.4)	
High school/Intermediate	66 (30.0)	
Bachelors and above	47 (21.4)	
Level of Income - Quartile (NPR) (n = 210)		
First (30,000 or less)	60 (28.6)[c]	
Second (30,001 to 40,000)	46 (21.9)[c]	
Third (40,001 to 53,500)	52 (24.8)[c]	
Fourth (53,501 and above)	52 (24.8)[c]	
Min = 2300, Max = 110,000, Mean = 42,491.9, SD = 16,835.0		

[a]*Source: CBS, 2014* [53]
[b]*% calculated based on population of 15 years and above*
[c]*Numbers not equally distributed across quartiles due to clustering of responses at cut-off points*

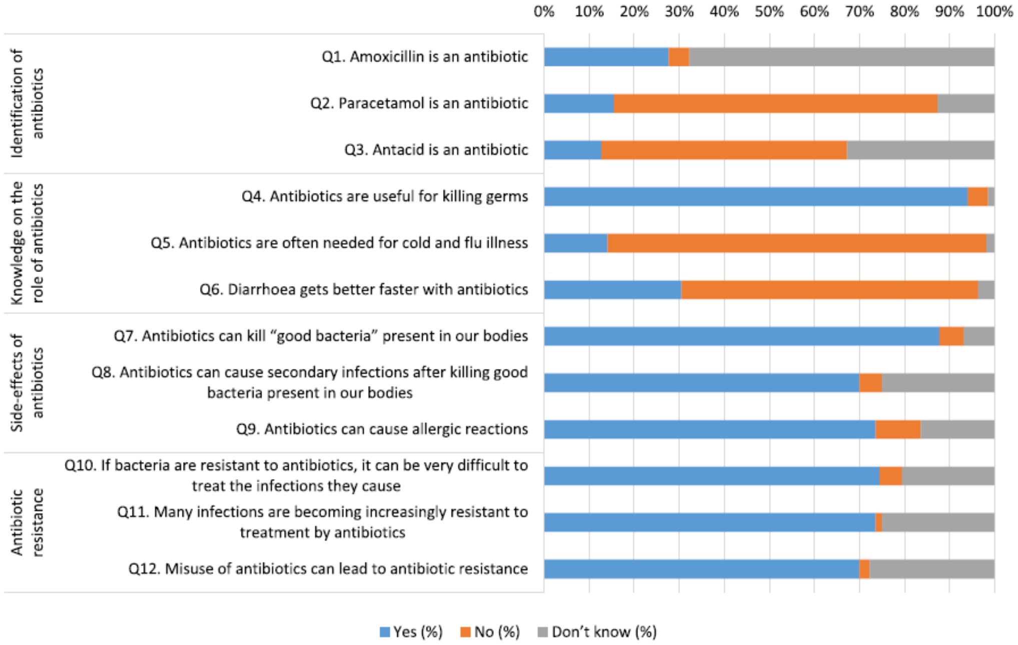

Fig. 1 Responses to questions related to knowledge about antibiotic use

which the "don't know" response was highest included that "*antibiotics can cause secondary infections after killing good bacteria present in our bodies*" (25.0%), "*many infections becoming increasingly resistant to treatment by antibiotics*" (25.0%) and "*misuse of antibiotics leading to antibacterial resistance*" (27.7%).

Respondents had relatively less knowledge in regard to "identification of antibiotics (Q1-Q3)". More than two-thirds (67.7%) did not answer correctly to the question that "*amoxicillin is an antibiotic*" and nearly one-third (32.7%) did not know that "*antacid is not an antibiotic*". However, most respondents (94.1 and 84.1% respectively) answered correctly that "*antibiotics are useful for killing germs*" and "*antibiotics are not often needed for cold and flu illness*" while more than two-thirds (71.5%) knew paracetamol was not an antibiotic.

The level of knowledge about antibiotics use was better for respondents who lived in urban areas compared to rural areas (X^2 = 16.257, $p = < 0.001$), for younger respondents (X^2 = 30.696, $p = < 0.001$) and those with higher levels of education (X^2 = 72.264, $p = < 0.001$) (Table 2).

Responses to questions about attitudes to antibiotics reflected varying points of view (Fig. 2). In terms of having a "preference for use of antibiotics (Q13-Q15)", most respondents were aware that they did not need to take antibiotics for a cold to prevent them getting a more serious illness (77.3%) and did not want to take an antibiotic if they did not need one (78.2%). However, almost half (47.7%) thought antibiotics would help them to get better more quickly if they had a fever.

In the domain of "antibiotic resistance and safety (Q16-Q18)", half of respondents (50.9%) were uncertain if skipping doses would not contribute to the development of antibiotic resistance and almost one fifth (17.3%) were uncertain about if taking an antibiotic contributed to the development of antibiotic resistance. Most respondents (81.8%) agreed antibiotics should not be commonly used.

Attitudes to prescribing of antibiotics by doctors were somewhat ambivalent. Most respondents (61.8%) were not less satisfied with a doctor's visit if they did not receive an antibiotic; however, the majority (88.2%) indicated if they were not prescribed an antibiotic when they thought one was needed, they would go to another doctor.

Attitudes to antibiotic use was significantly associated with areas of residence (X^2 = 5.197, p = 0.023) and education level (X^2 = 27.306, $p = < 0.001$) (Table 2). Respondents living in urban areas and those with higher levels

Table 2 Responses to questions related to knowledge, attitudes and practices in relation to antibiotics use

Variables	Knowledge level			Attitudes level			Practices level		
	Less n (%)	Better n (%)	X^2 (p = value)	Less appropriate n (%)	More appropriate n (%)	X^2 (p = value)	Poor n (%)	Better n (%)	X^2 (p = value)
Gender									
Male	55 (54.5)	46 (45.5)	0.010 (p = 0.920)	61 (60.4)	40 (39.6)	3.473 (p = 0.062)	76 (75.2)	25 (24.8)	5.984 (p = 0.014)
Female	64 (53.8)	55 (46.2)		86 (72.3)	33 (27.7)		71 (59.7)	48 (40.3)	
Area of Residence									
Urban	33 (37.5)	55 (62.5)	16.257 (p = < 0.001)	51 (58.0)	37 (42.0)	5.197 (p = 0.023)	46 (52.3)	42 (47.7)	13.996 (p = < 0.001)
Rural	86 (65.2)	46 (34.8)		96 (72.7)	36 (27.3)		101 (76.5)	31 (23.5)	
Age Group (Yr.)									
15–24	13 (52.0)	12 (48.0)	30.696 (p = < 0.001)	17 (68.0)	8 (32.0)	8.499 (p = 0.075)	10 (40.0)	15 (60.0)	17.921 (p = 0.001)
25–34	15 (30.0)	35 (70.0)		25 (50.0)	25 (50.0)		29 (58.0)	21 (42.0)	
35–44	40 (49.4)	41 (50.6)		58 (71.6)	23 (28.4)		55 (67.9)	26 (32.1)	
45–54	28 (73.7)	10 (26.3)		28 (73.7)	10 (26.3)		30 (78.9)	8 (21.1)	
55+	23 (88.5)	3 (11.5)		19 (73.1)	7 (26.9)		23 (88.5)	3 (11.5)	
Education Level									
General literate	36 (94.7)	2 (5.3)	72.264 (p = < 0.001)	33 (86.8)	5 (13.2)	27.306 (p = < 0.001)	31 (81.6)	7 (18.4)	42.452 (p = < 0.001)
Primary/ Secondary School	51 (73.9)	18 (26.1)		53 (76.8)	16 (23.2)		55 (79.7)	14 (20.3)	
High School/ Intermediate	25 (37.9)	41 (62.1)		43 (65.2)	23 (34.8)		48 (72.7)	18 (27.3)	
Bachelors and above	7 (14.9)	40 (85.1)		18 (38.3)	29 (61.7)		13 (27.7)	34 (72.3)	
Income Level - Quartile (NPR)									
First (30,000 or less)	36 (60.0)	24 40.0)	1.884 (p = 0.597)	44 (73.3)	16 (26.7)	1.512 (p = 0.680)	38 (63.3)	22 (36.7)	1.197 (p = 0.754)
Second (30,001 to 40,000)	24 (52.2)	22 (47.8)		30 (65.2)	16 (34.8)		29 (63.0)	17 (37.0)	
Third (40,001 to 53,500)	26 (50.0)	26 (50.0)		33 (63.5)	19 (36.5)		37 (71.2)	15 (28.8)	
Fourth (53,501 and above)	25 (48.1)	27 (51.9)		34 (65.4)	18 (34.6)		36 (69.2)	16 (30.8)	

of education had more appropriate attitudes than those living in rural areas and those with lower levels of education.

In responding to questions about practices the majority always or often consulted a doctor before starting an antibiotic (94.5%), checked the expiry date of antibiotics before using them (85.8%) and completed the full course of treatment (81.3%), and never or seldom preferred to obtain antibiotics from the pharmacy (76.8%). However, in contrast to good practice reflected with these questions, the majority (84.6%) reported at least sometimes preferring to take an antibiotic when they have a cough or sore throat and almost a third (31.8%) to using antibiotics as a prophylaxis (Fig. 3).

Practices in relation to antibiotic use were significantly associated with gender (X^2 = 5.984; p = 0.014), area of residence (X^2 = 13.996, p = < 0.001), age group (X^2 = 17.921, p = 0.001) and education level (X^2 = 42.452;

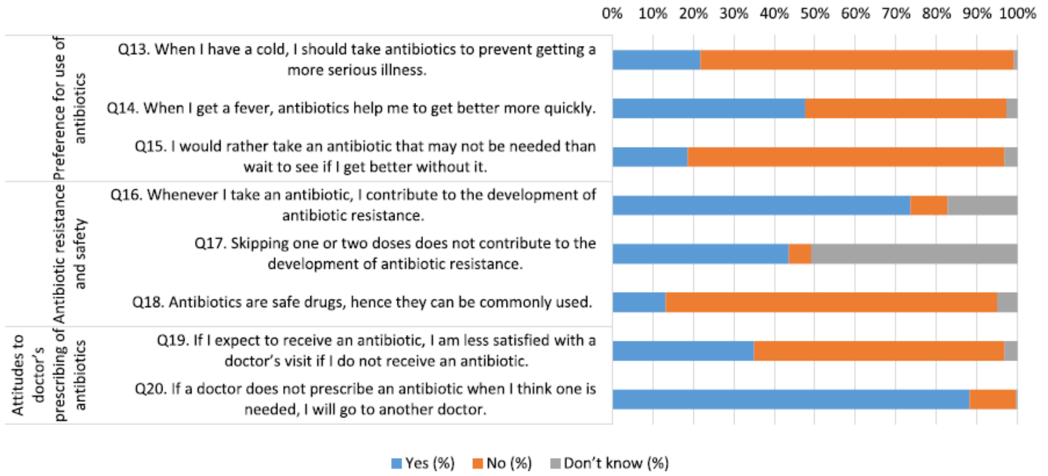

Fig. 2 Responses to questions related to attitudes towards antibiotic use

$p = < 0.001$) (Table 2). Female respondents, those who lived in urban areas, were younger and those with a higher level education reported better practices in regard to antibiotic use compared to males, respondents living in rural areas, older respondents and those with lower levels of education.

Factors associated with knowledge, attitudes and practices relating to antibiotics use

In multivariable logistic regression analysis (Table 3), after adjusting for other variables, education level was found to be significantly associated with each of knowledge, attitudes and practices, with respondents with a level of education of Bachelor degrees and above having better knowledge, more appropriate attitudes and better practices. Area of residence was significantly associated with better knowledge on antibiotics use, with rural respondents being less likely to have better knowledge compared to urban residents, and females being more likely to have better practices than males.

Relationship between knowledge, attitudes and practices

Spearman rank order correlation revealed a positive association between each pair of the knowledge, attitude and practice scores for respondents ($p = < 0.001$) (Table 4). The correlation was good between knowledge-attitudes and fair between knowledge-practices and attitudes-practices [54].

However, comparing responses to questions in different domains, a few inconsistencies were noted. For example, although most respondents (84.1%) correctly

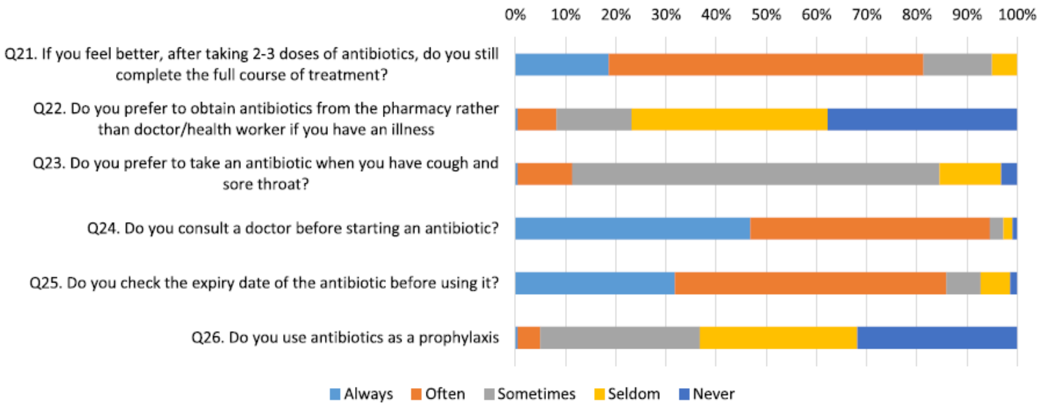

Fig. 3 Responses to questions related to practices in relation to antibiotic use

Table 3 Odds ratios (ORs) of having better knowledge, more appropriate attitudes and better practices in relation to antibiotic use

Variables	Knowledge level			Attitudes level			Practices level		
	Crude OR[a] (95% CI)	Adjusted OR[a] (95% CI)	*p* = value	Crude OR[a] (95% CI)	Adjusted OR[a] (95% CI)	*p* = value	Crude OR[a] (95% CI)	Adjusted OR[a] (95% CI)	*p* = value
Gender									
Male	0.973 (0.572, 1.657)	0.867 (0.404, 1.859)	0.714	1.709 (0.971, 3.009)	1.672 (0.844, 3.311)	0.141	0.487 (0.272, 0.870)	0.394 (0.187, 0.829)	0.014
Female	1	1		1	1		1	1	
Area of Residence									
Rural	0.321 (0.183, 0.562)	0.317 (0.149, 0.676)	0.003	0.517 (0.292, 0.915)	0.587 (0.095, 1.492)	0.119	0.336 (0.188, 0.601)	0.553 (0.281, 1.085)	0.085
Urban	1	1		1	1		1	1	
Age Group (Yr.)									
15–24	3.621 (1.341, 9.777)	0.271 (0.060, 1.212)	0.088	1.301 (0.475, 3.561)	0.376 (0.95, 1.492)	0.164	7.227 (2.579, 20.254)	1.272 (0.313, 5.163)	0.736
25–34	9.154 (3.880, 21.595)	2.714 (0.861, 8.558)	0.088	2.765 (1.262, 6.057)	1.377 (0.480, 3.945)	0.552	3.489 (1.479, 8.233)	1.027 (0.324, 3.256)	0.964
35–44	4.021 (1.902, 8.502)	1.837 (0.741, 4.558)	0.189	1.096 (0.525, 2.288)	0.669 (0.278, 1.611)	0.370	2.278 (1.024, 5.067)	1.089 (0.430, 2.756)	0.858
44+	1	1		1	1		1	1	
Education Level									
Below secondary level	0.093 (0.042, 0.207)	0.035 (0.010, 0.127)	< 0.001	0.152 (0.071, 0.323)	0.147 (0.053, 0.411)	< 0.001	0.093 (0.042, 0.207)	0.098 (0.033, 0.293)	< 0.001
High school & intermediate	0.143 (0.062, 0.331)	0.285 (0.090, 0.906)	0.033	0.332 (0.153, 0.721)	0.337 (0.140, 0.812)	0.015	0.143 (0.062, 0.331)	0.155 (0.061, 0.939)	< 0.001
Bachelor degree and above	1	1		1	1		1	1	

OR: Odds ratio.
[a]*OR for included explanatory factors: adjusted with gender, residence, age and education*
Reference categories: 1 and better or more appropriate
Respondents scoring higher than the median were assessed as having "better knowledge", "more appropriate attitudes" and "better practices" relating to antibiotic use.

answered the question in the knowledge section that antibiotics are not often needed for cold and flu illness (Fig. 1), in the practices section the majority (84.1%), answered that sometimes or often they preferred to take an antibiotic when they had a cough or sore throat (Fig. 3). Another example was respondents seemingly having good knowledge about antibiotic resistance (correct answers of between 70.0 to 74.5% for relevant questions) (Fig. 1), however more than one-third (35.0%) were less satisfied with a doctor's visit if they did not receive an antibiotic and the majority (88.2%) would go to another doctor if a doctor did not prescribe an antibiotic when one was needed (Fig. 2).

Table 4 Correlations between knowledge, attitudes, and practices

Variables	Correlation coefficient	*p*= value
Knowledge - Attitudes	0.649	< 0.001
Knowledge - Practices	0.428	< 0.001
Attitudes - Practices	0.370	< 0.001

Discussion

This is the first study to identify the knowledge, attitudes and practices of the general population in Nepal regarding antibiotic use and to identify any factors associated with these main outcomes of interest.

Overall, the respondents in our study had relatively good knowledge about antibiotic use, with an exception being in regard to identification of antibiotics. More than two-thirds of respondents (67.7%) did not know that *"amoxicillin is an antibiotic"*, a significantly higher percentage than found in a study conducted in Bhutan (32.4%) [5]. Less than one-third of respondents (28.5%) did not know *"paracetamol is not an antibiotic"*, a similar result to that found in a Lebanese study (21.6%) [55]. We found that 15.9% of respondents were unsure whether *"antibiotics are often needed for cold and flu illness"*, a lower percentage than was found in studies conducted in Britain (42%) [11] and Lebanon (39%) [56].

With regard to attitudes towards antibiotic use, nearly half of respondents (47.7%) still believed that *"when they get a fever, antibiotics help them to get better more quickly"*, a comparable result to that found in a study conducted in Indonesia [14]. In the current study most respondents (88.2%) intended *"to go to another doctor if a doctor does not prescribe an antibiotic when they think one is needed"*. This suggests a high expectation in regard to using antibiotics for some illnesses or a low level of trust to prescribing practices of doctors. The latter was found in a Kuwaiti study, with one-third of respondents not trusting doctors who were not prescribing antibiotics [6].

Although respondents were aware that antibiotic resistance was a problem, half (50.9%) were still unsure whether *"skipping one or two doses does not contribute to the development of antibiotic resistance"*. This finding is consistent with a Palestinian study that found one-third of respondents knew the meaning of antibiotic resistance, however nearly one-third of them incorrectly agreed that antibiotics' effectiveness would not be affected if antibiotics are taken less or more than the prescribed dose [57].

The only sociodemographic factor found to be associated with each of knowledge, attitudes and practices relating to antibiotics use was education. Respondents with higher education had better knowledge and more appropriate attitudes and practices, a finding consistent with other studies [5, 7, 13, 55, 57–60]. Our findings also suggest respondents in urban areas had better knowledge on antibiotic use than those in rural areas, a similar observation to that found in a Lithuanian study [61] but contrasting with a Polish study that found no such difference [62]. We found females to have better practices with regard to antibiotic use, a comparable result to a Hong Kong study [7].

A number of implications flow from our findings. Bringing about behavioural change is never easy, especially when it is deeply entrenched [63]. Our study provides an evidence base from which to develop education programmes for the community about antibiotic use. For example, given that several respondents failed to identify antibiotics, which could potentially risk antibiotics being used in a similar way to other drugs, educating the public on the roles of antibiotics and the ability to differentiate antibiotics from other drugs could help to minimise antibiotic misuse. The concept of antibiotic resistance is known but problems associated with antibiotic misuse were found to be imperfectly understood. The findings of the study also indicated that the community has high expectations with regard to being prescribed antibiotics, which increases the likelihood of non-prescription use of antibiotics. Village doctors or health workers could provide education to community members, and mass education campaigns conducted to emphasise the potential risks of resistance by using non-prescription antibiotics and the inappropriateness of using antibiotic therapy for minor ailments.

The study also identified a relationship between respondents having less knowledge, less appropriate attitudes and poor practices regarding the appropriate use of antibiotics. Groups, such as those with lower formal education, who had less knowledge and less appropriate attitudes and practices to antibiotic use and who could be targeted in education campaigns. A positive finding was females having better practices in regard to antibiotic use. In most developing countries, including Nepal, females hold the responsibility of taking care of their children and other family members, thus their better practices should contribute to some extent to the control of antimicrobial resistance.

Education of community members alone will not be enough to minimise any misuse of antibiotics. A multifaceted approach involving policy makers, prescribers, and the general public using both educational and regulatory measures is needed. Such measures should be embedded in a general policy to change the culture of antibiotic use by improving awareness among the general public and professionals about the risks associated with antibiotic use as well as reducing public misconceptions about the benefit of taking antibiotics for minor illnesses.

This is the first known community survey conducted in Nepal to examine knowledge, attitudes and practices towards antibiotic use among the public. As such its findings provide baseline evidence about the knowledge, attitudes and practices regarding antibiotics use among the Nepalese population and offers insight in designing interventions to reduce antibiotic misuse.

The study used standard guidelines, developed by WHO [43, 44] for selecting the households. These guidelines have been refined continuously based on the lessons learned and used widely across many low and middle income countries to generate reliable information on medicines. Clustering and sampling techniques, described in the guidelines, are designed in a way to get optimum representation. Likewise, key aspects relating to antibiotic use in the community were covered by the survey questions, which were drawn from an USAID module on antimicrobial resistance [47] and previous studies [48, 49], which contributed to the validity of our study and allowed for comparison with previous results.

Another strength of the study was the high response rate (97%), which demonstrated representative results minimising the possible bias. However, the study was only conducted in one district in the low-land region of Nepal, so the results are more generalisable to districts in low-land regions. Also, surveys such as the one conducted in this study depend very much on the information given by respondents thus, the findings rely partly on the respondents' honesty and ability to recall. Moreover, it is possible that respondents may over-report socially desirable behaviours or under-report socially undesirable behaviours. A limitation of the study was not using a social desirability scale to assess the extent of these behaviours. Additionally, the survey did not identify household structure and the knowledge, attitudes and practices might differ say among households with young children compared to those with older residents.

A possible problem in studies of antibiotic use involving lay people is whether the respondents know what antibiotics are. Respondents who had not heard the word "antibiotics" were asked if they had heard of widely used antibiotics such as penicillin or metronidazole before being asked the main questions. While nearly one-fifth (17%) of respondents did not understand the word "antibiotics", all respondents were familiar with specific types of antibiotics following explanation by research assistants, thus to some extent combating this problem.

Conclusion

This study is an important step towards a better understanding of the knowledge, attitudes and practices regarding antibiotic issues in the adult population in the Rupandehi district of Nepal. Its findings may be generalisable more broadly across the country, especially low-land regions. Our findings are important to the campaign to reduce the inappropriate use of antibiotics, and its findings can be used to inform the design of effective and targeted interventions to decrease misconceptions about antibiotic use and to increase awareness regarding the risks of inappropriate use. Its findings can also be used as a baseline for monitoring future interventions. Future studies should focus on the development and implementation of such public education measures to improve antibiotic use among community members in Nepal.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12889-019-7924-5.

Additional file 1. Questionnaire.

Abbreviations

CI: Confidence Interval; KAP: Knowledge, Attitudes and Practices; NPR: Nepalese Rupees; OR: Odds Ratio; SPSS: Statistical Package for the Social Sciences; USAID: United States Agency for International Development; VDCs: Village Development Committees; WHO: World Health Organization

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Authors' contributions

AN designed the study with input from DH, SR and LS. AN conducted the research including the analysis. DH conducted the coding check. AN drafted the manuscript and DH edited the manuscripts. All authors contributed to revisions and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All respondents were informed of the nature of the study and written consent was sought to interviews being conducted. All respondents were 18 years and older. The study was approved by the Human Research Ethics Committee, Curtin University (HRE2017–0394) and the ethics committee of the Nepal Health Research Council (Reg no.189/2017).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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